Current Landscape of Type 2 Diabetes Treatment

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Director, Diabetes and Obesity Research Program

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Executive Director, Global Diabetes Program,
Parkland Health & Hospital System

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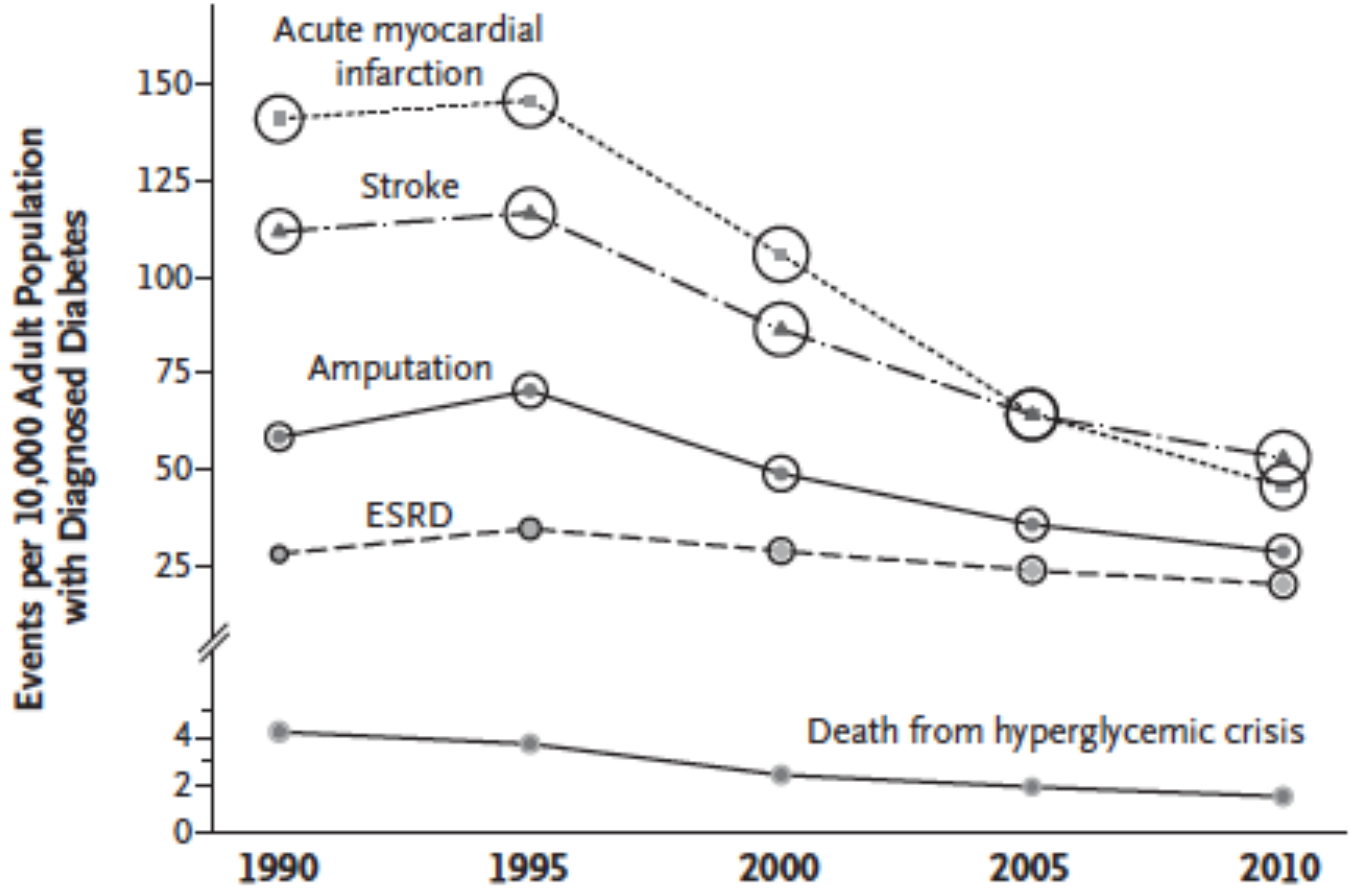
What would you say is your professional designation (i.e. nurse, physician, administrator, IT, etc.)

Complications in people with diabetes over 2 decades



-68%

-53%

-51%

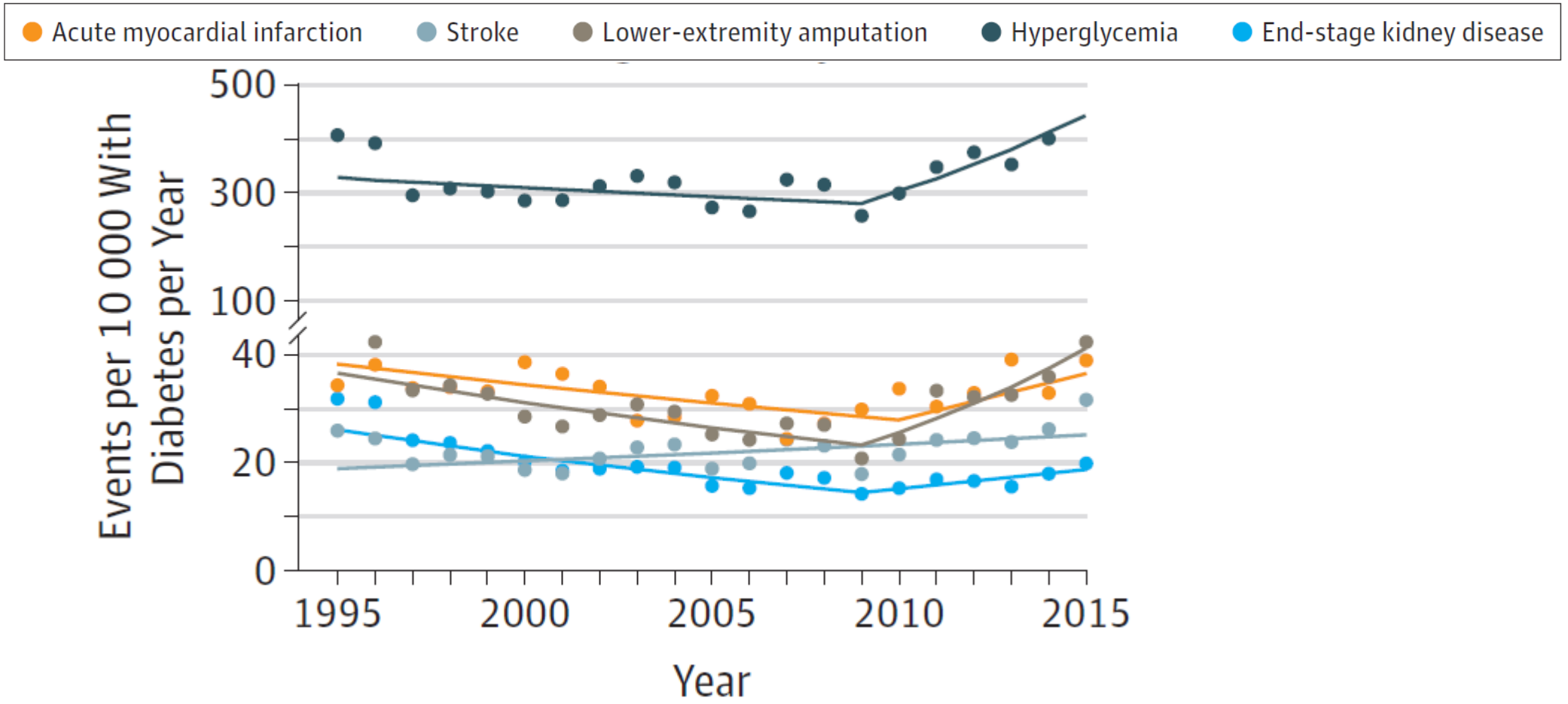
-28%

-64%

Gregg EW, et al. *N Engl J Med*. 2014;370(16):1514-1523.

Resurgence of Diabetes complications

Especially in the younger patients (18-44 yrs)



Gregg EW et al, JAMA 2019

Cardiovascular risks in adults with diabetes

HTN

71%

Dyslipidemia

65%

ESRD

1.1%

Obesity

57%

Smoking

20%

CVD death rates ~1.7x higher among adults ≥18 years with diabetes

http://www.diabetes.org/diabetes-basics/statistics/?loc=db-slabnav, http://www.cdc.gov/diabetes/statistics/risk_factors_national.htm. United States Renal Data System. Annual Data Report: Epidemiology of Kidney Disease in the United States. Bethesda, MD, National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases, 2016

