Farmaci innovativi e terapie di associazione: quali opportunità?

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Congresso della Diabetologia Toscana

AMD ASSOCIAZIONE MEDICI DIABETOLOGI TOSCANA

Nodi ed intrecci di una rete:
evidenze scientifiche ed esperienze a confronto

Presidente: Dott.ssa Loredana Rizzo

Grosseto, 30 novembre/1 dicembre 2018

Hotel La Principina - Principina Terra (GR)

Dichiarazione esplicita di trasparenza delle fonti di finanziamento e dei rapporti con soggetti portatori di interessi commerciali

Il sottoscritto Dr. Giuseppe Penno

in qualità di

Moderatore **Relatore**

ai sensi dell'art. 3.3 sul Conflitto di Interessi, pag. 17 del Reg. Applicativo dell'Accordo Stato-Regione del 5 novembre 2009,
dichiara
che negli ultimi due anni ha avuto i seguenti rapporti anche di finanziamento con soggetti portatori di interessi commerciali in campo sanitario:

AstraZeneca, Boerhinger Ingelheim, Eli-Lilly, Janssen, Merck Sharp & Dohme, Novo Nordisk, Takeda

Grosseto, 30 novembre - 1 dicembre 2018

Progression of Contents

- DIABETES BURDEN TODAY

Prevalence Rates of CV Comorbidities in Persons With T2DM: Results of a Systematic Literature Review

57 articles with **4,549,481** persons having T2DM: 2007 - March 2017

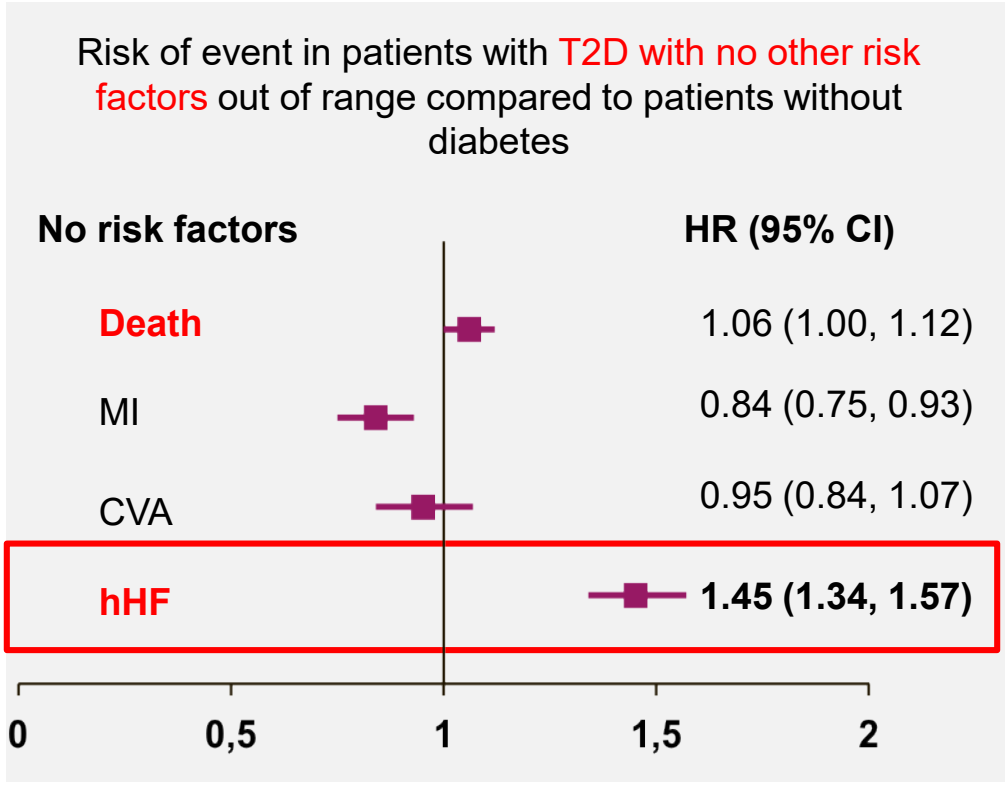
Sex	CV Outcome	Studies	N	Rate (%)	95% Confidence Interval (%)
Both	Stroke	39	3,901,505	7.6	6.6, 8.6
	MI	13	3,518,833	10.0	7.5, 12.5
	Angina pectoris	4	354,743	14.6	12.0, 17.3
	Heart failure	14	601,154	14.9	13.0. 16.7
	Atherosclerosis	4	1153	29.1	21.7, 36.4
	Coronary artery disease	42	3,833,200	21.2	20.3, 22.2
	CVD (any)	53	4,289,140	32.2	30.0, 34.4

Globally, more than 30% of persons with T2DM have some form of CV disorder. CVD is a major cause of mortality in patients with T2DM.

Einarson TR et al., Cardiovasc Diabetol 2018, 17: 83

Despite control of known CV risk factors, patients with T2D remain at elevated risk of developing HF

Swedish National Disease Register



- **In this analysis the risk of hHF in patients with T2D (n=271,174) was compared to those without T2D (n=1,355,870)**
- The following risk factors were either not present or within guideline range: HbA1c, systolic and diastolic BP, LDL-C, albuminuria and tobacco use
- **A substantial higher risk for hHF remained among patients who had all the variables within target range**

On average, the patients with T2D had a 45% increase in the risk of hHF, despite other major risk factors in guideline recommended range or absent

BP, blood pressure; CV, cardiovascular; CVA, cerebrovascular accident; HF, heart failure; hHF, hospitalisation for HF; HR, hazard ratio; LDL-C, low density–lipoprotein cholesterol; MI, myocardial infarction; T2D, type 2 diabetes.

Rawshani A et al., New Engl J Med 2018, 379: 633-644

Progression of Contents

Management of Hyperglycemia in Type 2 Diabetes, 2018. A Consensus Report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD)

CHOOSING GLUCOSE-LOWERING MEDICATION IN THOSE WITH ESTABLISHED ATHEROSCLEROTIC CARDIOVASCULAR DISEASE (ASCVD) OR CHRONIC KIDNEY DISEASE (CKD)

Use metformin unless contraindicated or not tolerated

If not at HbA_{1c} target:

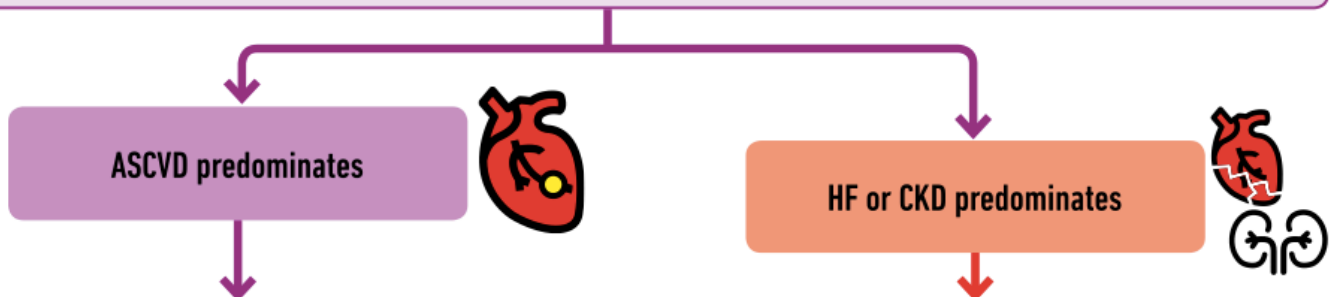
- Continue metformin unless contraindicated (remember to adjust dose/stop metformin with declining eGFR)
- Add SGLT2i or GLP-1 RA with proven cardiovascular benefit[1] (see below)

If at HbA_{1c} target:

- If already on dual therapy, or multiple glucose-lowering therapies and not on an SGLT2i or GLP-1 RA, consider switching to one of these agents with proven cardiovascular benefit[1] (see below)

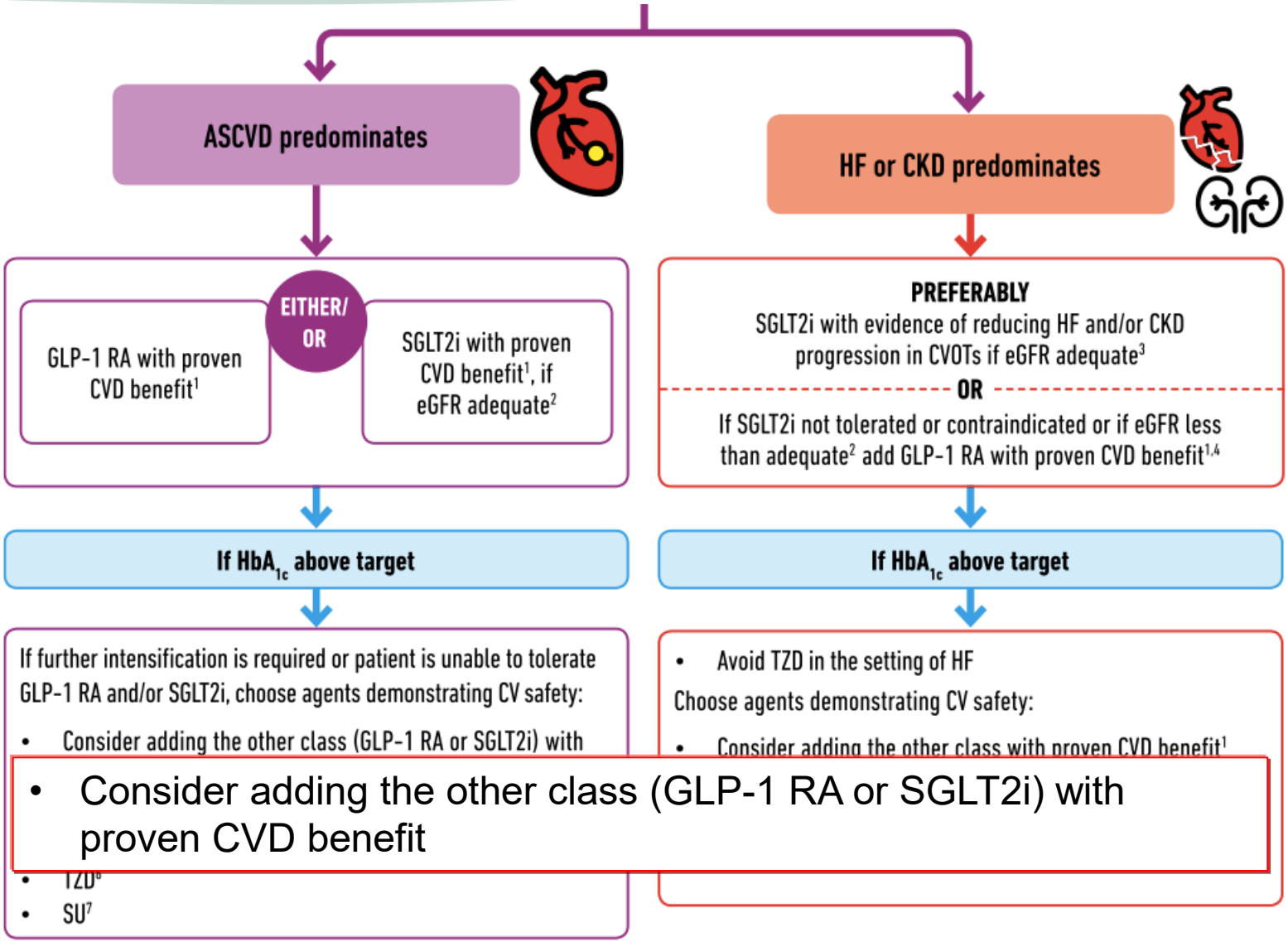
OR reconsider/lower individualized target and introduce SGLT2i or GLP-1 RA

OR reassess HbA_{1c} at 3-month intervals and add SGLT2i or GLP-1 RA if HbA_{1c} goes above target



Devies MJ et al., Diabetologia & Diabetes Care 2018, October 5

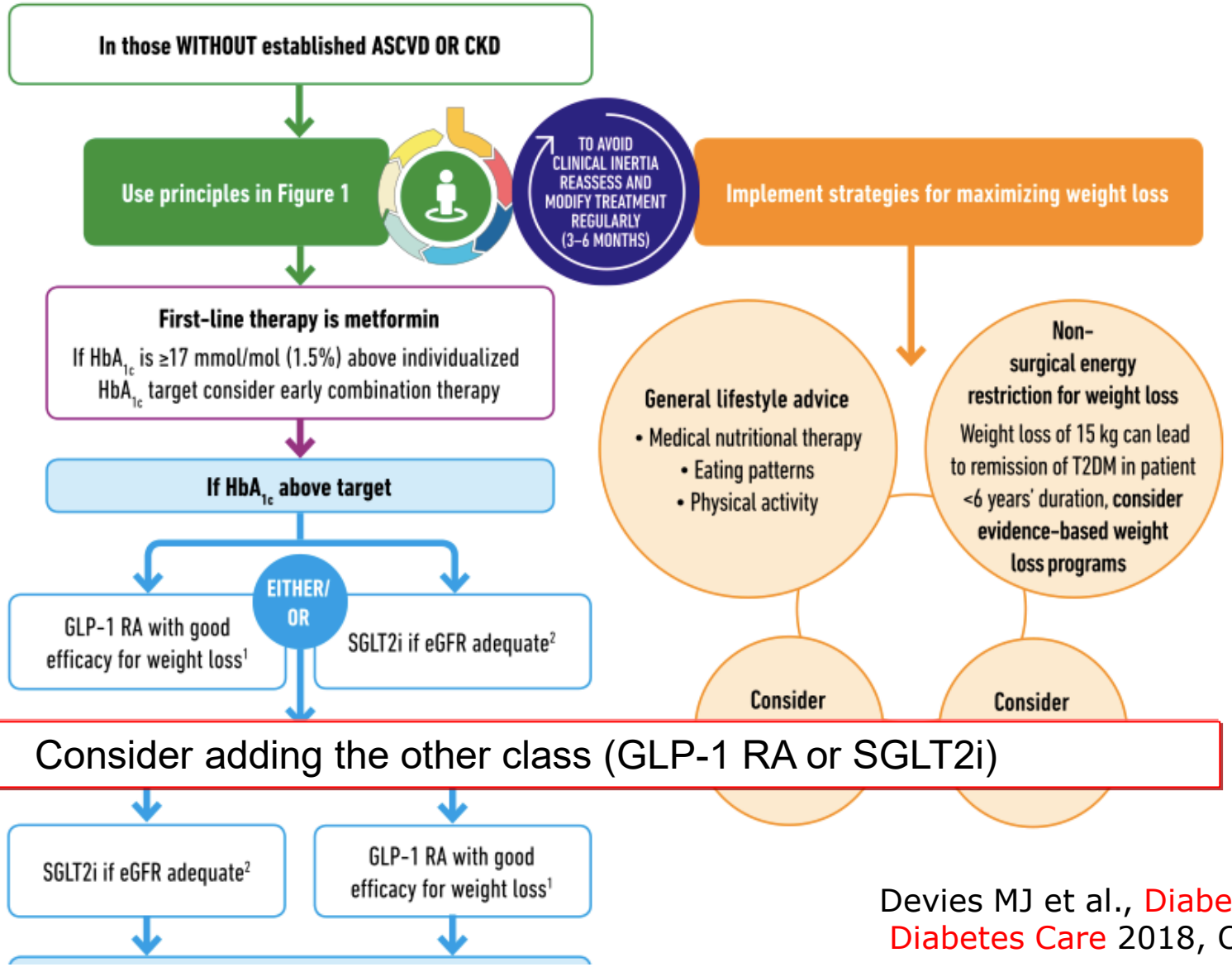
Management of Hyperglycemia in Type 2 Diabetes, 2018. A Consensus Report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD)



- Consider adding the other class (GLP-1 RA or SGLT2i) with proven CVD benefit

Devies MJ et al., Diabetologia & Diabetes Care 2018, October 5

CHOOSING GLUCOSE-LOWERING MEDICATION IF COMPELLING NEED TO MINIMIZE WEIGHT GAIN OR PROMOTE WEIGHT LOSS



- Consider adding the other class (GLP-1 RA or SGLT2i)

Devies MJ et al., Diabetologia & Diabetes Care 2018, October 5

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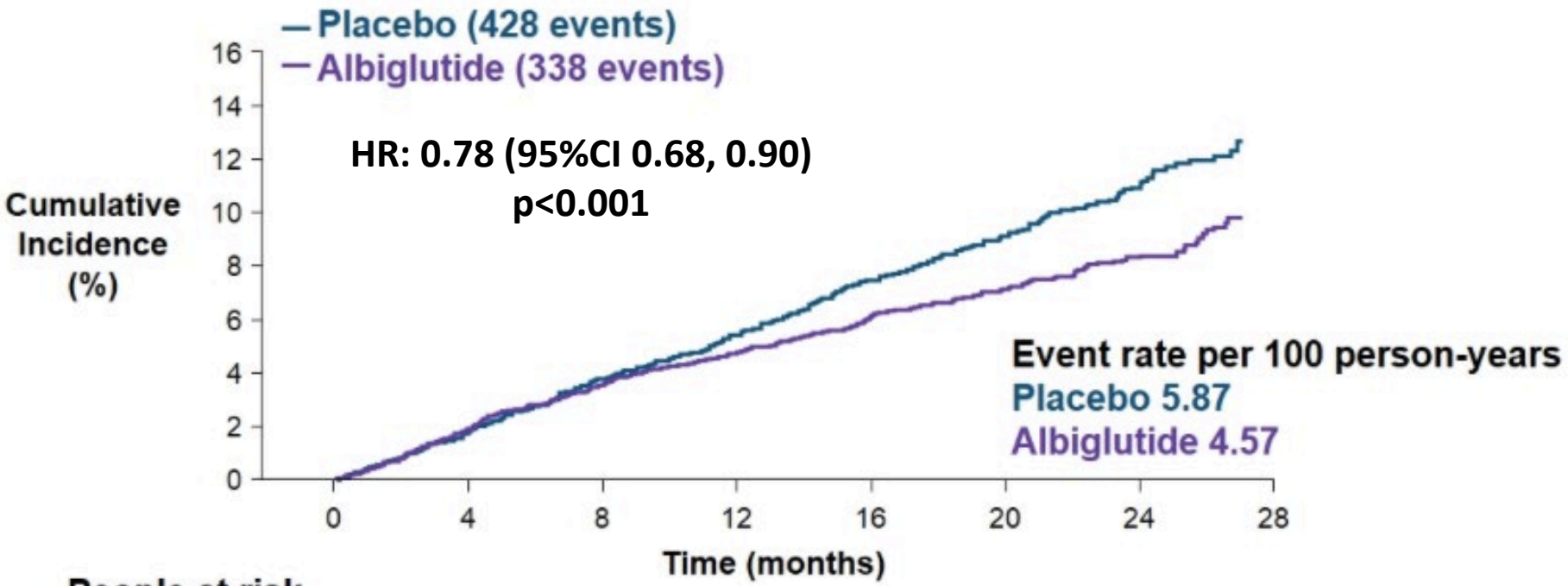
Albiglutide and cardiovascular outcomes in patients with type 2 diabetes and cardiovascular disease (Harmony Outcomes): a double-blind, randomised placebo-controlled trial

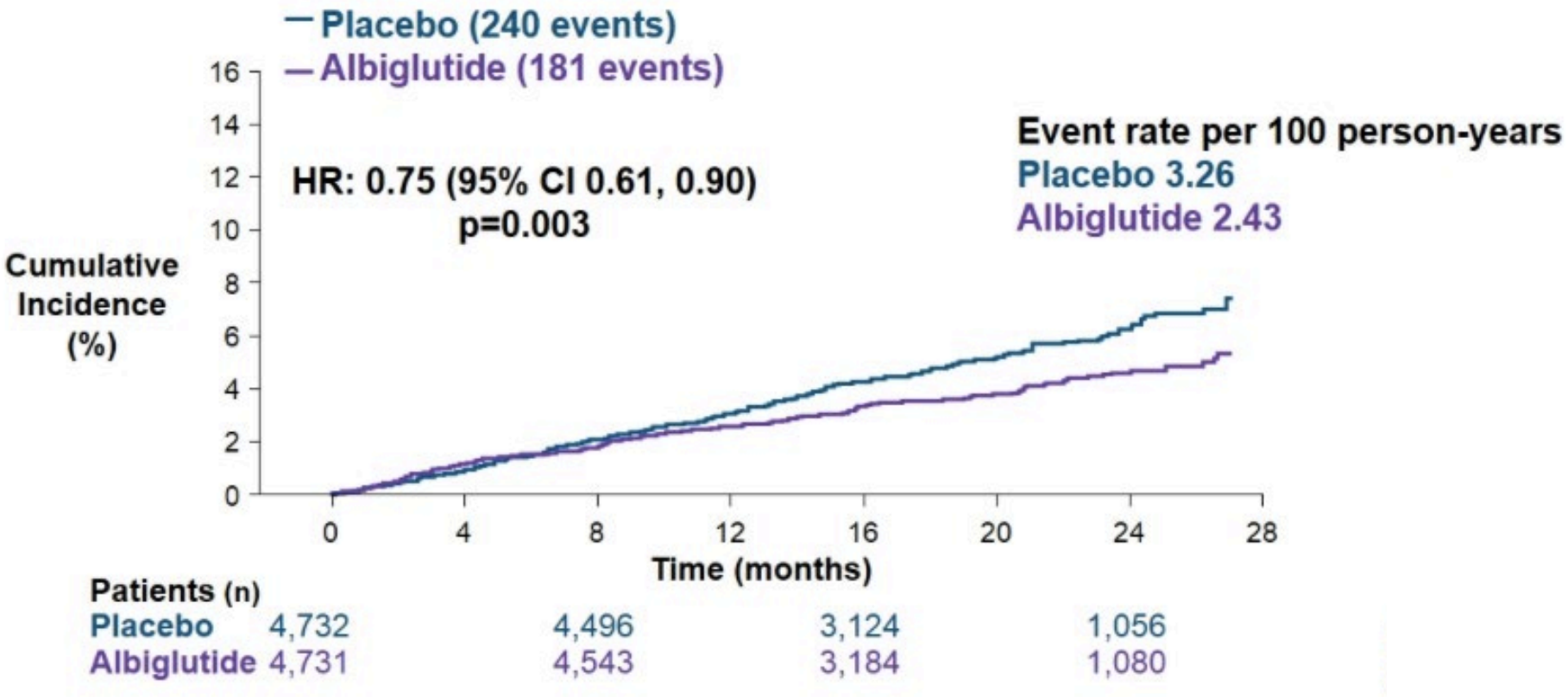
Primary Outcome: Time to CV Death, MI or Stroke (MACE)



Hernandez AF et al., Lancet 2018, October 2

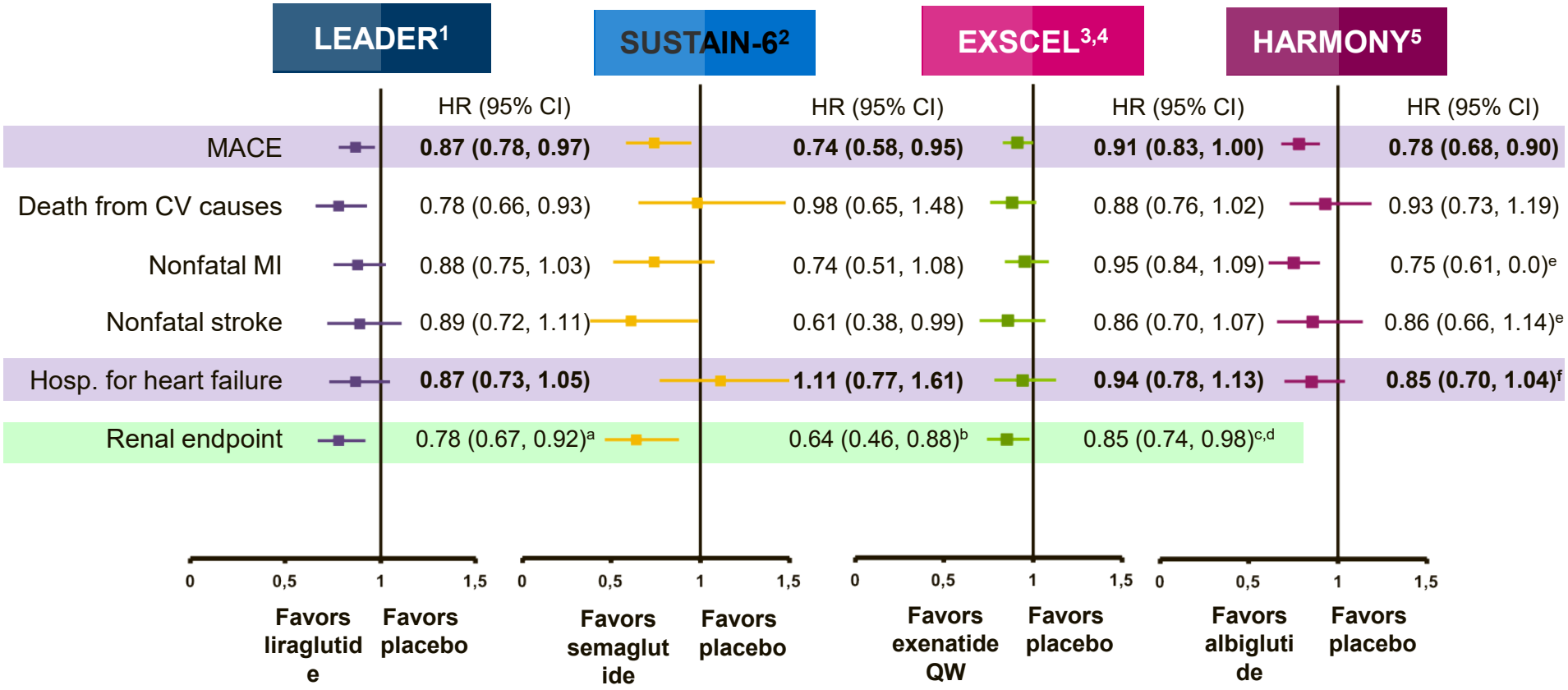
Albiglutide and cardiovascular outcomes in patients with type 2 diabetes and cardiovascular disease (Harmony Outcomes): a double-blind, randomised placebo-controlled trial