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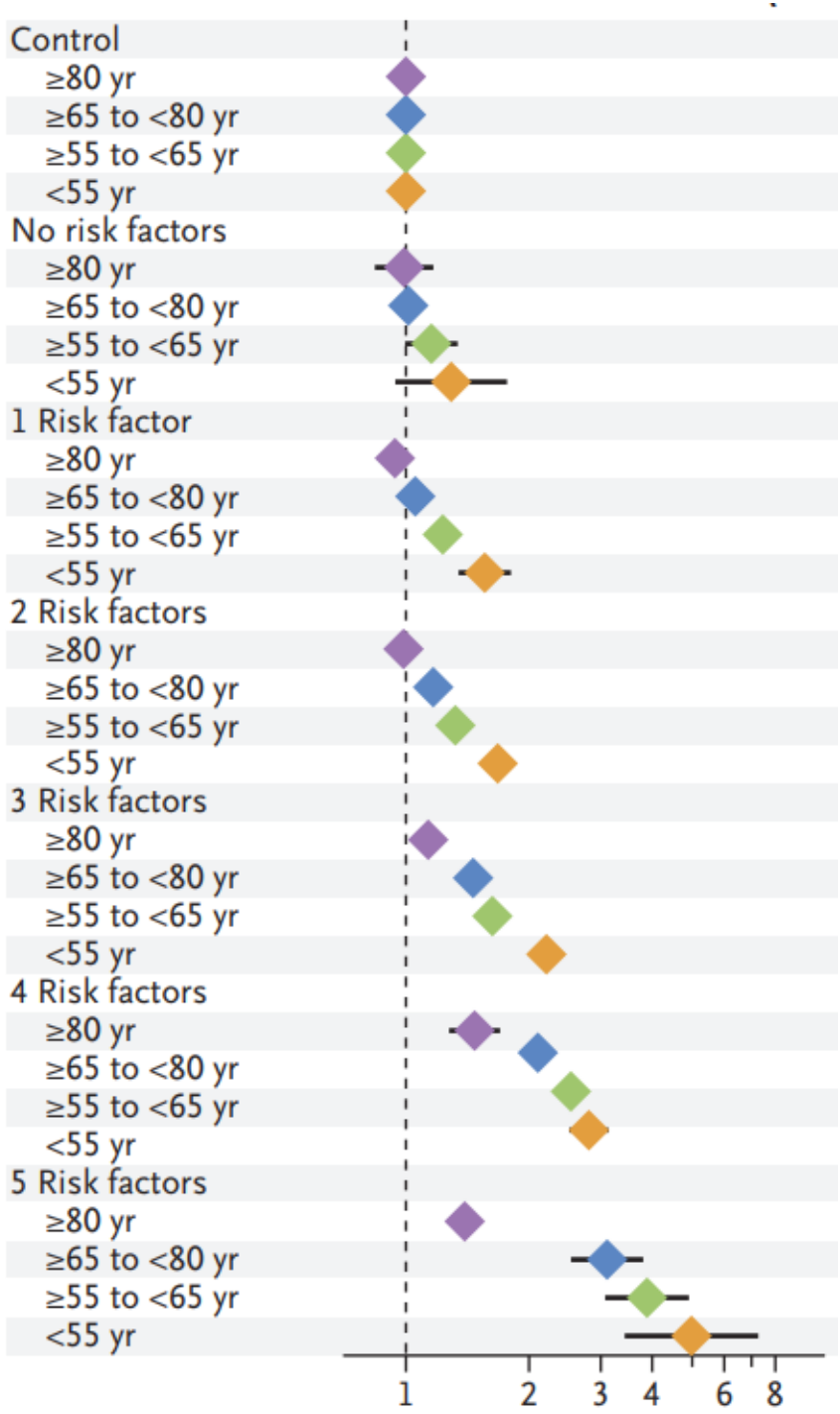
What do you think contributes to the excess mortality in people with diabetes?

Excess Mortality in Diabetes Depends on Risk Factor Burden

Risk factors:
-elevated HbA1c
-uncontrolled HTN
-elevated LDL
-microalbuminuria
-smoking



Rawshani A. NEJM 2018:633

Does glycemic control reduce the risk of diabetes complications?

Glycemic Control & Vascular Complications in Diabetes

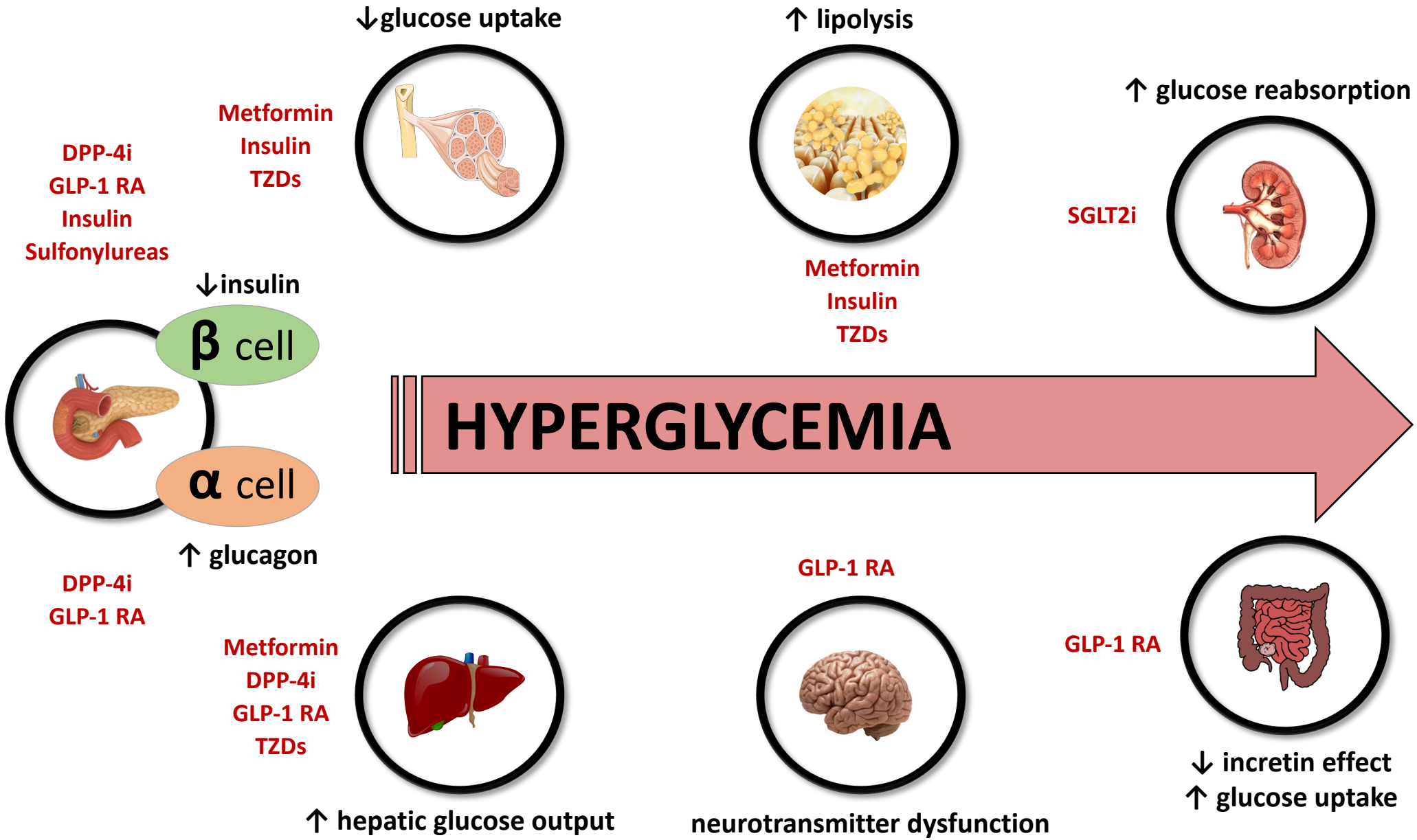
	MICROVASCULAR		MACROVASCULAR		MORTALITY	
DCCT/EDIC	↓	↓	=	↓	=	↓
UKPDS	↓	↓	=	↓	=	↓
ACCORD	±	±	=	=	↑	=
ADVANCE	↓	↓	=	=	=	=
VADT	=	=	=	↓	=	=

Observational follow-up

In ACCORD, progression of retinopathy in patients with mild baseline retinopathy was positively impacted; similar benefits were seen for fenofibrate use. In ACCORD, baseline CKD was associated with higher CV & overall mortality in the intensive group. In ADVANCE, the intensive group had lower rates of ESRD in both active trial and FU.

UKPDS Group. Lancet 1998;352:837-53. Gerstein et al, NEJM 2008;358:2545-59. Duckworth et al, NEJM 2009;360:129-39. Patel et al, NEJM 2008;358:2560-72. ACCORD Study Group. Diabetes Care 2016; Jan 28. pii: dc152283. [Epub ahead of print]. Chew, et al. Ophthal 2014; 121: 2443–2451. Papademetriou, et al. Kidney International (2015) 87, 649–659. Hayward, et al. N Engl J Med 2015;372:2197-206. Zoungas, et al. N Engl J Med. 2014 Oct 9;371(15):1392-406. DCCT-EDIC Study Group. JAMA. 2015;313(1):45-53

Type 2 DM Treatment Targets



DeFronzo RA. *Diabetes.* 2009;58(4):773-795

How many different classes of medications do you think are available to treat hyperglycemia in diabetes?

Timeline of Diabetes Medications in USA

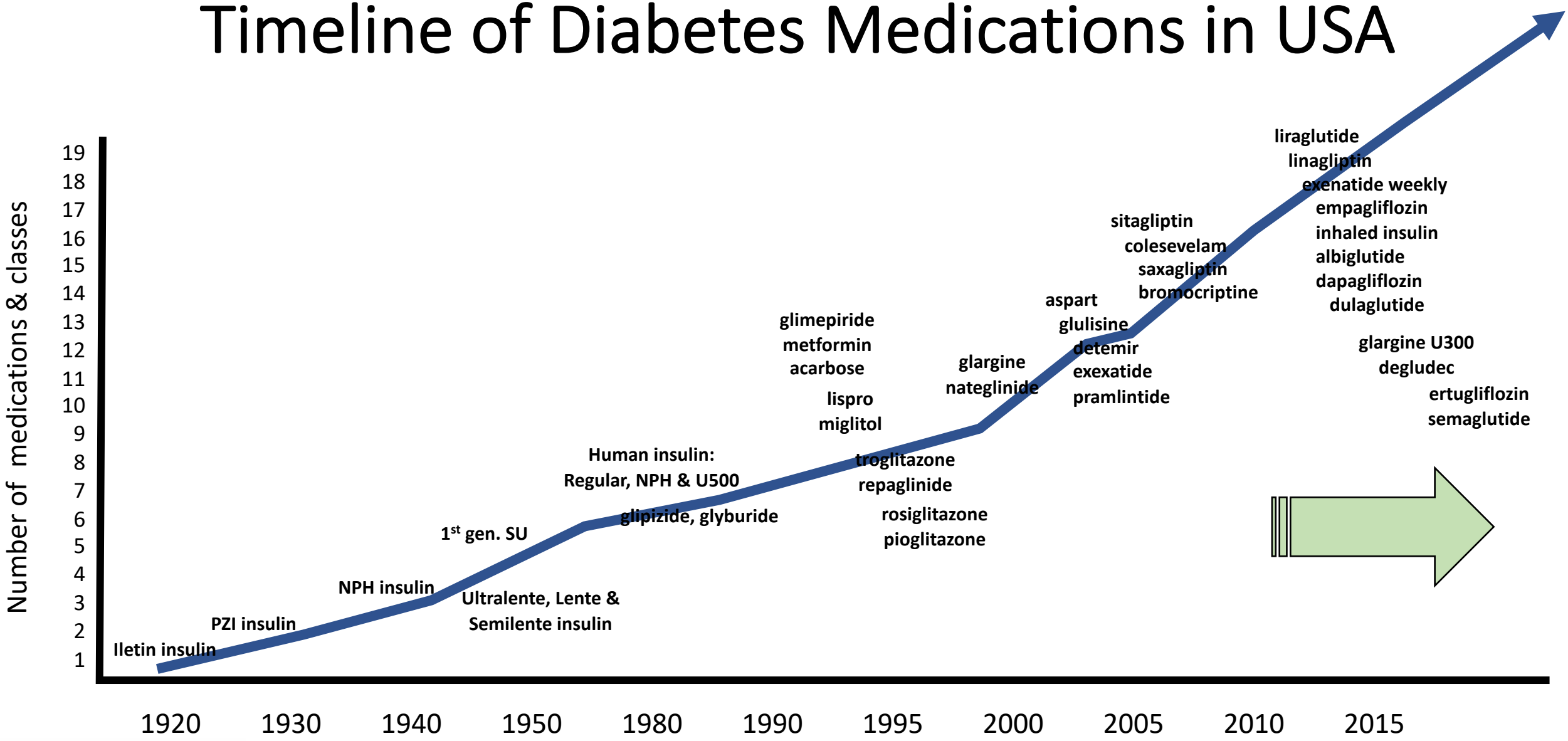


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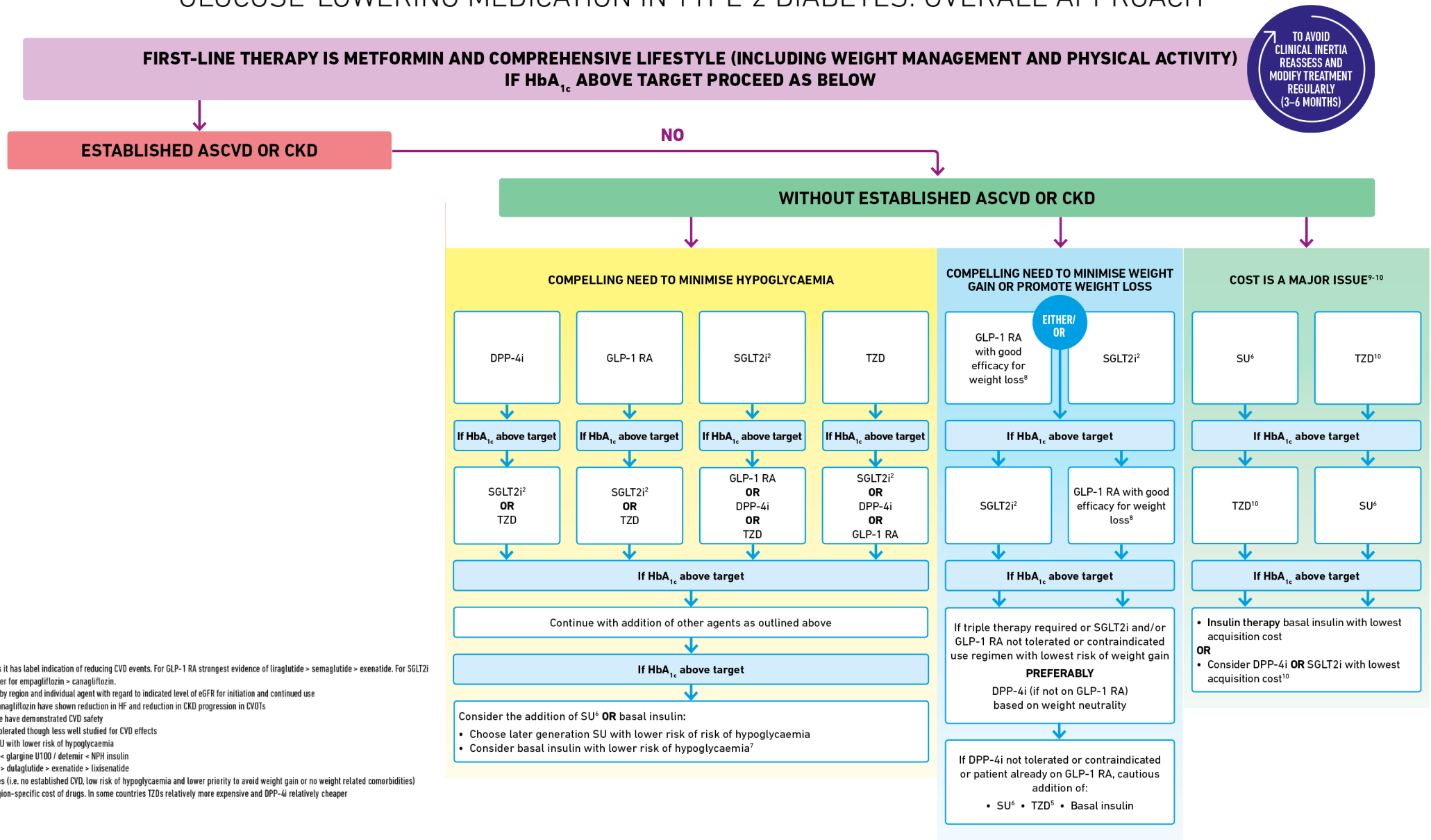
Figure 2

GLUCOSE-LOWERING MEDICATION IN TYPE 2 DIABETES: OVERALL APPROACH



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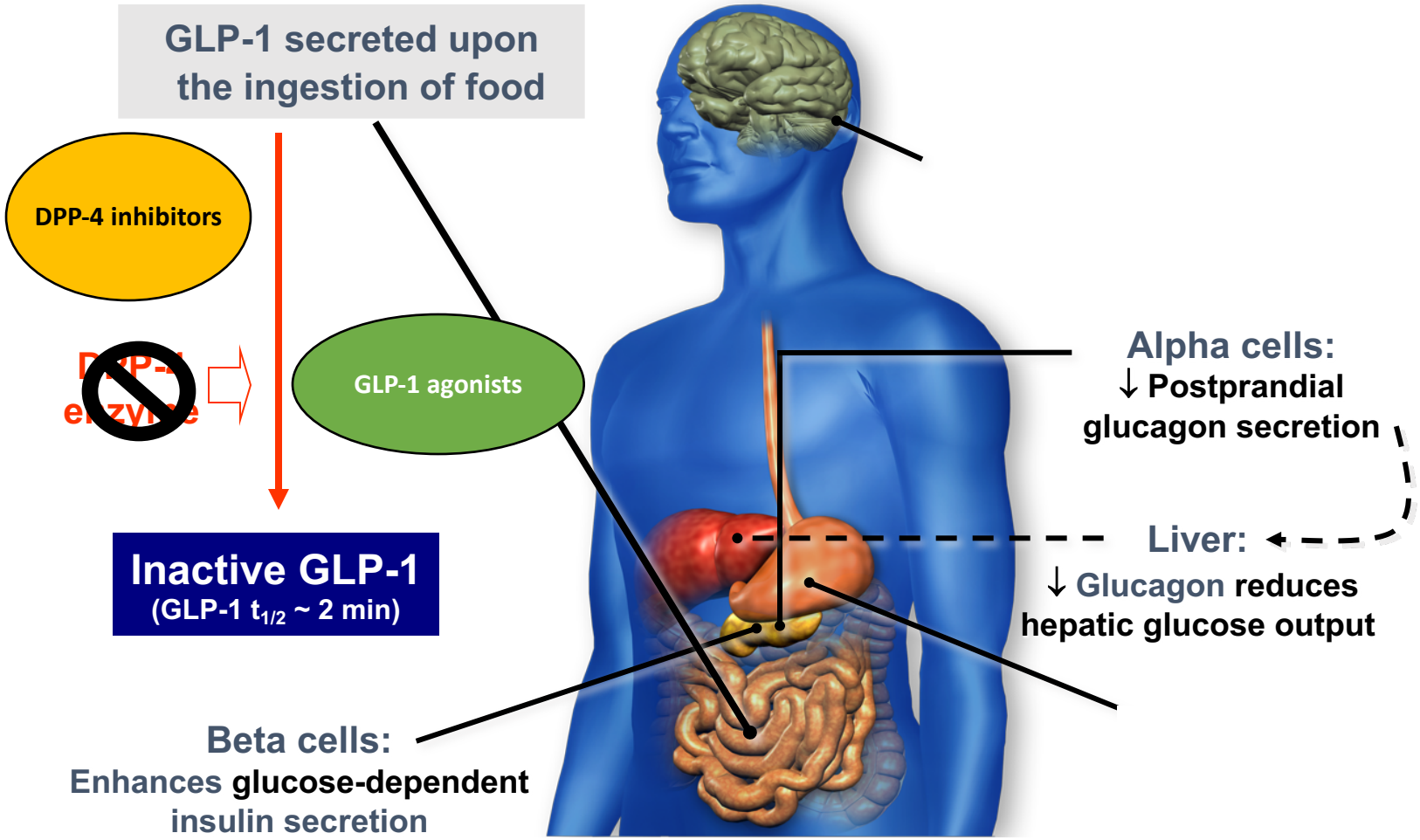
10. Consider country- and region-specific cost of drugs. In some countries TZDs relatively more expensive and DPP-4i relatively cheaper

DPP-4 inhibitors

GLP-1 activity enhanced 2-3 fold with DPP-4 inhibitors & 8-9 fold with GLP-1 RA



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Adapted from Nauck MA, et al. *Diabetologia*. 1996;39:1546-1553
Adapted from Drucker DJ. *Diabetes*. 1998;47:159-169

What is the difference between a DPP-4 inhibitor (like linagliptin) and a GLP-1 receptor agonist (like liraglutide)?