Primary Endpoint Components: MI, Fatal and Non-fatal



Hernandez AF et al., Lancet 2018, October 2

Earlier studies with diabetes treatments did not definitively show benefit for CV disease and HF, GLP-1 RAs are shown to have CV benefits driven by fewer atherosclerotic events

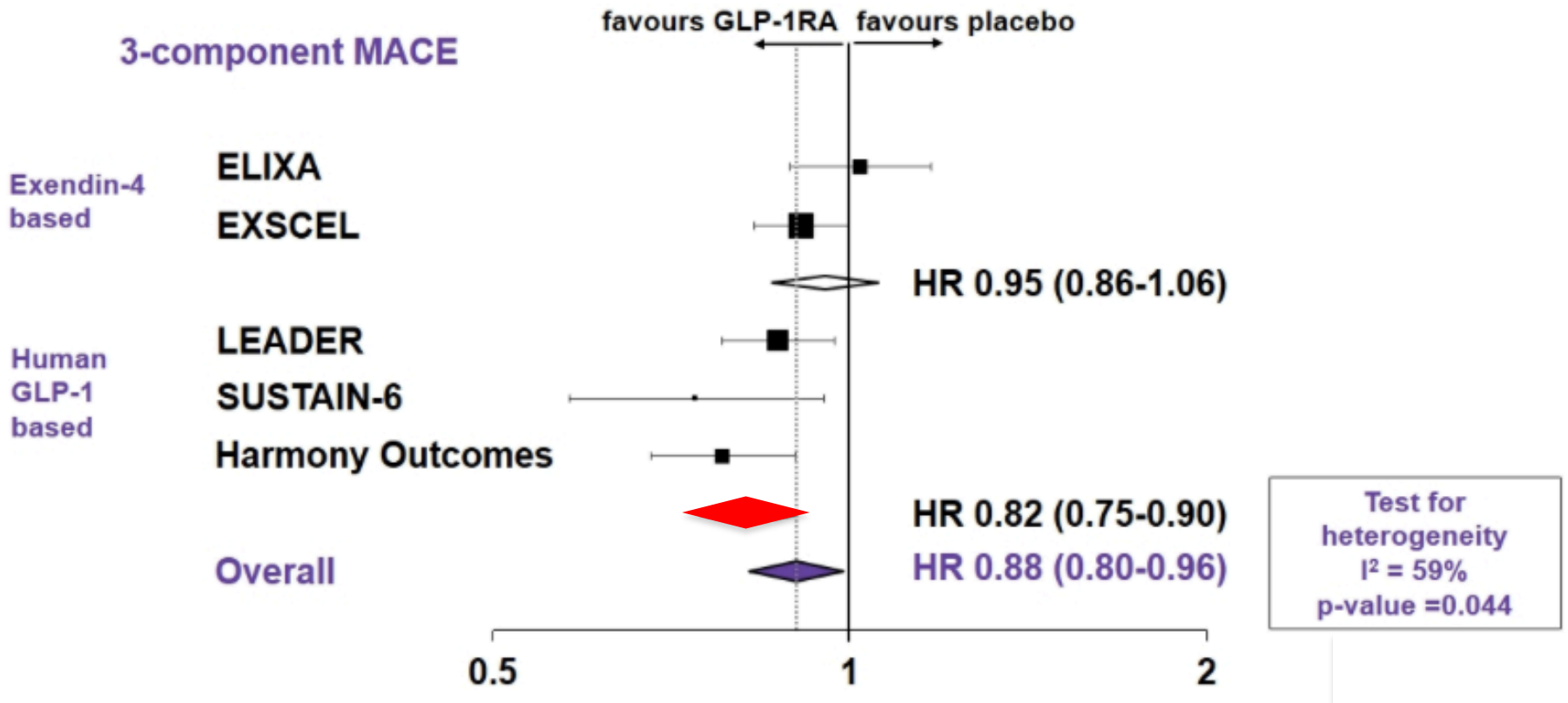


[a]New onset of macroalbuminuria or a doubling of the serum creatinine level and an eGFR of ≤45 ml/min/1.73 m^2, the need for continuous renal-replacement therapy, or death from renal disease; [b]New or worsening nephropathy includes persistent macroalbuminuria, persistent doubling of the serum creatinine level and a creatinine clearance of less than 45 ml/min/1.73 m^2 (according to the Modification of Diet in Renal Disease criteria), or the need for continuous renal-replacement therapy; [c]40% eGFR decline, renal replacement, renal death, or new-onset macroalbuminuria; [d]Adjusted for age, sex, ethnicity, race, region, duration of diabetes, prior history of CV event, insulin use, baseline glycated hemoglobin, eGFR, and body-mass index [e]Includes fatal and nonfatal events; [f]Composite of CV death or hospitalization for heart failure. CI, confidence interval; CV, cardiovascular; eGFR, estimated glomerular filtration rate; GLP-1 RA, GLP-1 receptor agonists; HR, hazard ratio; MACE, major adverse cardiovascular events; MI, myocardial infarction; QW, once weekly

1. Marso SP, et al. *N Engl J Med* 2016;375:311–322; 2. Marso SP, et al. *N Engl J Med* 2016;375:1834–1844; 3. Holman RR, et al. Article and supplementary appendix. *N Engl J Med* 2017;377:1228-1239;
4. Bethel MA, et al. Presented at: ADA 78th Scientific Sessions; June 22-26, 2018; Orlando, FL. Poster 522-P; 5. Hernandez AF, et al. Online ahead of print. *Lancet.* 2018.

Albiglutide and cardiovascular outcomes in patients with type 2 diabetes and cardiovascular disease (Harmony Outcomes): a double-blind, randomised placebo-controlled trial

Findings in Context with Other GLP-1R Agonist CV Outcome Trials



Hernandez AF et al., Lancet 2018, October 2

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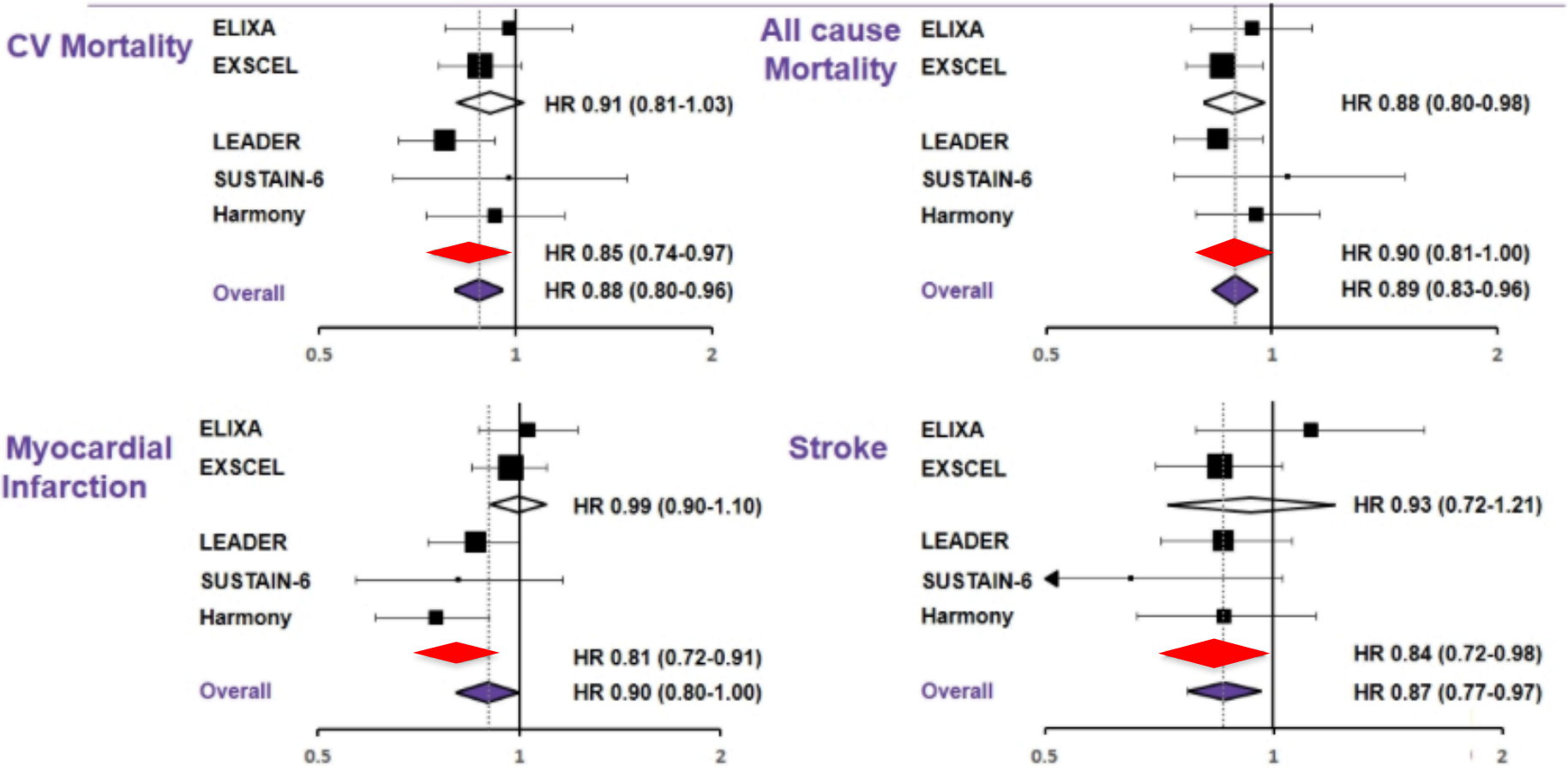
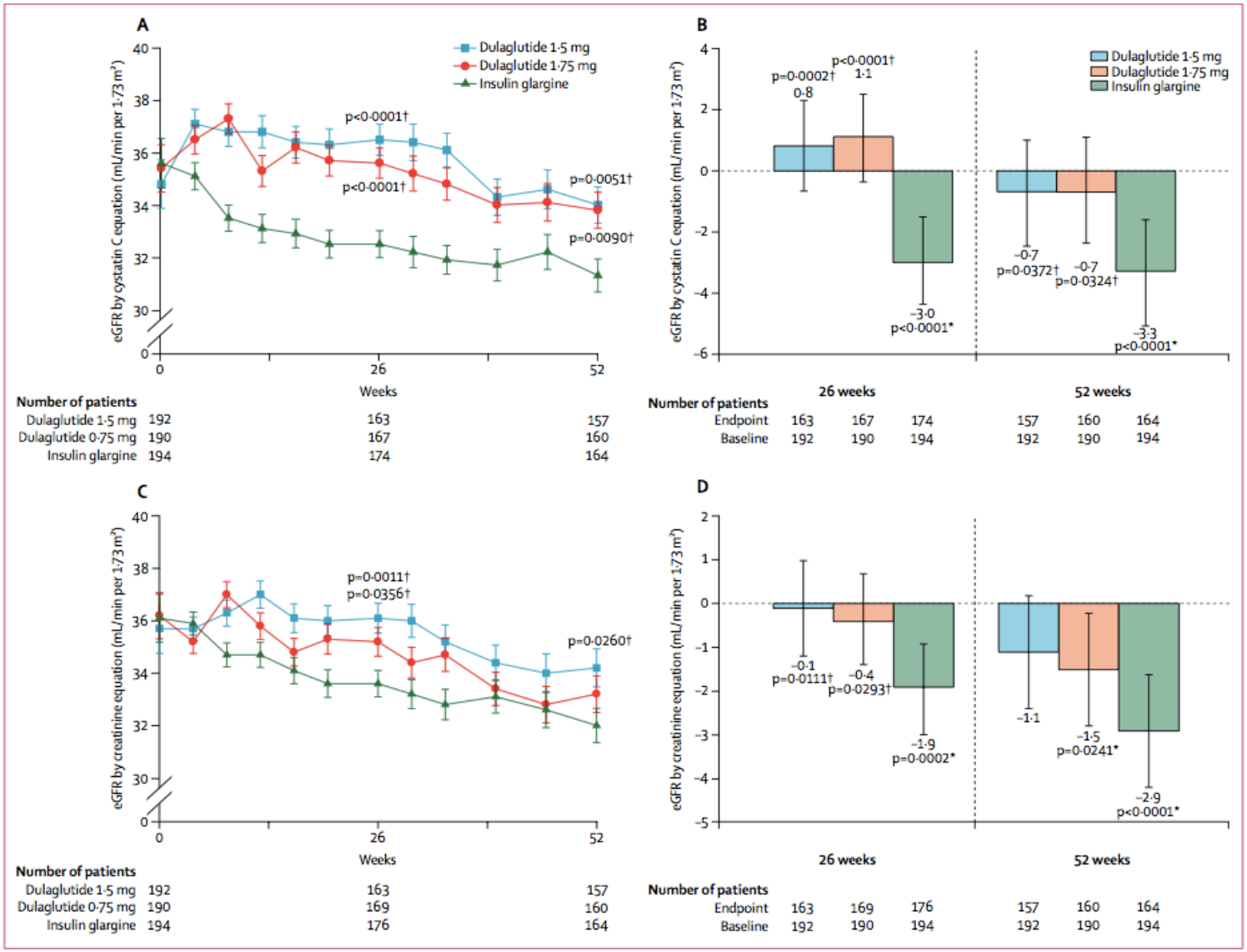
Findings in Context with Other GLP-1R Agonist CV Outcome Trials



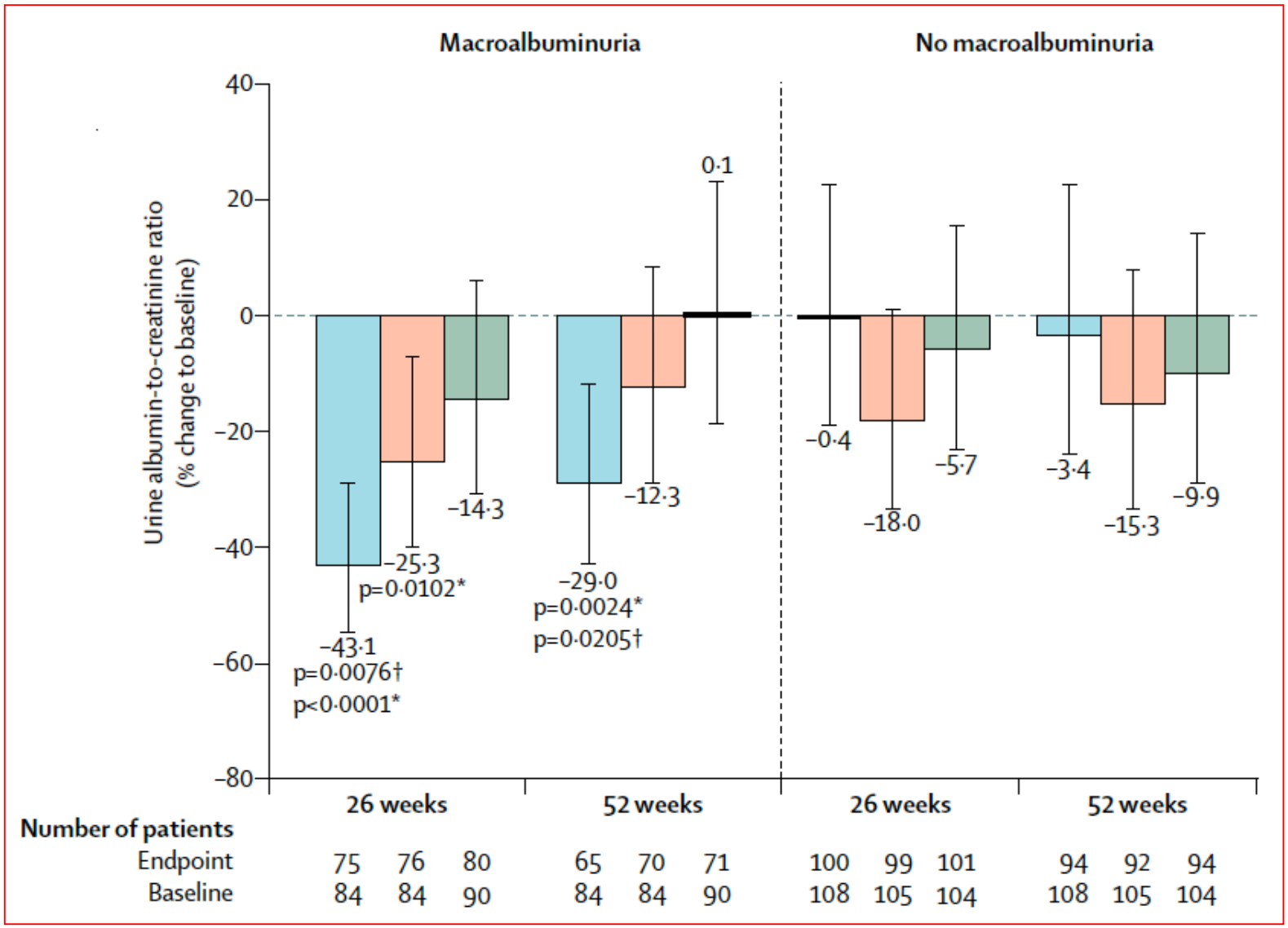
Hernandez AF et al., Lancet 2018, October 2

Dulaglutide versus insulin glargine in patients with type 2 diabetes and moderate-to-severe chronic kidney disease (AWARD-7): a multicentre, open-label, randomised trial



Tuttle KR et al, Lancet Diabetes Endocrinol 2018; 6: 605-617

Dulaglutide versus insulin glargine in patients with type 2 diabetes and moderate-to-severe chronic kidney disease (AWARD-7): a multicentre, open-label, randomised trial



Tuttle KR et al, Lancet Diabetes Endocrinol 2018; 6: 605-617

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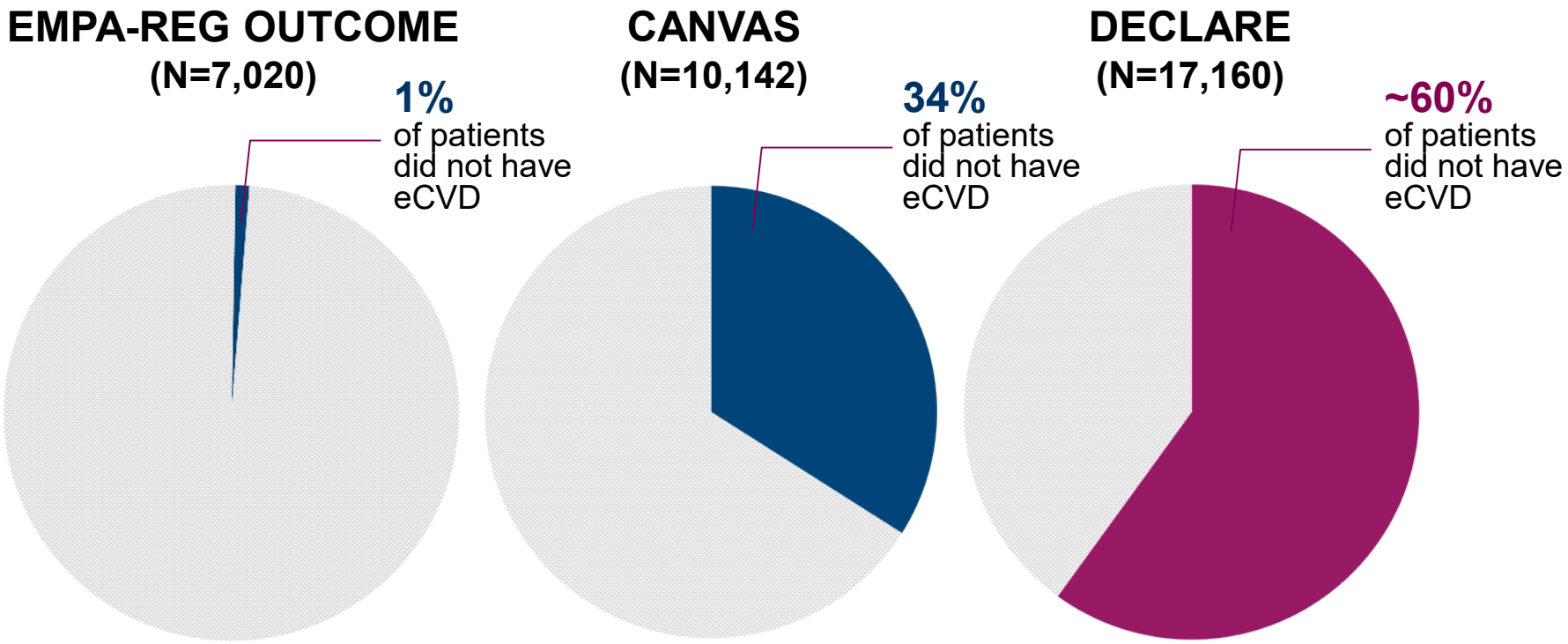
Representation of the T2D patients with CV risk among the of the SGLT2i CV outcomes studies

Rates of pts with and without established CVD varied across the three SGLT2i CVOTs

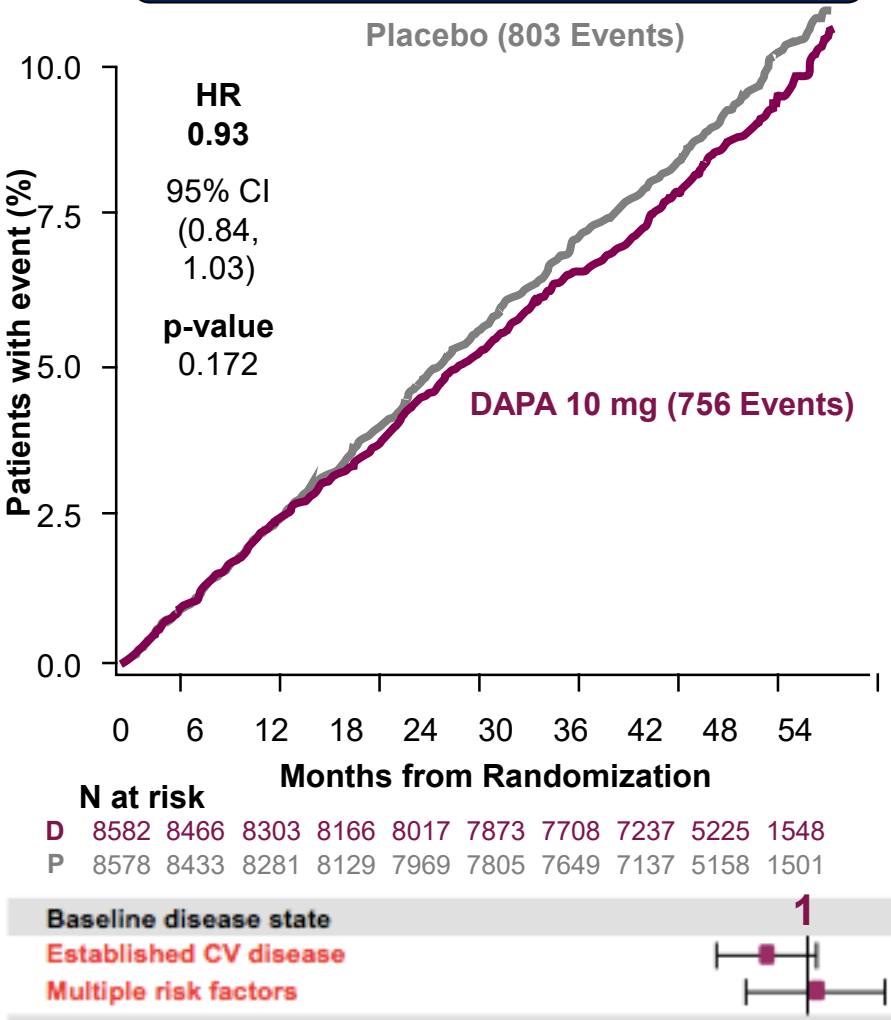


	EMPA-REG OUTCOME[1]	CANVAS Program[2]	DECLARE-TIMI 58[3]
Drug	Empagliflozin	Canagliflozin	Dapagliflozin
Patients with eGFR <60 mL/min per 1·73 m²	1819 (25·9%)	2039 (20·1%)	1265 (7·4%)

1. Zinman B, et al. *N Engl J Med* 2015;373:2117–2128;; 2. Neal B, et al. *N Engl J Med* 2017; DOI: 10.1056/NEJMoa1611925;3. Sattar Diabetologia (2013) 56:686–695 4. Raz I, et al. *Diabetes Obes Metab* 2018. http://dx.doi.org/10.1111/dom.13217