GLP-1 agonists are easier to administer

DPP-4 inhibitors are associated with weight loss

GLP-1 agonists are more effective at lowering A1C

Gastrointestinal side effects are the most common issue with DPP-4 inhibitors

Incretin therapies: effects & differences

GLP-1 receptor agonists

- **Short-acting**
  - Exenatide
  - Lixisenatide
- **Intermediate-acting**
  - Liraglutide
- **Long-acting**
  - Exenatide XR
  - Dulaglutide
  - Semaglutide

DPP-4 inhibitors

- Sitagliptin
- Saxagliptin
- Linagliptin
- Alogliptin

Comparison of DPP-4 inhibitors and GLP-1 receptor agonists

DPP-4 inhibitors

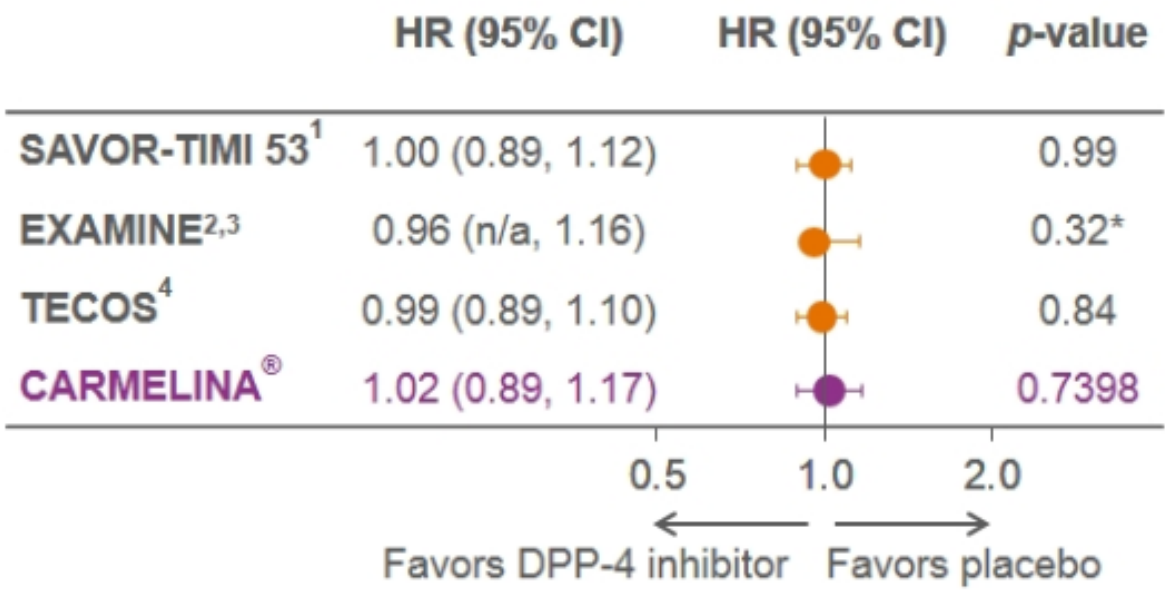
- Increase native GLP-1 by 2-3 fold
- Reduces A1C ~ 0.6-1.0%
- No effect on appetite or weight
- Low hypoglycemia risk
- Can exacerbate pancreatitis
- No GI side effects

GLP-1 RA

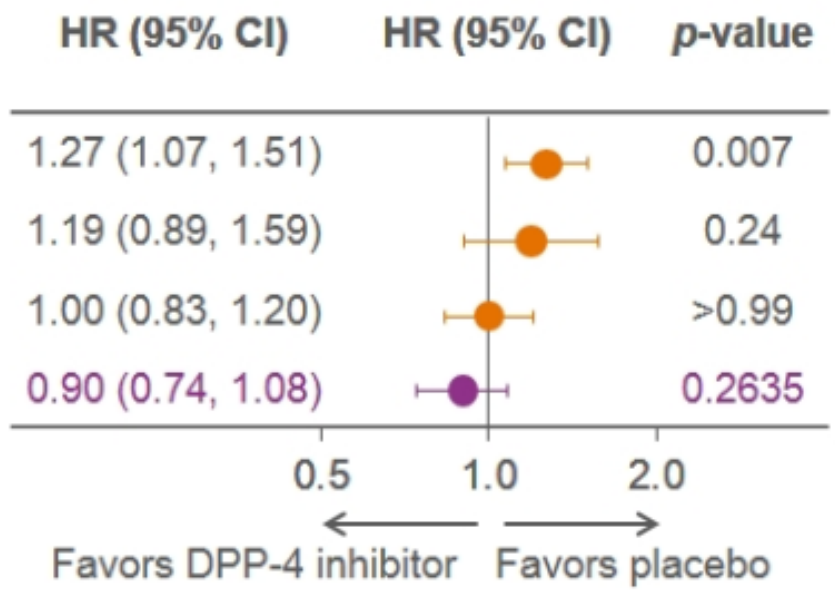
- Increase GLP-1 receptor action by 8-9 fold
- Reduces A1C ~ 0.8-1.5%
- Reduces appetite and weight
- Low hypoglycemia risk
- Can exacerbate pancreatitis
- Slows gastric emptying causing GI side effects

DPP – 4 inhibitor CVOT trials

3P-MACE



Hospitalization for heart failure[5]



Presented at EASD 2018.

	Glucose lowering	Hypoglycemia Risk	Weight effect	ASCVD	HF	Cost	Route of administration
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Metformin							Oral
DPP IV							Oral

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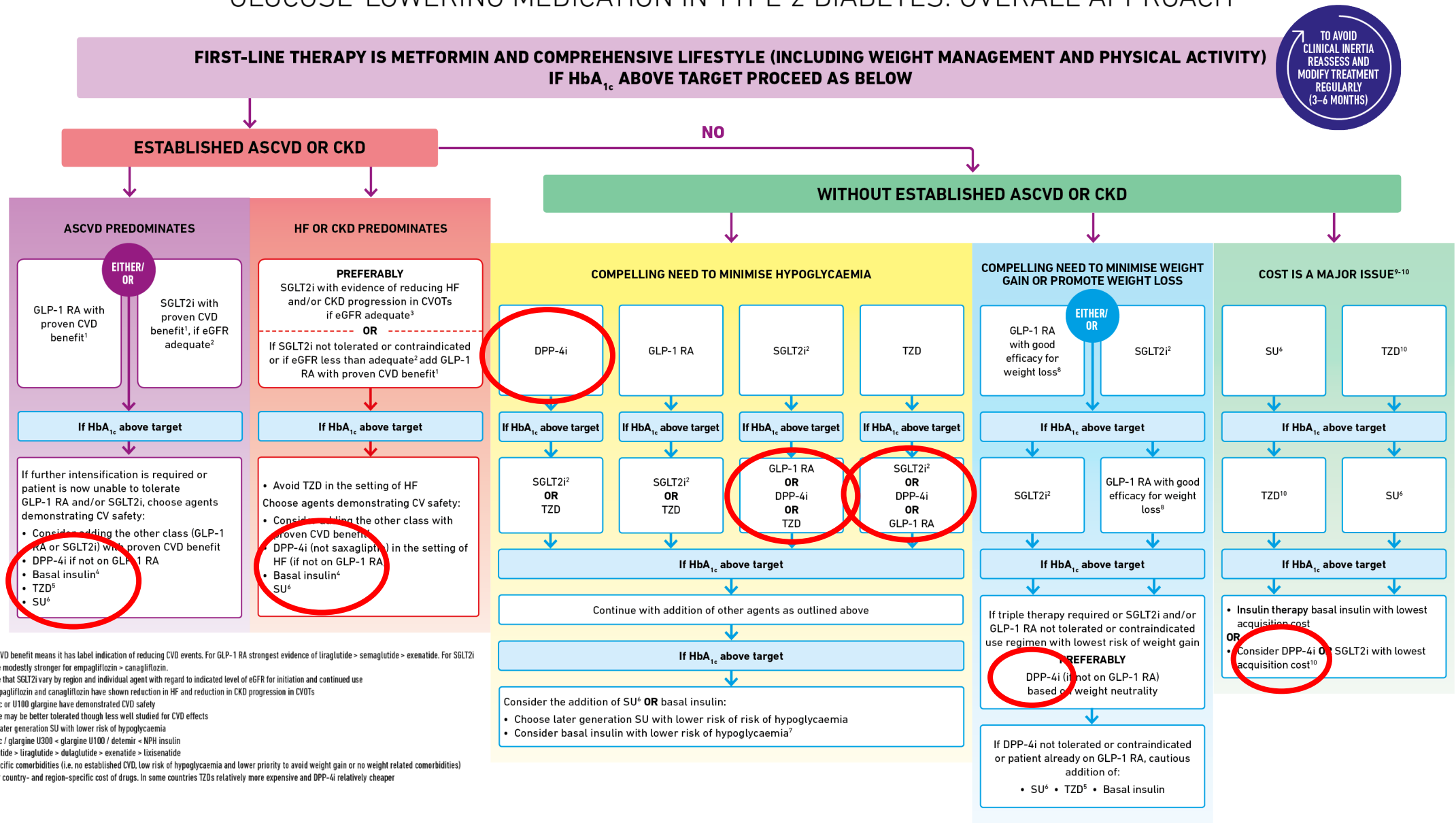

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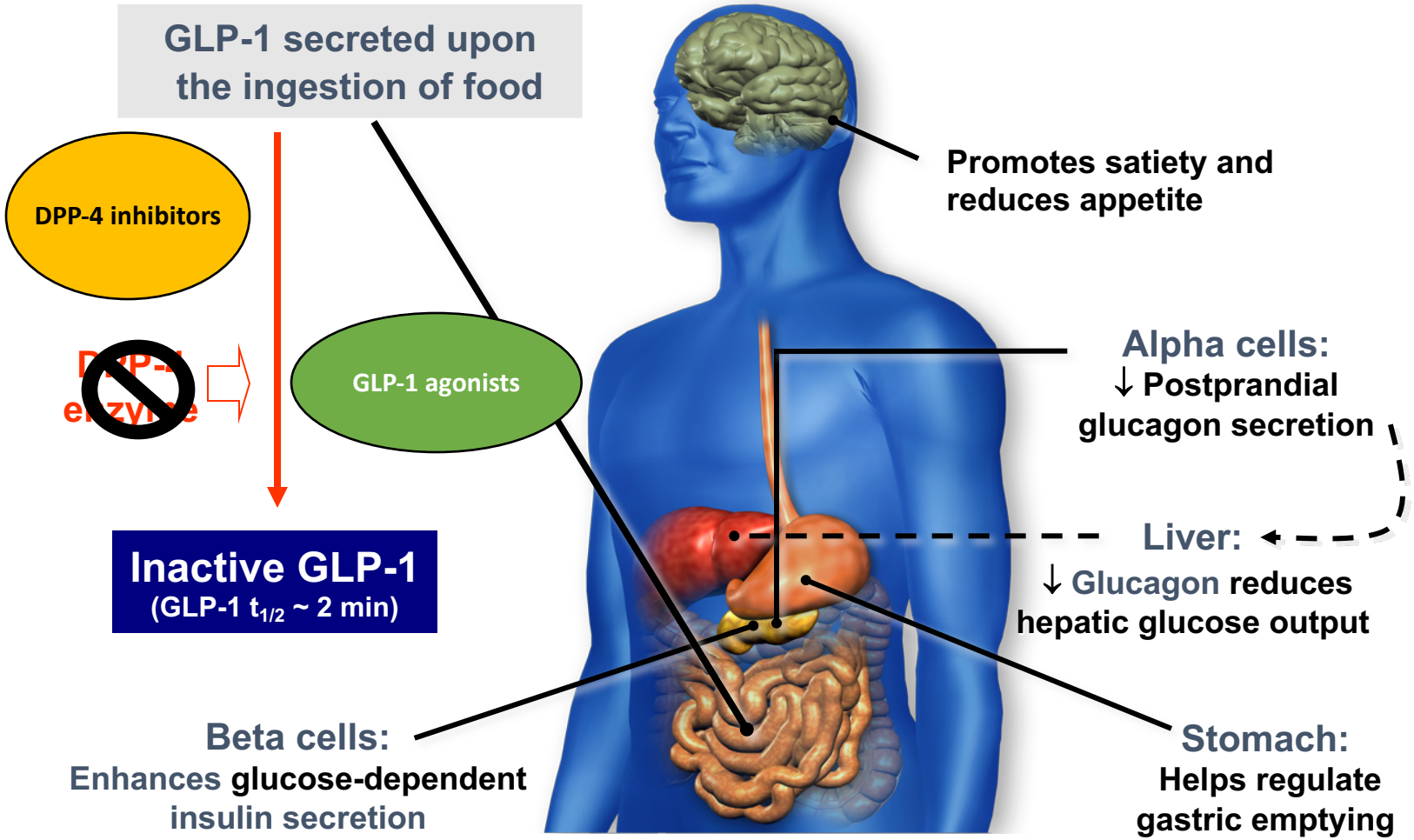