Dapagliflozin and Cardiovascular Outcomes in Type 2 Diabetes

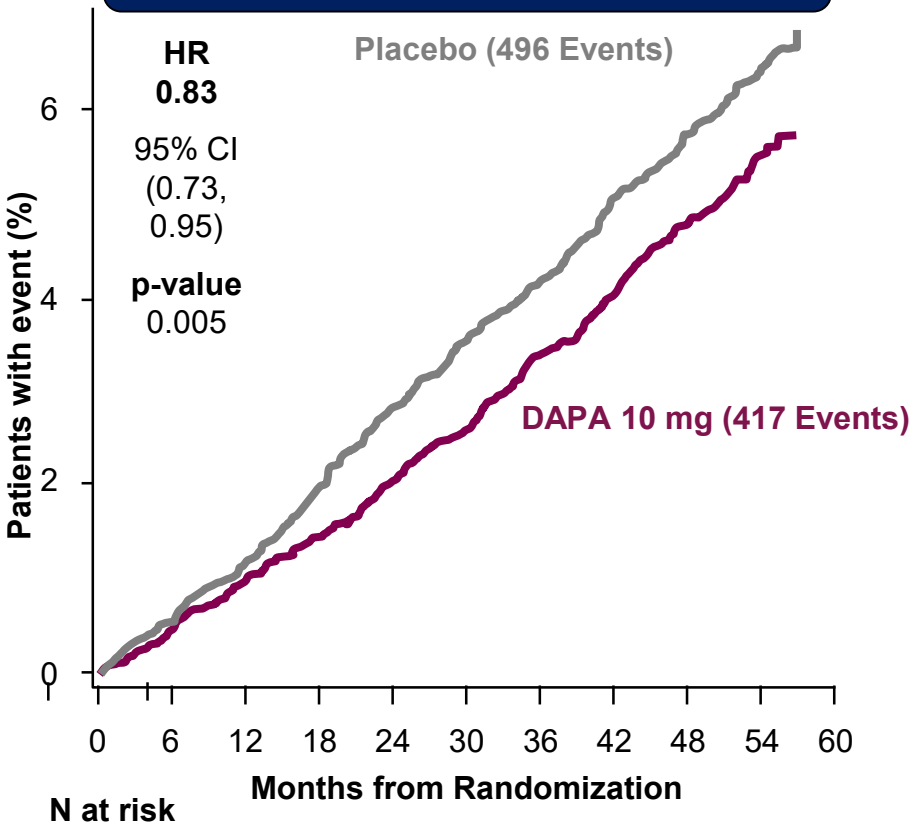
MACE



N at risk

D	8582	8466	8303	8166	8017	7873	7708	7237	5225	1548
P	8578	8433	8281	8129	7969	7805	7649	7137	5158	1501

hHF or CV Death



N at risk

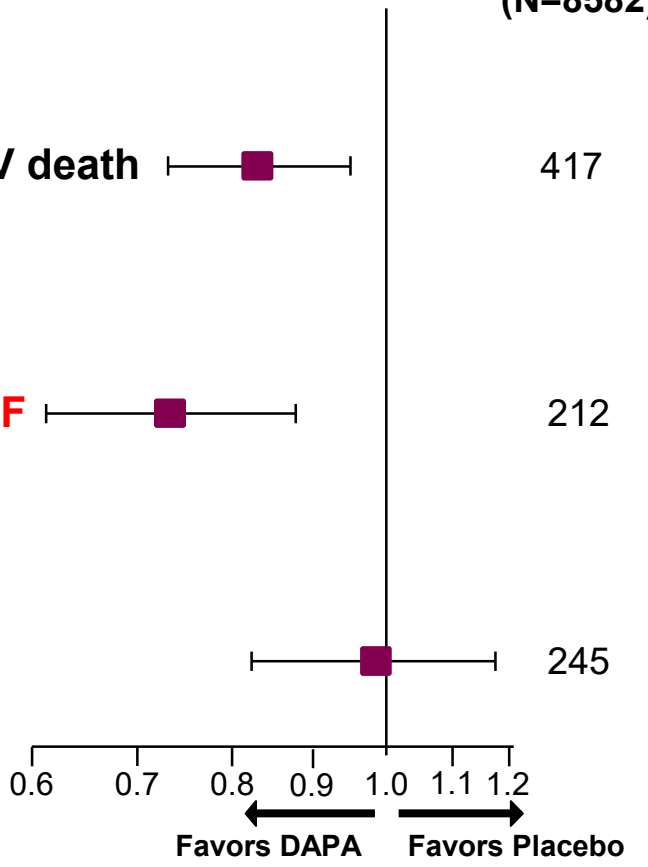
D	8582	8517	8415	8322	8224	8110	7970	7497	5445	1626
P	8578	8485	8387	8259	8127	8003	7880	7367	5362	1573

N at risk is the number of subjects at risk at the beginning of the period. 2-sided p-value is displayed; HR, CI, and p-value are from cox proportional hazard model. CV, cardiovascular; Dapa, dapagliflozin; hHF, hospitalization for heart failure; MACE, major adverse cardiac event

Wiviott SD et al. Online ahead of print. *N Engl J Med*. 2018;

Dapagliflozin and Cardiovascular Outcomes in Type 2 Diabetes

hHF or CV Death



	Number of events: DAPA 10 mg (N=8582)	Number of events: Placebo (N=8578)	HR (95%CI)	p-value
Composite of hHF/CV death	417	496	**0.83 (0.73, 0.95)**	**0.005**
Hospitalization for HF	212	286	**0.73 (0.61, 0.88)**	
CV death	245	249	0.98 (0.82, 1.17)	

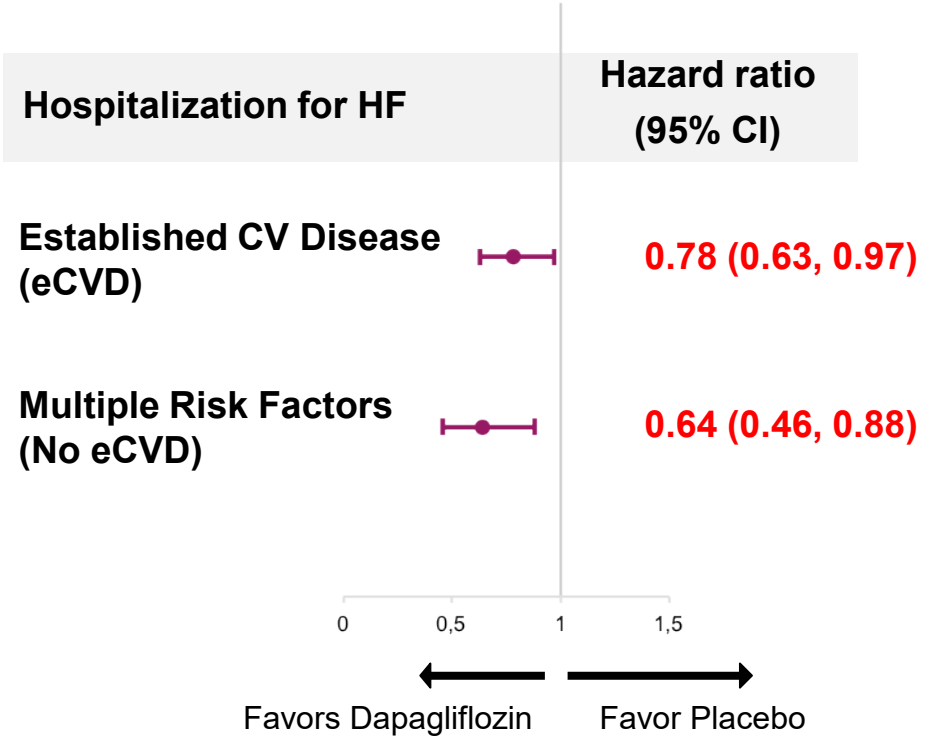
Two-sided p-value is shown for the primary efficacy composite outcome of CV death or hHF.

CV, cardiovascular; DAPA, dapagliflozin; HF, heart failure; hHF, hospitalization for heart failure.

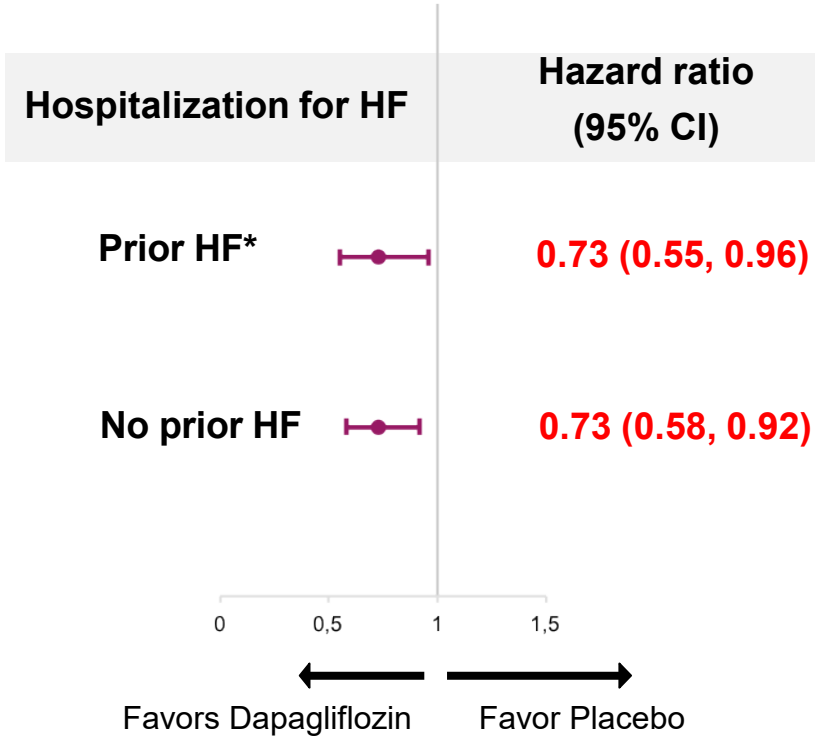
Wiviott SD et al. Online ahead of print. *New Engl J Med.* 2018.

Dapagliflozin prevents hHF consistently across a broad range of T2D patients regardless of history of eCVD or HF

hHF by presence/absence of eCVD



hHF by presence/absence of previous HF



***10% of patients in DECLARE had prior HF**

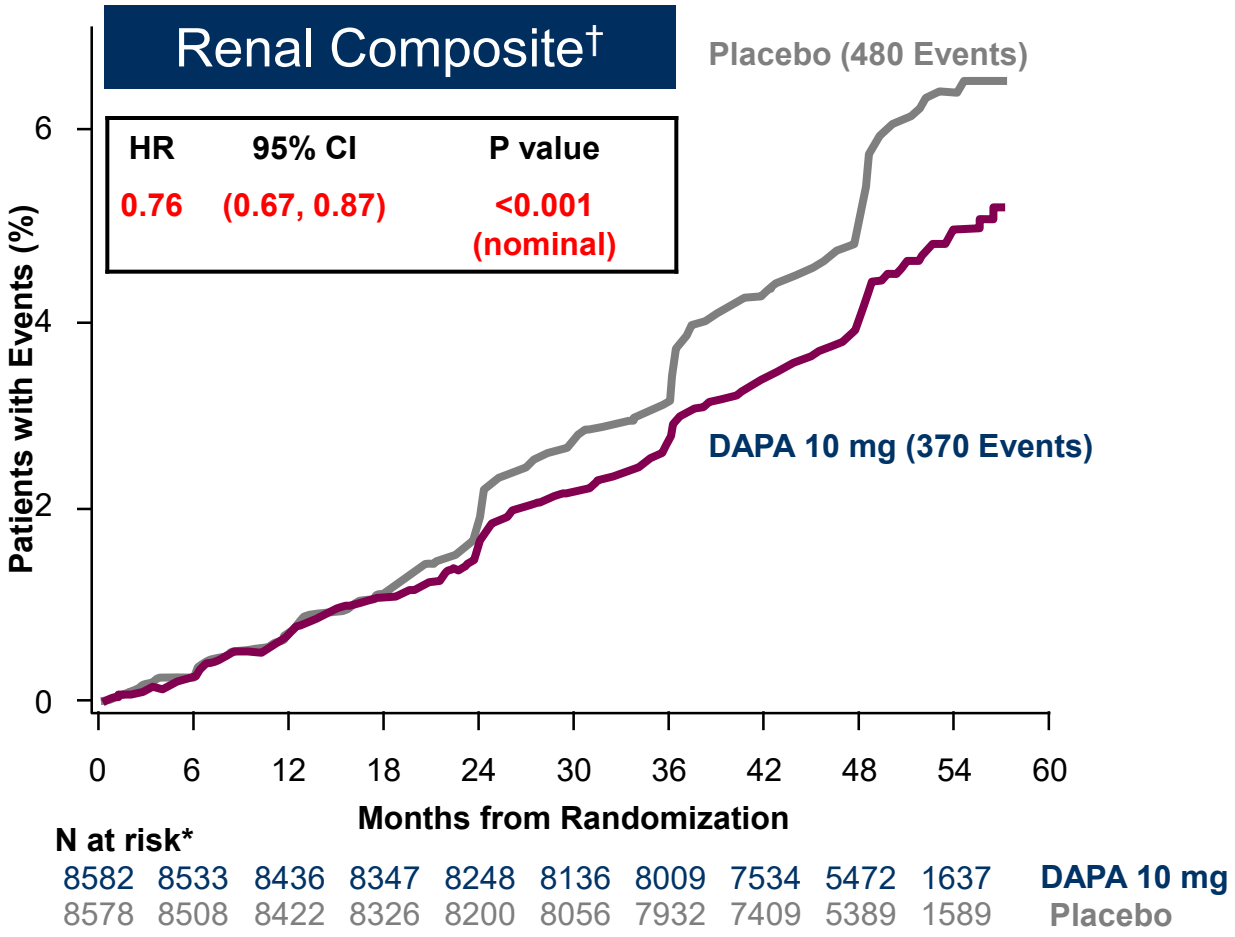
CV, cardiovascular; eCVD, established CV disease; HF, heart failure; hHF, hospitalized heart failure; SGLT-2i, SGLT co-transporter 2 inhibitor; T2D, type 2 diabetes