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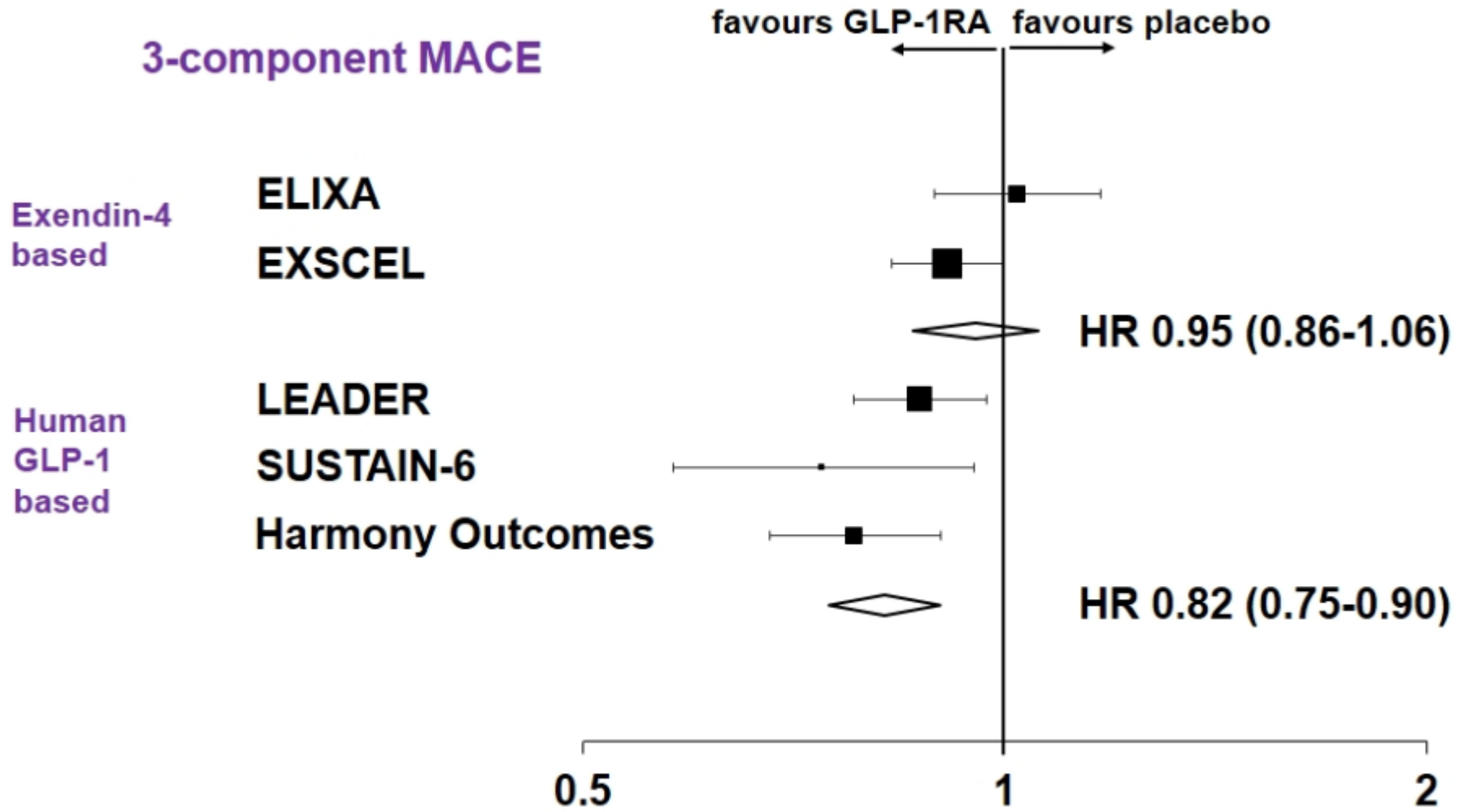
GLP-1 agonist CVOT Studies



Presented at EASD 2018.

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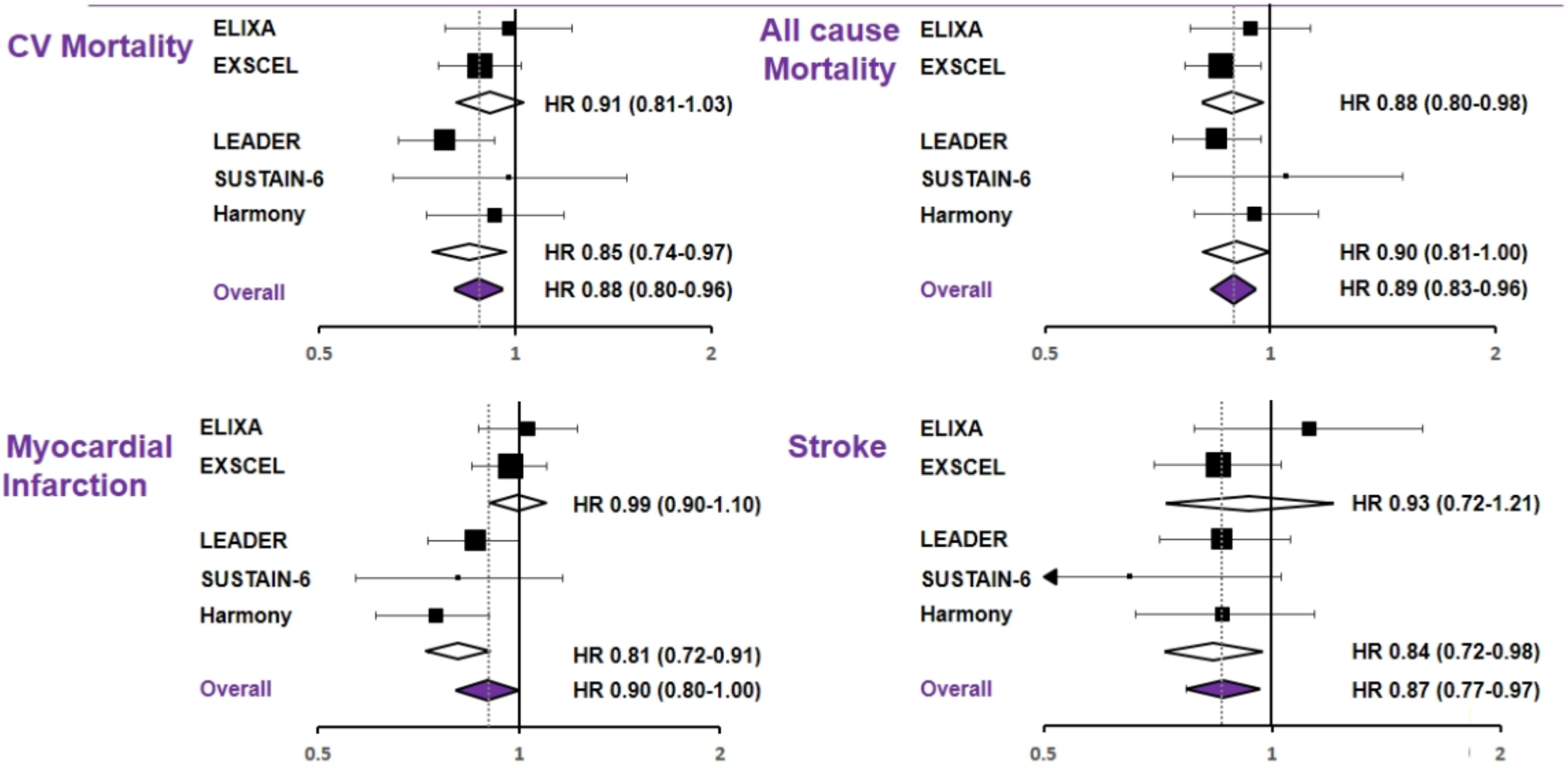
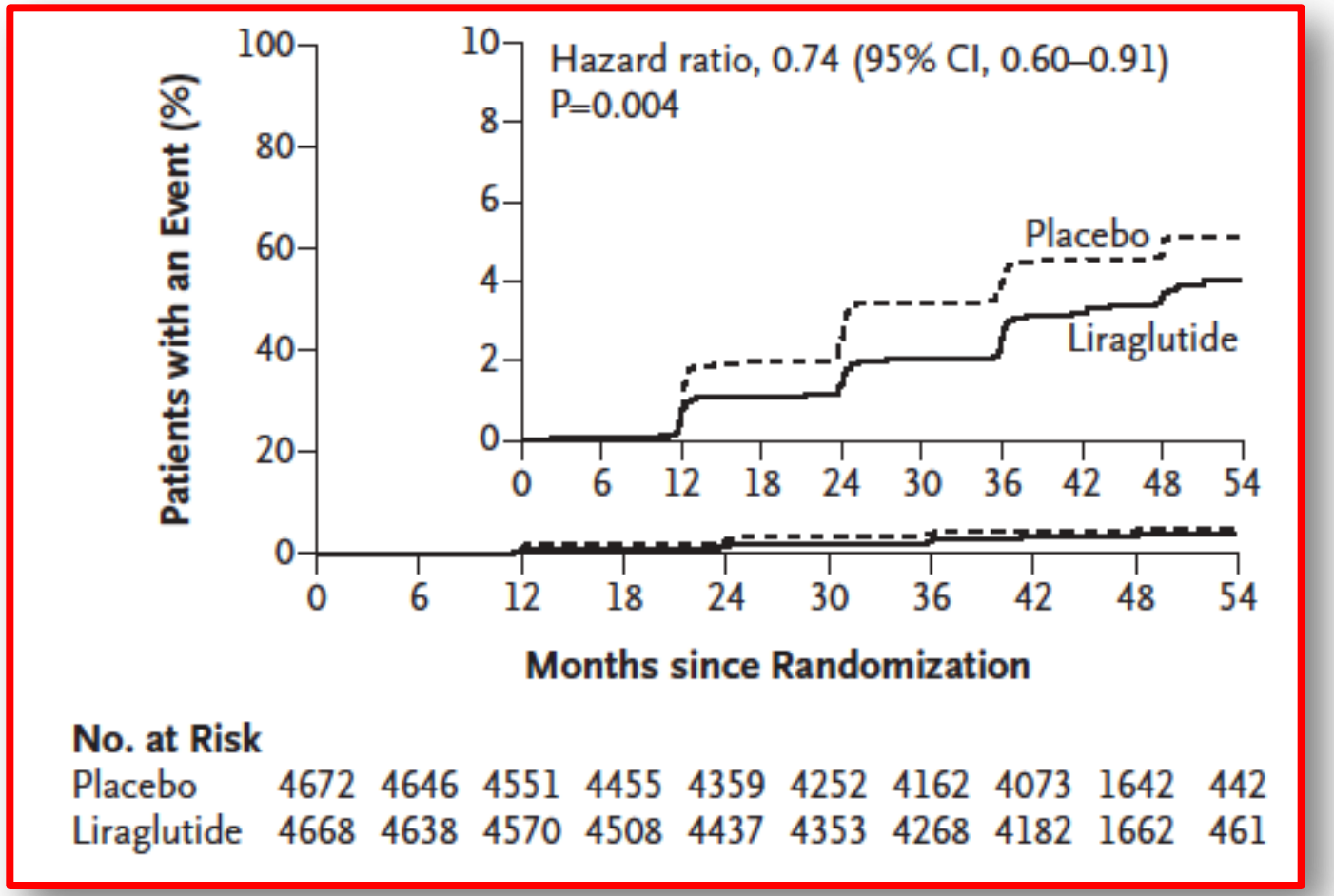


Presented at EASD 2018.

Liraglutide & renal outcomes in T2 diabetes:

New onset of persistent macroalbuminuria



Mann JFE, et al. N Engl J Med 2017;377:839-48.

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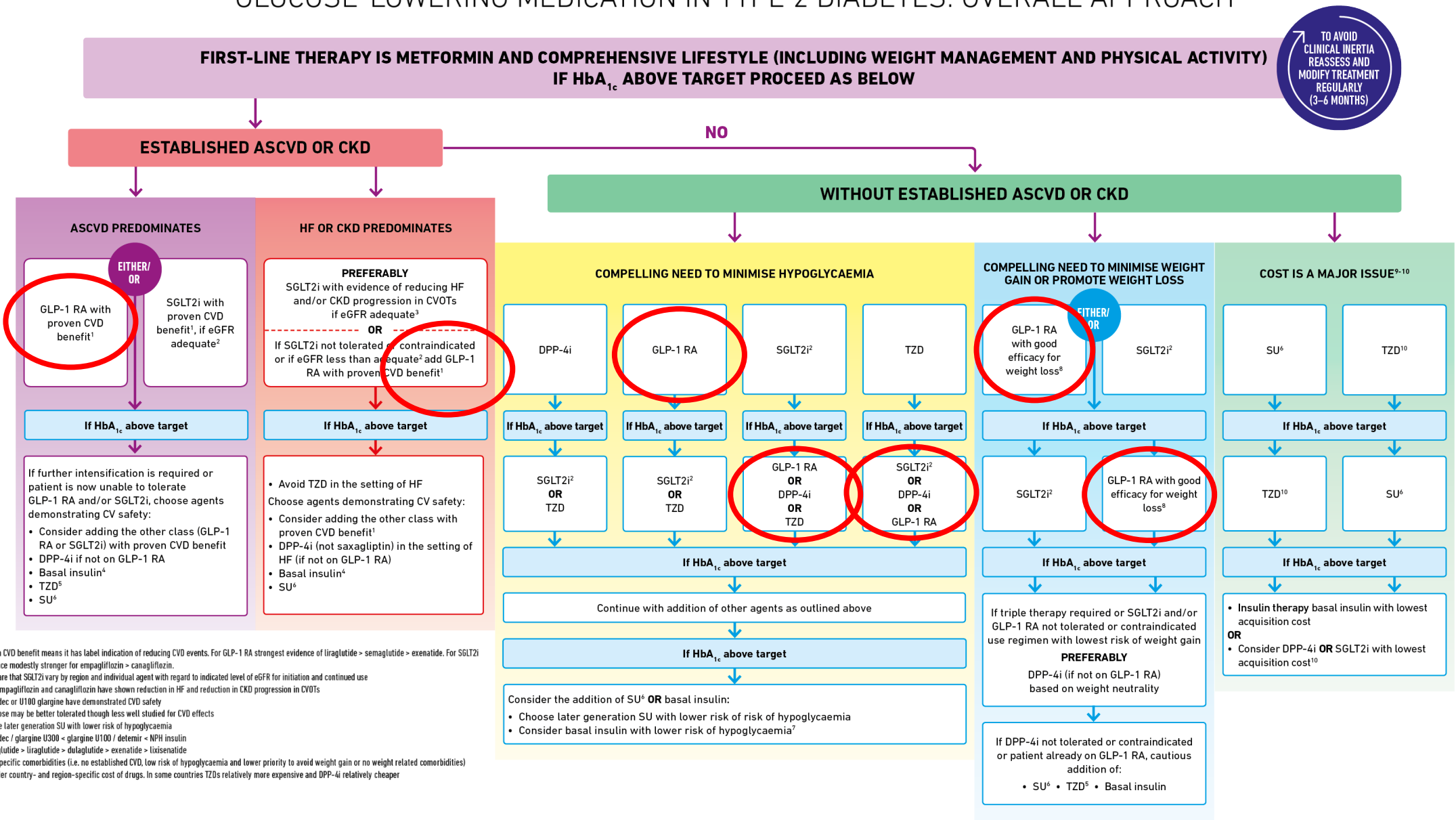

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SGLT-2 inhibitors

SGLT2 inhibitors (like empagliflozin) are associated with all of the following, except:

Weight loss

Renal (kidney) protection in patients with diabetic nephropathy

An increased risk for heart failure

An increased risk of yeast infections

SGLT2i on Heart Failure hospitalization & CV death

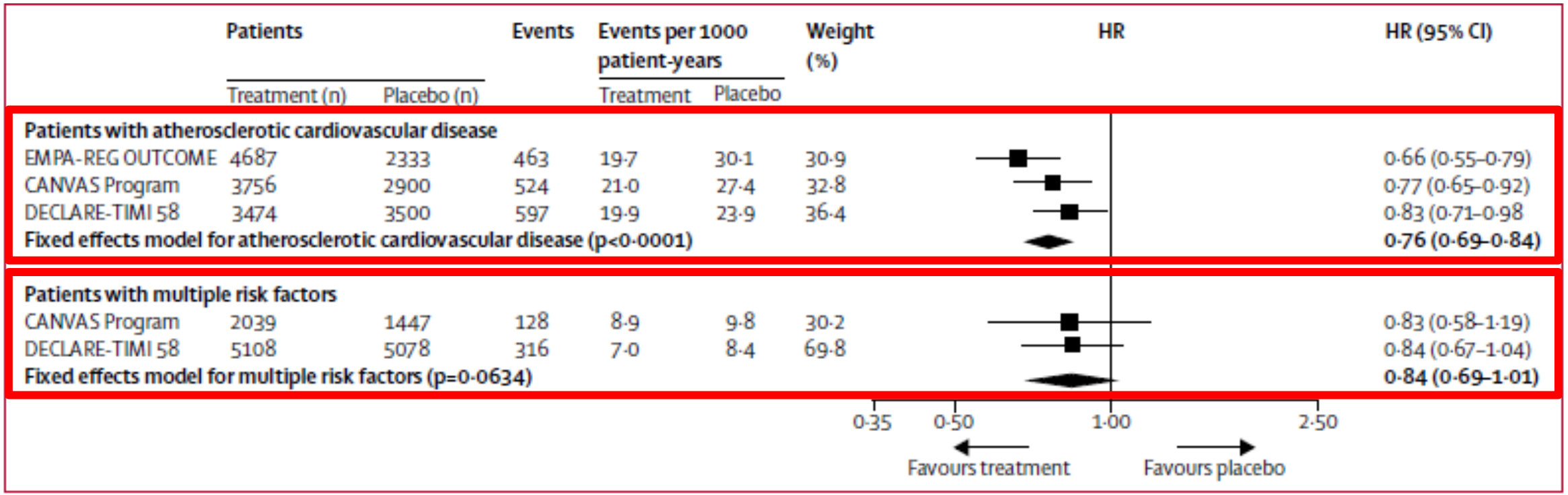

Figure 2: **Meta-analysis of SGLT2i trials on hospitalisation for heart failure and cardiovascular death stratified by the presence of established atherosclerotic cardiovascular disease**

Atherosclerotic cardiovascular disease: Q statistic=3·49, p=0·17, I^2=42·7%; multiple risk factors: Q statistic=0·00, p=0·96, I^2=0%. The p value for subgroup differences was 0·41. Tests for subgroup differences were based on F tests in a random effect meta-regression estimated using restricted maximum likelihood and Hartung Knapp adjustment. HR=hazard ratio. SGLT2i=sodium-glucose cotransporter-2 inhibitors.