Wiviott SD et al. Online ahead of print. *N Engl J Med*. 2018

Dapagliflozin slowed renal disease progression in T2D patients with relatively good baseline renal function

The patients in the DECLARE[1,2] trial had better baseline renal function than the EMPA-REG OUTCOME[3] or CANVAS[4] trials

	DECLARE	CANVAS	EMPA-REG
eGFR, mean (mL/min/1.73m^2)	**85.2**	76.5	74.1
Micro-/macro-albumin-uria (%)	**30.2**	30.2	40.6



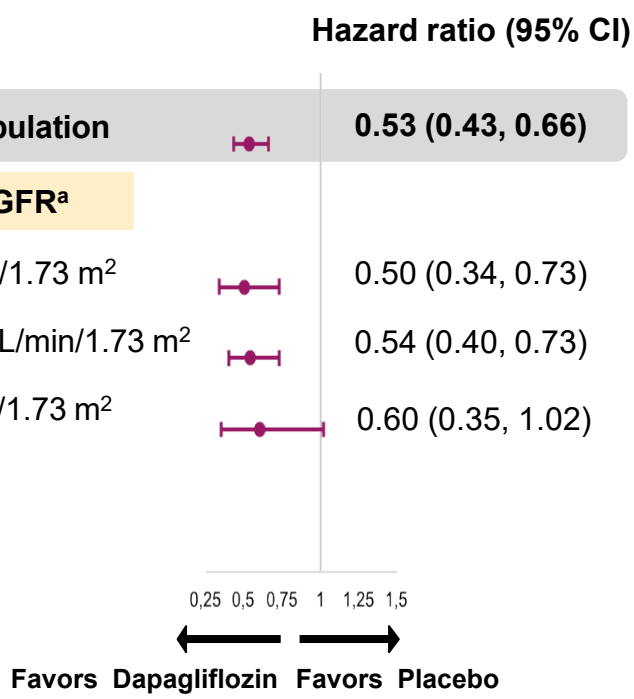
†Renal composite endpoint defined as sustained confirmed eGFR decrease ≥ 40% to eGFR < 60 ml/min/1.73m^2 using CKD-EPI equation and/or ESRD (dialysis ≥ 90 days or kidney transplantation, sustained confirmed eGFR < 15 ml/min/1.73m^2) and/or renal or CV death (pre-specified secondary outcome)

CV, cardiovascular; CKD, chronic kidney disease; Dapa, dapagliflozin; eGFR, estimated glomerular filtration rate; ESRD, end-stage renal disease

1. Raz I, et al. *Diabetes Obes Metab* 2018;20:1102–1110; 2. Wiviott SD et al. Online ahead of print. *N Engl J Med*. 2018; ; 3. Zinman B, et al. *N Engl J Med* 2015;373:2117–2128; 4. Neal B, et al. *N Engl J Med* 2017;377:644–657

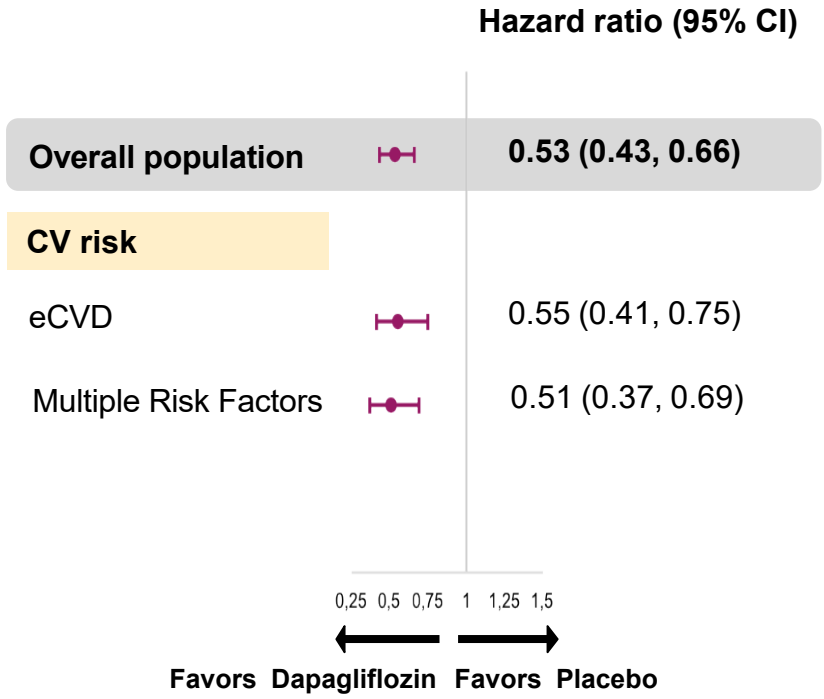
This renal benefit† is demonstrated across eGFR subgroups and in patients with and without established CV disease

Composite of ≥40% decrease in eGFR[a] to <60 mL/min/1.73 m², ESRD, or renal death[c]



Interaction
P value = 0.87

Composite of ≥40% decrease in eGFR[a] to <60 mL/min/1.73 m², ESRD, or renal death[c]



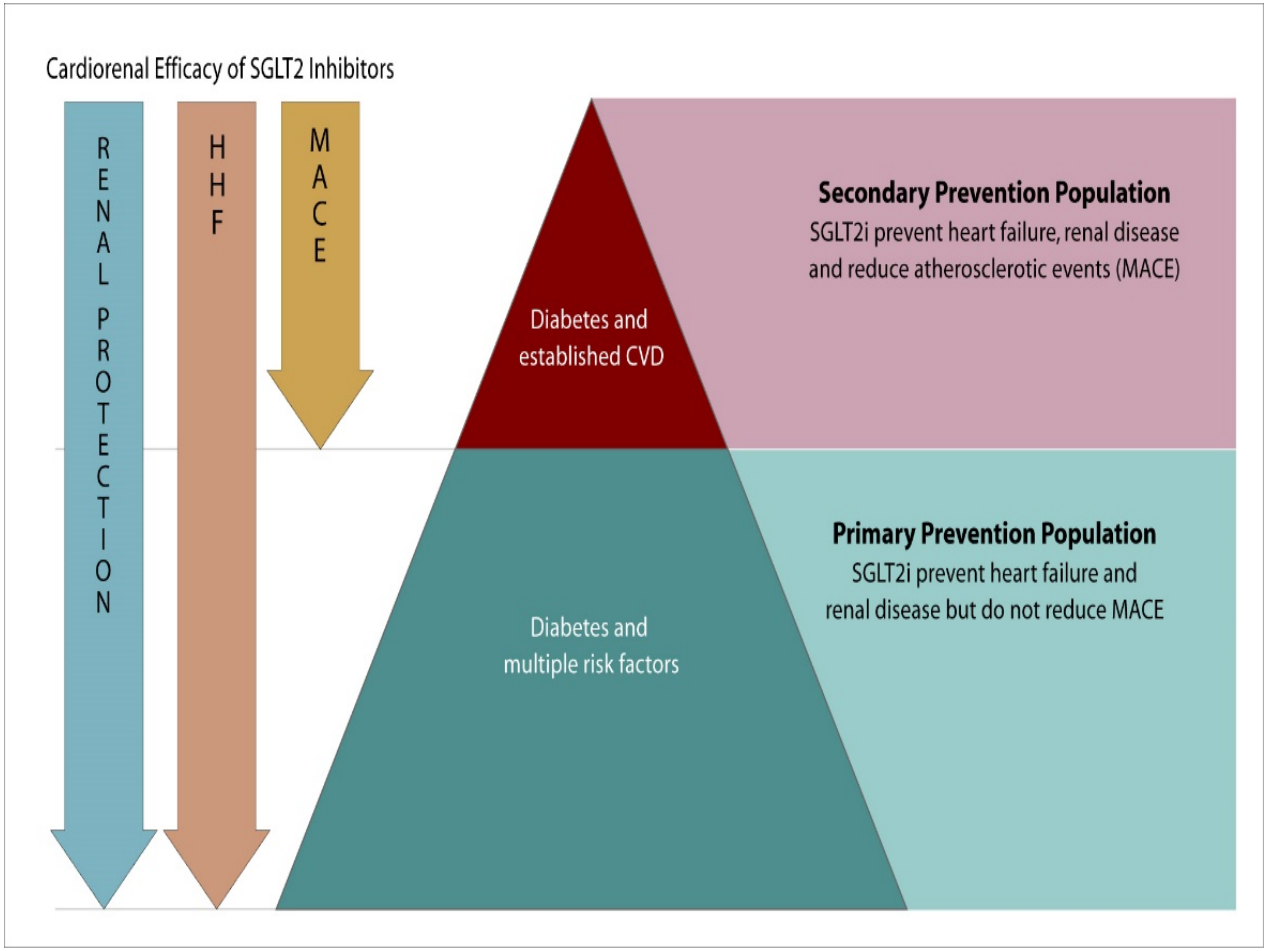
Interaction
P value = 0.72

†Renal composite endpoint without CV death defined as sustained confirmed eGFR decrease ≥ 40% to eGFR < 60 ml/min/1.73m² using CKD-EPI equation and/or ESRD (dialysis ≥ 90 days or kidney transplantation, sustained confirmed eGFR < 15 ml/min/1.73m²) and/or renal death (pre-specified additional renal composite outcome)

CV, cardiovascular; CKD, chronic kidney disease; Dapa, dapagliflozin; eGFR, estimated glomerular filtration rate; ESRD, e

Wiviott SD et al. Online ahead of print. *N Engl J Med*. 2018;

Key messages



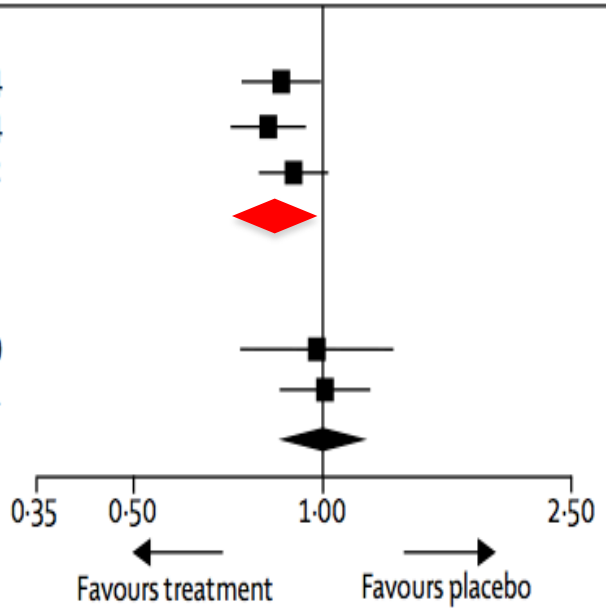
These data with dapagliflozin from **DECLARE- TIMI 58 extend the benefit of SGLT2i to a broader population of patients** for **primary** and **secondary** prevention

Verma S, Jüni P, Mazer CD, The Lancet 2018, **in press**

SGLT2 inhibitors for primary and secondary prevention of cardiovascular and renal outcomes in type 2 diabetes: a systematic review and meta-analysis of cardiovascular outcome trials