Zelniker TA et al Lancet 2019;393:1016631-39

SGLT2i on Cardiovascular Events

	Patients		Events	Events per 1000 patient-years		Weight (%)	HR	HR (95% CI)
	Treatment (n)	Placebo (n)		Treatment	Placebo			
Patients with atherosclerotic cardiovascular disease								
EMPA-REG OUTCOME	4687	2333	772	37·4	43·9	29·4		0·86 (0·74–0·99)
CANVAS Program	3756	2900	796	34·1	41·3	32·4		0·82 (0·72–0·95)
DECLARE-TIMI 58	3474	3500	1020	36·8	41·0	38·2		0·90 (0·79–1·02)
Fixed effects model for atherosclerotic cardiovascular disease (p=0·0002)								**0·86 (0·80–0·93)**
Patients with multiple risk factors								
CANVAS Program	2039	1447	215	15·8	15·5	25·9		0·98 (0·74–1·30)
DECLARE-TIMI 58	5108	5078	539	13·4	13·3	74·1		1·01 (0·86–1·20)
Fixed effects model for multiple risk factors (p=0·98)								**1·00 (0·87–1·16)**

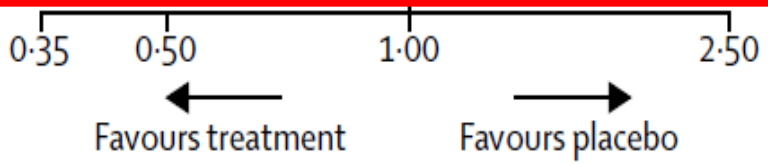

Figure 1: Meta-analysis of SGLT2i trials on the composite of myocardial infarction, stroke, and cardiovascular death (major adverse cardiovascular events) stratified by the presence of established atherosclerotic cardiovascular disease

Zelniker TA et al Lancet 2019;393:1016631-39

SGLT2i on Renal outcomes

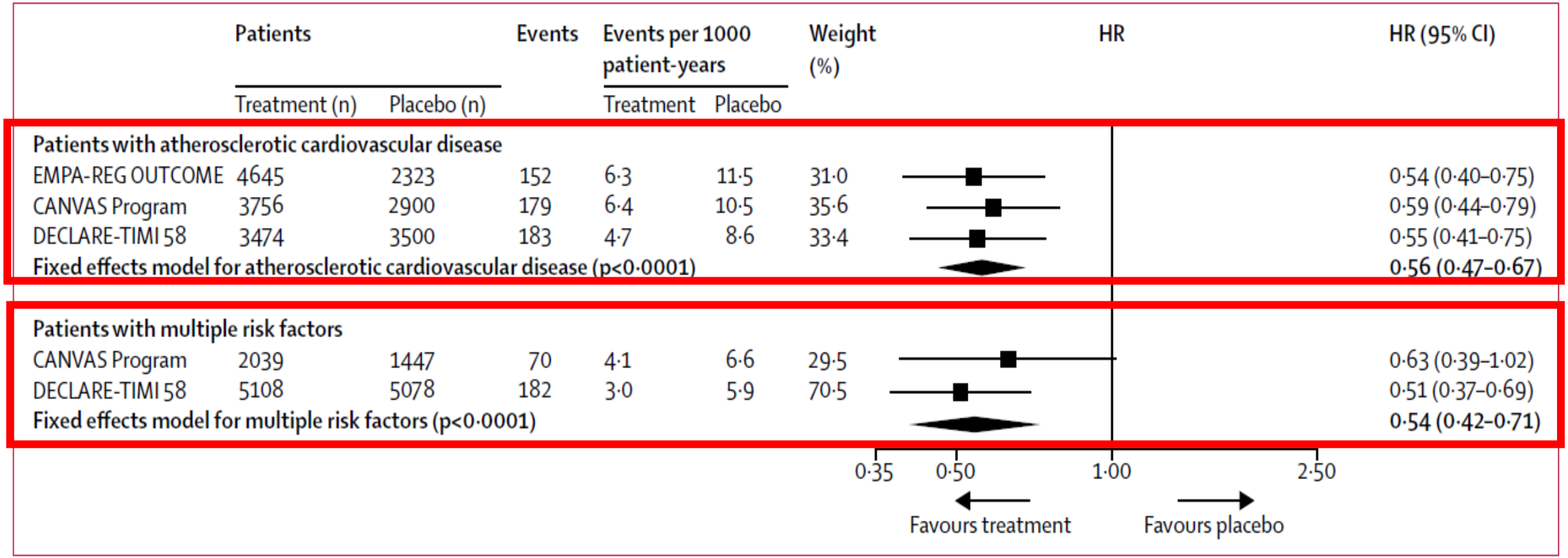

Figure 4: Meta-analysis of SGLT2i trials on the composite of renal worsening, end-stage renal disease, or renal death stratified by the presence of established atherosclerotic cardiovascular disease

Zelniker TA et al Lancet 2019;393:1016631-39

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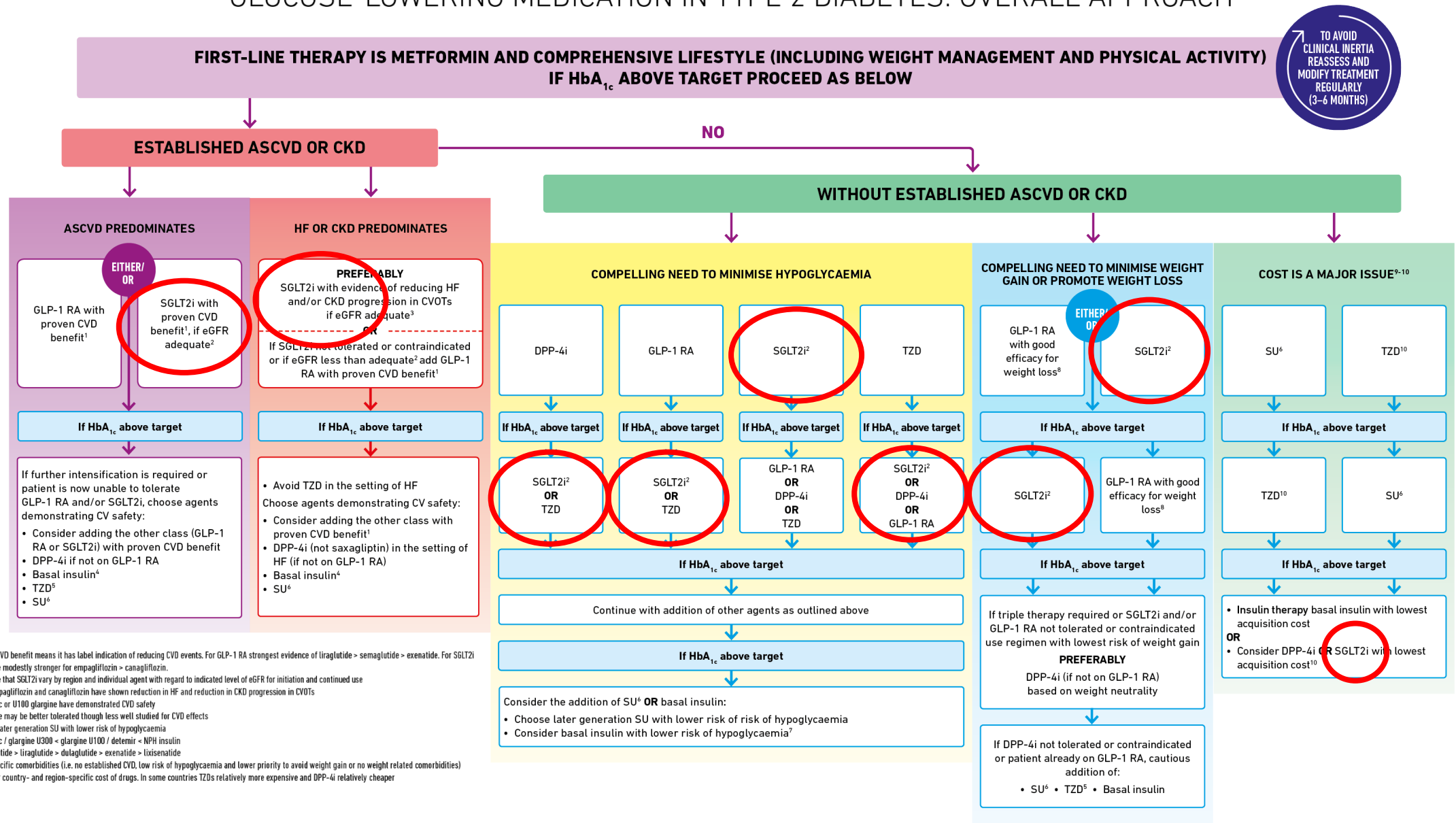

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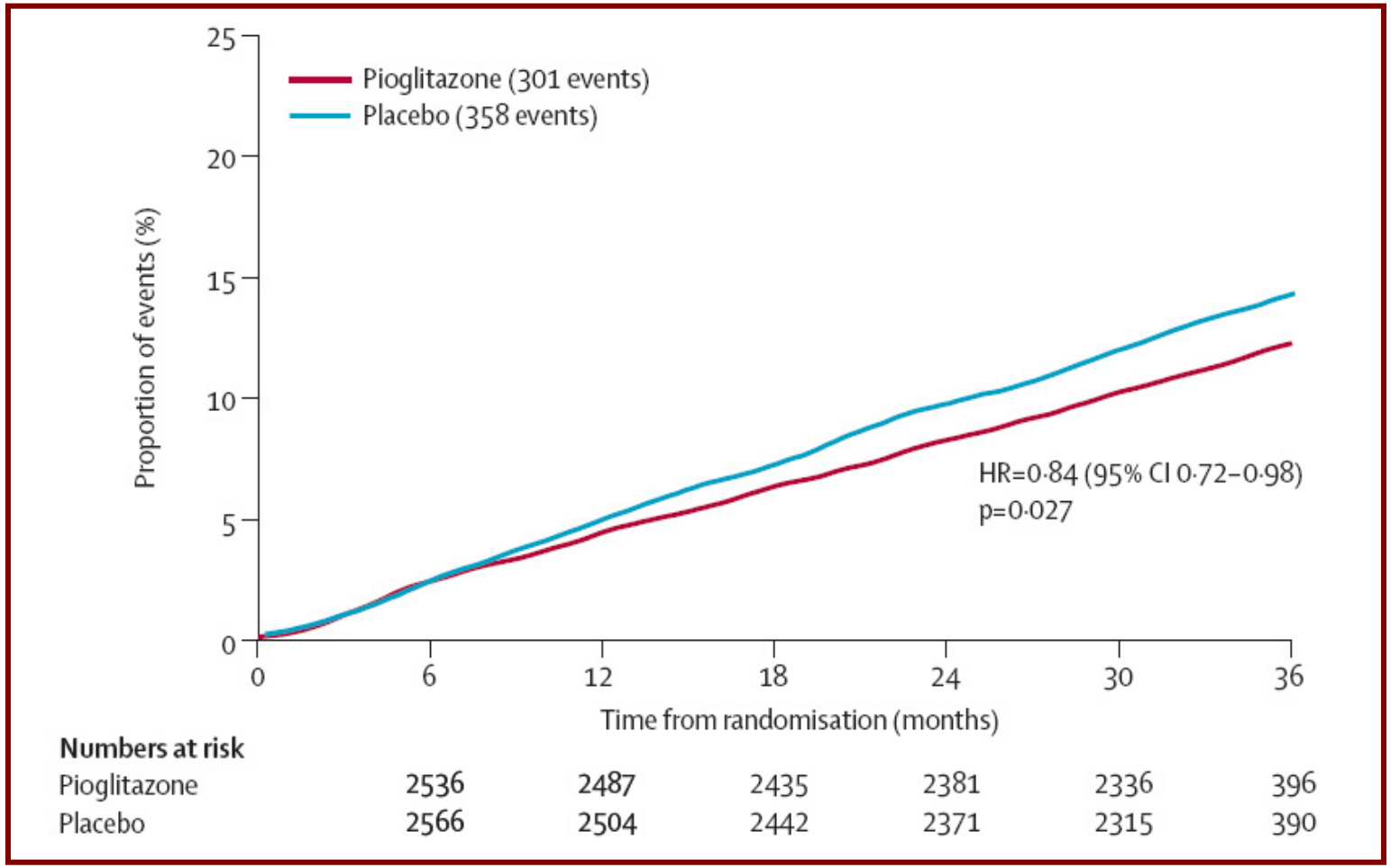
TZD (Pioglitazone)

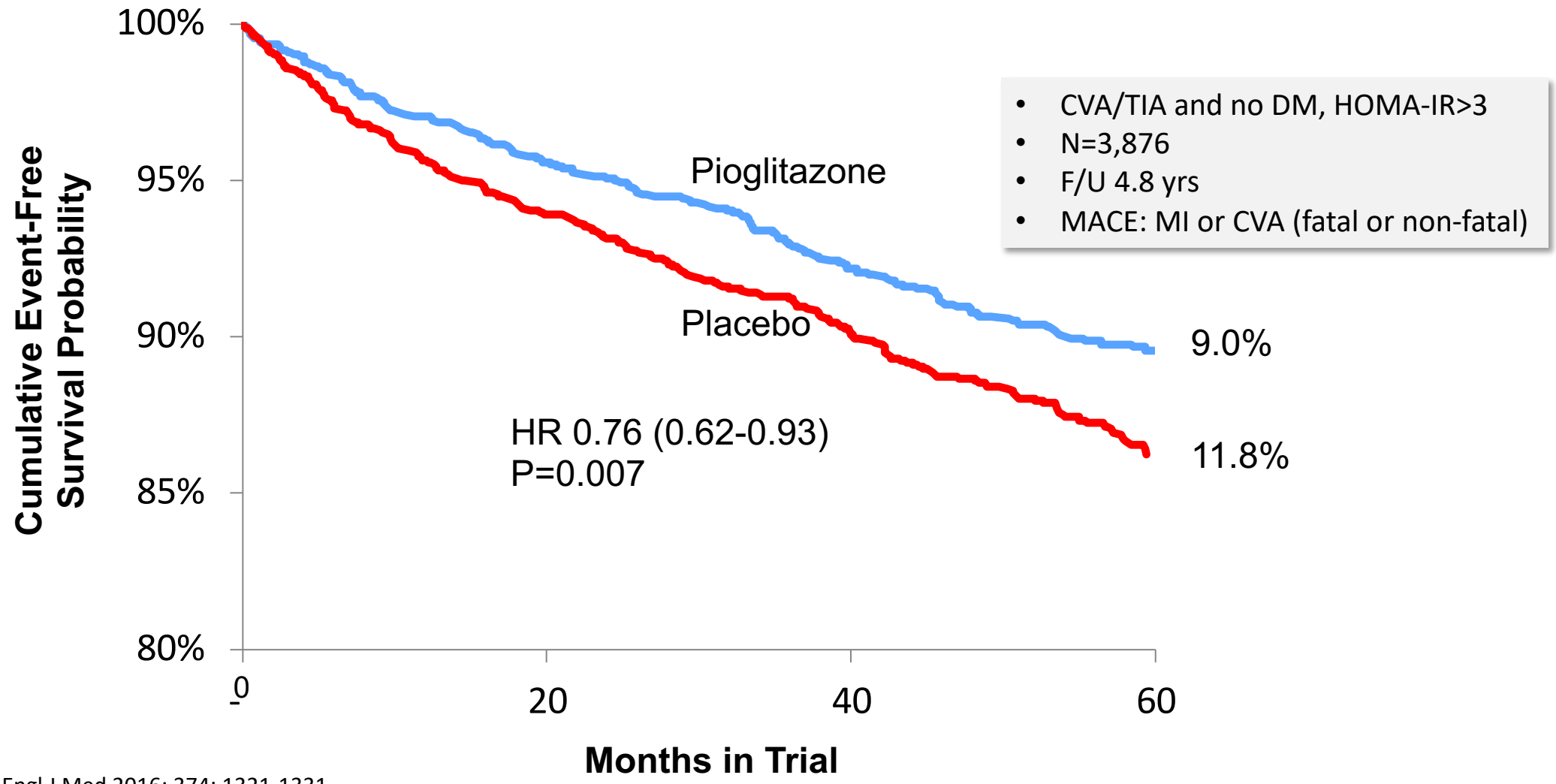
PROactive: Principal 2º Composite Endpoint (traditional MACE) would have been significant…



Death, MI, CVA

Dormandy JA, et al. Lancet 2005; 366: 1279

IRIS CVOT: Pioglitazone 45 mg reduced MACE in patients with insulin resistance S/P cerebrovascular event



Kernan WN, et al. N Engl J Med 2016; 374: 1321-1331

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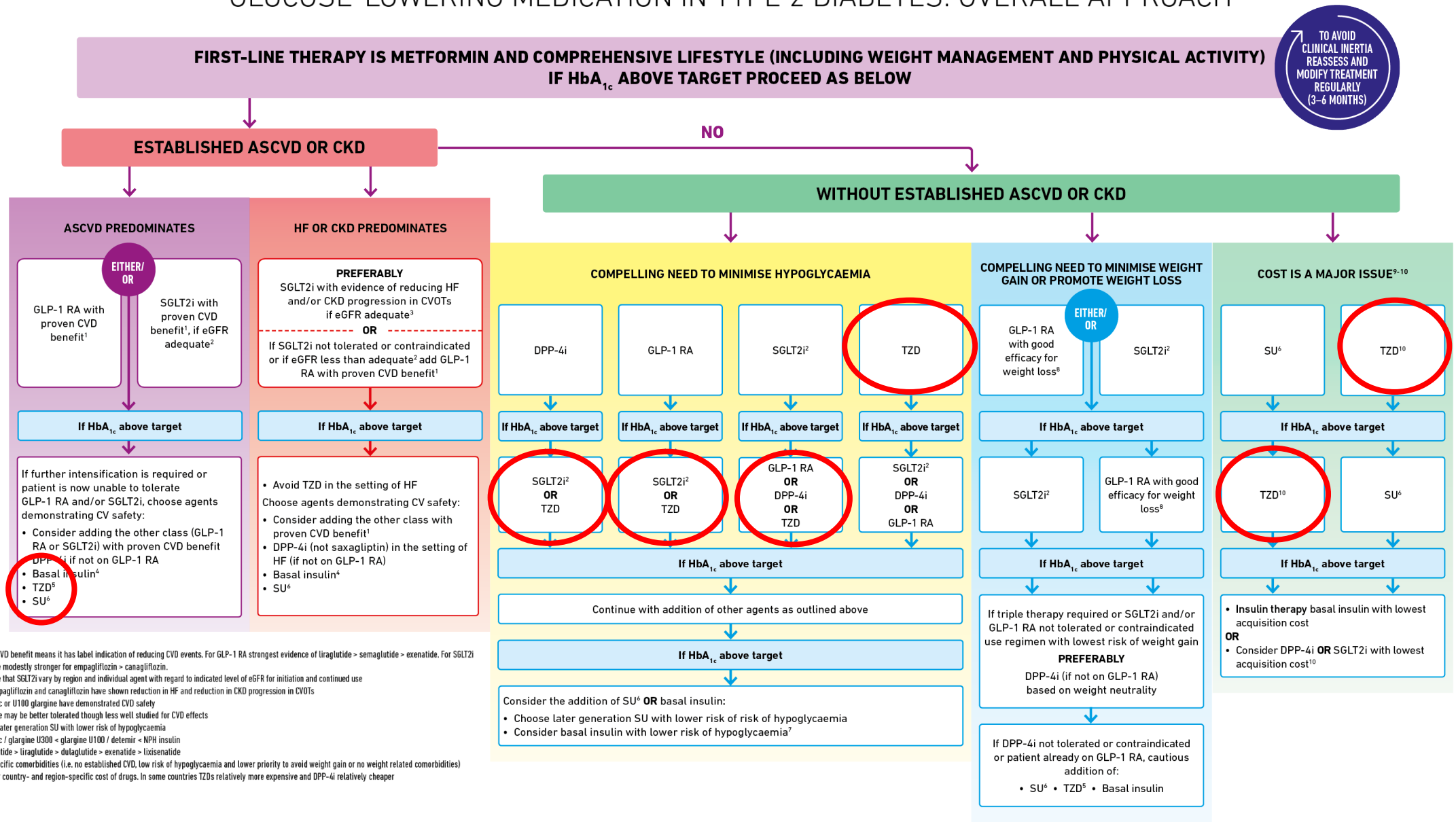

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Current Management of Type 2 Diabetes

- Control **all** risk factors
- **Metformin** is the first line treatment
- **GLP-1 agonists** (liraglutide or semaglutide) and **SGLT-2 inhibitors** (empagliflozin, dapagliflozin, or canagliflozin)
  - Reduce Major Adverse Cardiovascular Events (MACE)
  - Recommended **second line** after metformin for most patients
- **DPP IV inhibitors** are good alternatives to SU in patients with high risk of hypoglycemia
- **TZDs** may have beneficial cardiovascular effects

What else would you like to discuss during the upcoming Q&A session?

A huge thanks to Dr. Darren McGuire for sharing his slides and expertise with us.