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

	Patients		Events	Events per 1000 patient-years		Weight (%)	HR	HR (95% CI)
	Treatment (n/N)	Placebo (n/N)		Treatment	Placebo			
Patients with atherosclerotic cardiovascular disease								
EMPA-REG OUTCOME	4687/7020	2333/7020	772	37·4	43·9	29·4		0·86 (0·74–0·99)
CANVAS Program	3756/6656	2900/6656	796	34·1	41·3	32·4		0·82 (0·72–0·95)
DECLARE-TIMI 58	3474/6974	3500/6974	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	2039/3486	1447/3486	215	15·8	15·5	25·9		0·98 (0·74–1·30)
DECLARE-TIMI 58	5108/10 186	5078/10 186	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)**



Similar pattern for:
Myocardial infarction, CV death, all-cause mortality
No effect on stroke

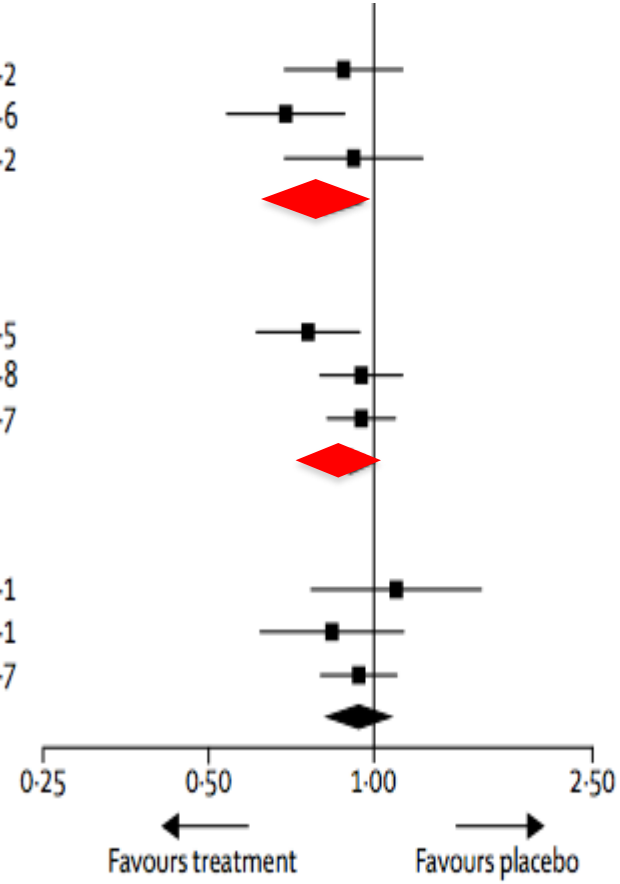
Zelniker TA et al., The Lancet 2018, November 10

SGLT2 inhibitors for primary and secondary prevention of cardiovascular and renal outcomes in type 2 diabetes: a systematic review and meta-analysis of cardiovascular outcome trials

Meta-analysis of SGLT2i trials on **major adverse cardiovascular events (MACE)** stratified by the eGFR level

A

	Patients		Events	Events per 1000 patient-years		Weight (%)	HR	HR (95% CI)
	Treatment (n/N)	Placebo (n/N)		Treatment	Placebo			
eGFR <60 mL/min per m²								
EMPA-REG OUTCOME	1212/1819	607/1819	275	52·7	60·5	36·2		0·88 (0·69–1·13)
CANVAS Program	NA/2039	NA/2039	261	36·3	49·5	36·6		0·69 (0·54–0·89)
DECLARE-TIMI 58	606/1265	659/1265	189	37·3	43·1	27·2		0·92 (0·69–1·23)
Fixed effects model for eGFR <60 (p=0·0077)								**0·82 (0·70–0·95)**
eGFR 60 to <90 mL/min per m²								
EMPA-REG OUTCOME	2423/3661	1238/3661	351	30·8	40·6	22·5		0·76 (0·61–0·94)
CANVAS Program	NA/5625	NA/5625	563	26·8	29·0	32·8		0·95 (0·80–1·13)
DECLARE-TIMI 58	3838/7732	3894/7732	757	24·5	25·8	44·7		0·95 (0·82–1·09)
Fixed effects model for eGFR 60 to <90 (p=0·0520)								**0·91 (0·82–1·00)**
eGFR ≥90 mL/min per m²								
EMPA-REG OUTCOME	1050/1538	488/1538	146	35·4	32·2	15·1		1·10 (0·77–1·57)
CANVAS Program	NA/2476	NA/2476	187	20·8	23·6	21·1		0·84 (0·62–1·13)
DECLARE-TIMI 58	4137/8162	4025/8162	613	18·8	19·7	63·7		0·94 (0·80–1·10)
Fixed effects model for eGFR ≥90 (p=0·35)								**0·94 (0·82–1·07)**

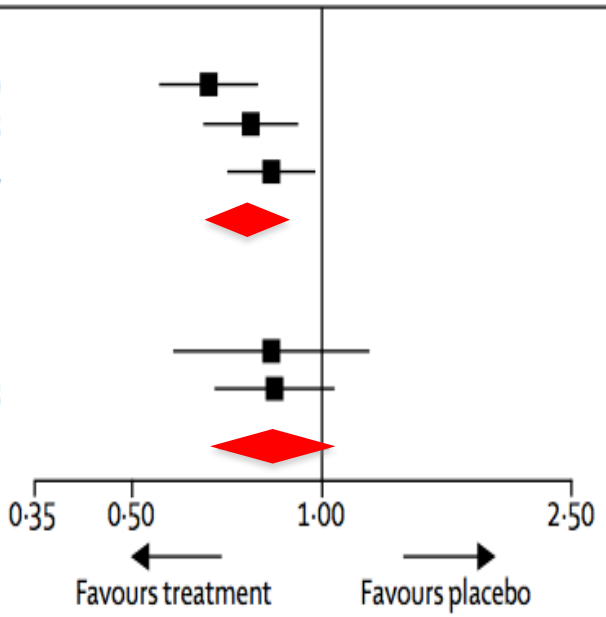


Zelniker TA et al., The Lancet 2018, November 10

SGLT2 inhibitors for primary and secondary prevention of cardiovascular and renal outcomes in type 2 diabetes: a systematic review and meta-analysis of cardiovascular outcome trials

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

	Patients		Events	Events per 1000 patient-years		Weight (%)	HR (95% CI)
	Treatment (n/N)	Placebo (n/N)		Treatment	Placebo		
Patients with atherosclerotic cardiovascular disease							
EMPA-REG OUTCOME	4687/7020	2333/7020	463	19·7	30·1	30·9	0·66 (0·55–0·79)
CANVAS Program	3756/6656	2900/6656	524	21·0	27·4	32·8	0·77 (0·65–0·92)
DECLARE-TIMI 58	3474/6974	3500/6974	597	19·9	23·9	36·4	0·83 (0·71–0·98
Fixed effects model for atherosclerotic cardiovascular disease (p<0·0001)							**0·76 (0·69–0·84)**
Patients with multiple risk factors							
CANVAS Program	2039/3486	1447/3486	128	8·9	9·8	30·2	0·83 (0·58–1·19)
DECLARE-TIMI 58	5108/10 186	5078/10 186	316	7·0	8·4	69·8	0·84 (0·67–1·04)
Fixed effects model for multiple risk factors (p=0·0634)							**0·84 (0·69–1·01)**

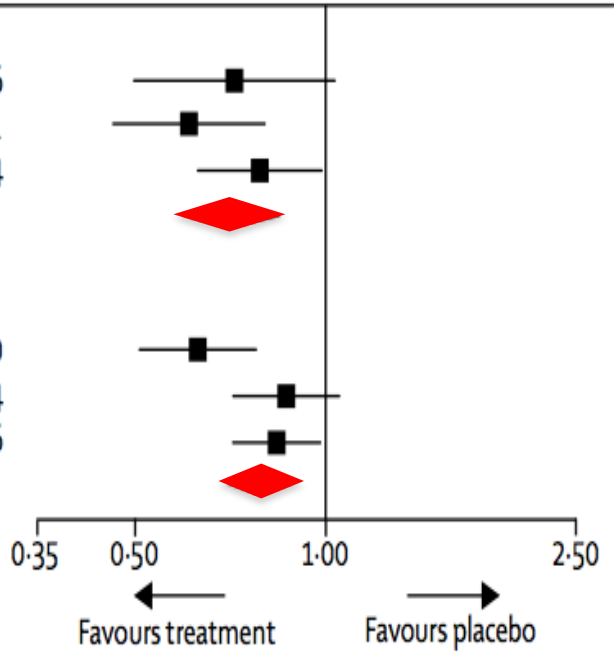


Zelniker TA et al., The Lancet 2018, November 10

SGLT2 inhibitors for primary and secondary prevention of cardiovascular and renal outcomes in type 2 diabetes: a systematic review and meta-analysis of cardiovascular outcome trials

Meta-analysis of SGLT2i trials on **hospitalisation for heart failure and cardiovascular death** stratified by history of heart failure

	Patients		Events	Events per 1000 patient-years		Weight (%)	HR	HR (95% CI)
	Treatment (n/N)	Placebo (n/N)		Treatment	Placebo			
Patients with history of heart failure								
EMPA-REG OUTCOME	462/706	244/706	124	63·6	85·5	23·6		0·72 (0·50–1·04)
CANVAS Program	803/1461	658/1461	203	35·4	56·8	34·1		0·61 (0·46–0·80)
DECLARE-TIMI 58	852/1724	872/1724	314	45·1	55·5	42·4		0·79 (0·63–0·99)
Fixed effects model for history of heart failure (p<0·0001)								**0·71 (0·61–0·84)**
Patients with no history of heart failure								
EMPA-REG OUTCOME	4225/6314	2089/6314	339	15·5	24·9	30·0		0·63 (0·51–0·78)
CANVAS Program	4992/8681	3689/8681	449	13·6	15·2	32·4		0·87 (0·72–1·06)
DECLARE-TIMI 58	7730/15 436	7706/15 436	599	8·9	10·5	37·6		0·84 (0·72–0·99)
Fixed effects model for no history of heart failure (p<0·0001)								**0·79 (0·71–0·88)**



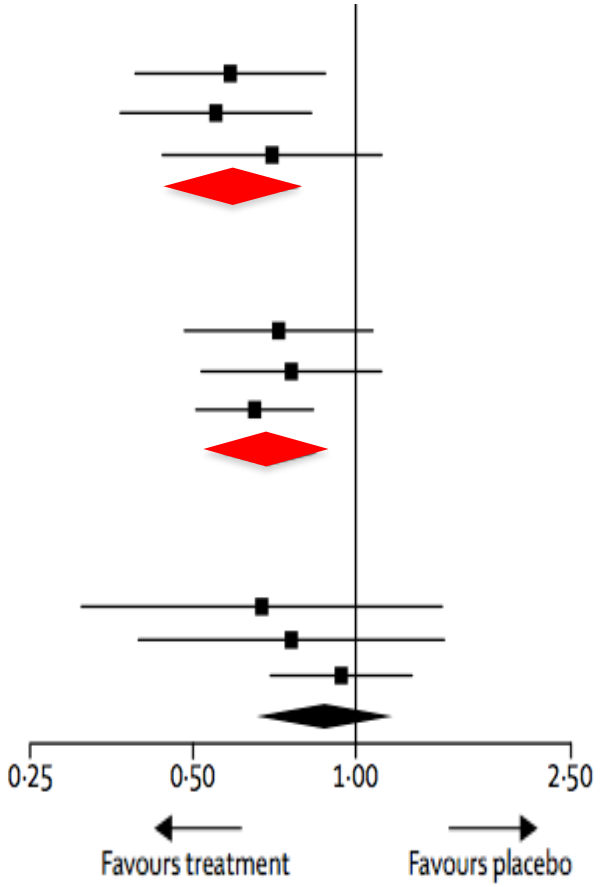
Zelniker TA et al., The Lancet 2018, November 10

SGLT2 inhibitors for primary and secondary prevention of cardiovascular and renal outcomes in type 2 diabetes: a systematic review and meta-analysis of cardiovascular outcome trials

Meta-analysis of SGLT2i trials on **hospitalization for heart failure** stratified by the eGFR level

A

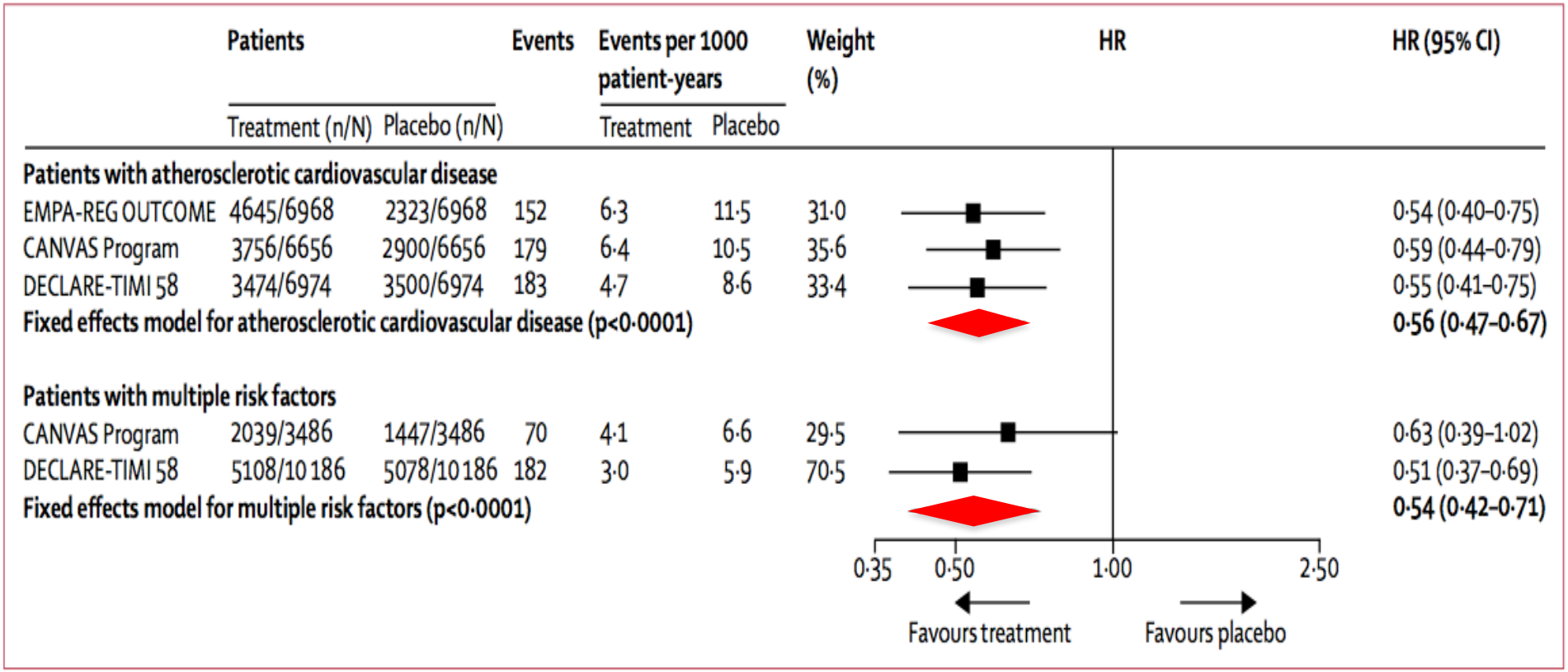
	Patients		Events	Events per 1000 patient-years		Weight (%)	HR	HR (95% CI)
	Treatment (n/N)	Placebo (n/N)		Treatment	Placebo			
eGFR <60 mL/min per m²								
EMPA-REG OUTCOME	1212/1819	607/1819	94	14·9	25·8	36·5		0·59 (0·39–0·88)
CANVAS Program	NA/2039	NA/2039	98	11·6	21·3	36·1		0·55 (0·37–0·83)
DECLARE-TIMI 58	606/1265	659/1265	77	12·3	19·3	27·4		0·70 (0·44–1·12)
Fixed effects model for eGFR <60 (p<0·0001)								**0·60 (0·47–0·77)**
eGFR 60 to <90 mL/min per m²								
EMPA-REG OUTCOME	2423/3661	1238/3661	100	8·4	11·7	21·3		0·72 (0·48–1·07)
CANVAS Program	NA/5625	NA/5625	108	4·6	6·1	23·4		0·76 (0·52–1·12)
DECLARE-TIMI 58	3838/7732	3894/7732	251	6·5	9·9	55·2		0·65 (0·51–0·84)
Fixed effects model for eGFR 60 to <90 (p<0·0001)								**0·69 (0·57–0·83)**
eGFR ≥90 mL/min per m²								
EMPA-REG OUTCOME	1050/1538	488/1538	27	5·4	7·9	11·3		0·67 (0·31–1·44)
CANVAS Program	NA/2476	NA/2476	37	3·7	5·1	15·7		0·76 (0·40–1·47)
DECLARE-TIMI 58	4137/8162	4025/8162	170	5·1	5·4	73·0		0·94 (0·69–1·26)
Fixed effects model for eGFR ≥90 (p=0·31)								**0·88 (0·68–1·13)**



Zelniker TA et al., The Lancet 2018, November 10

SGLT2 inhibitors for primary and secondary prevention of cardiovascular and renal outcomes in type 2 diabetes: a systematic review and meta-analysis of cardiovascular outcome trials

Meta-analysis of SGLT2i trials on the **composite of renal worsening, ESRD, or renal death** stratified by the presence of established atherosclerotic cardiovascular disease



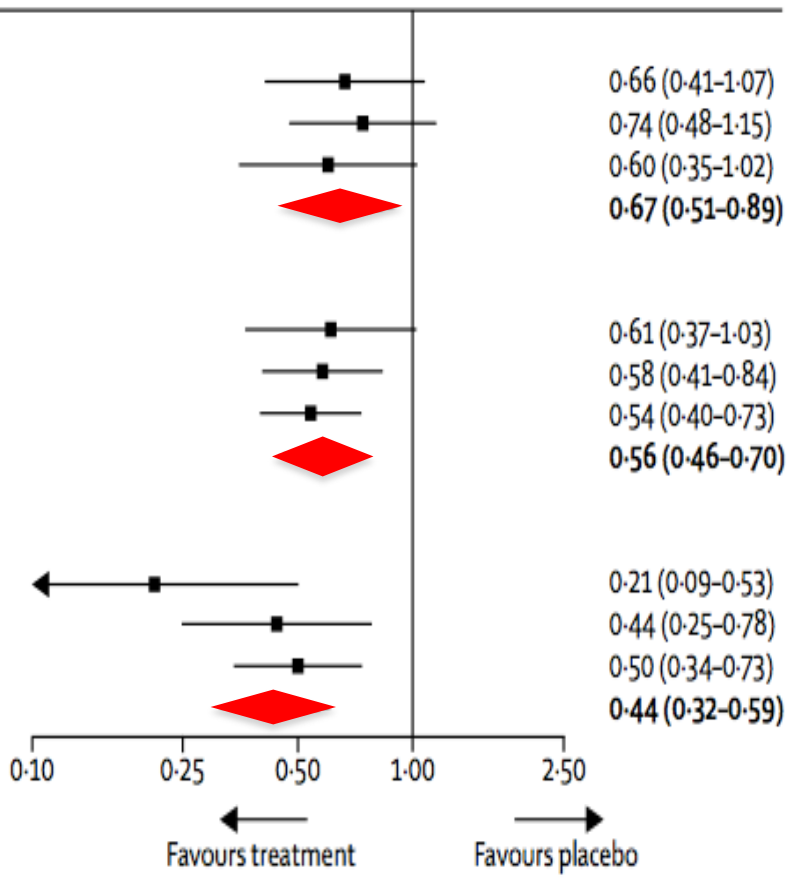
Zelniker TA et al., The Lancet 2018, November 10

SGLT2 inhibitors for primary and secondary prevention of cardiovascular and renal outcomes in type 2 diabetes: a systematic review and meta-analysis of cardiovascular outcome trials

Meta-analysis of SGLT2i trials on **composite of worsening of renal function, ESRD, or renal death** stratified by the eGFR level

A

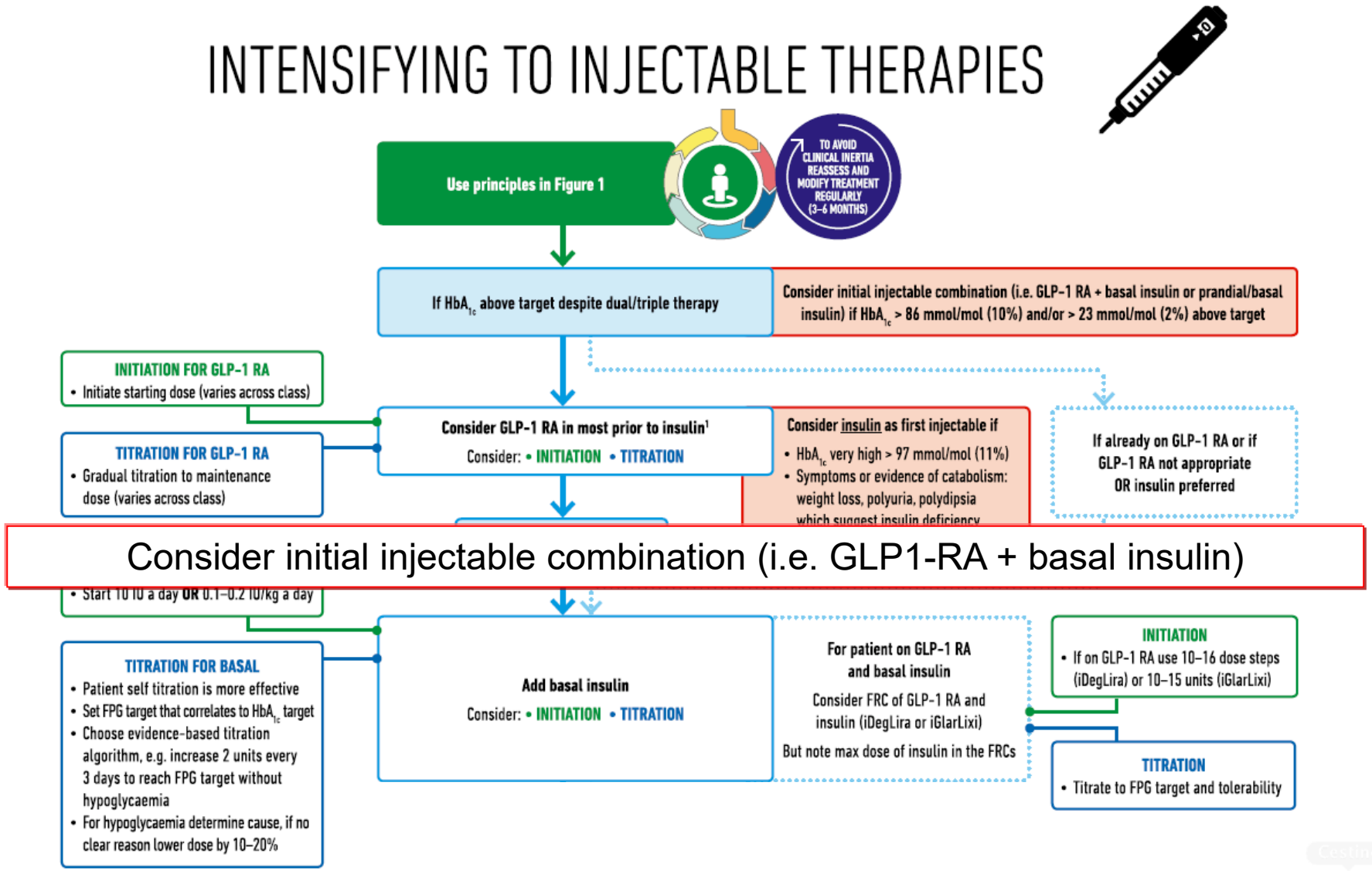
	Patients		Events	Events per 1000 patient-years		Weight (%)	HR	HR (95% CI)
	Treatment (n/N)	Placebo (n/N)		Treatment	Placebo			
eGFR <60 mL/min per m²								
EMPA-REG OUTCOME	1196/1801	605/1801	NA	NA	NA	33·5		0·66 (0·41–1·07)
CANVAS Program	NA/2039	NA/2039	83	11·4	15·1	39·6		0·74 (0·48–1·15)
DECLARE-TIMI 58	606/1265	659/1265	59	8·9	15·2	27·0		0·60 (0·35–1·02)
Fixed effects model for eGFR <60 (p=0·0054)								**0·67 (0·51–0·89)**
eGFR 60 to <90 mL/min per m²								
EMPA-REG OUTCOME	2406/3638	1232/3638	NA	NA	NA	16·8		0·61 (0·37–1·03)
CANVAS Program	NA/5625	NA/5625	118	4·6	7·4	34·4		0·58 (0·41–0·84)
DECLARE-TIMI 58	3838/7732	3894/7732	186	4·2	7·8	48·9		0·54 (0·40–0·73)
Fixed effects model for eGFR 60 to <90 (p<0·0001)								**0·56 (0·46–0·70)**
eGFR ≥90 mL/min per m²								
EMPA-REG OUTCOME	1043/1529	486/1529	NA	NA	NA	11·7		0·21 (0·09–0·53)
CANVAS Program	NA/2476	NA/2476	48	3·8	8·1	27·5		0·44 (0·25–0·78)
DECLARE-TIMI 58	4137/8162	4025/8162	120	2·5	4·9	60·8		0·50 (0·34–0·73)
Fixed effects model for eGFR ≥90 (p<0·0001)								**0·44 (0·32–0·59)**



Zelniker TA et al., The Lancet 2018, November 10

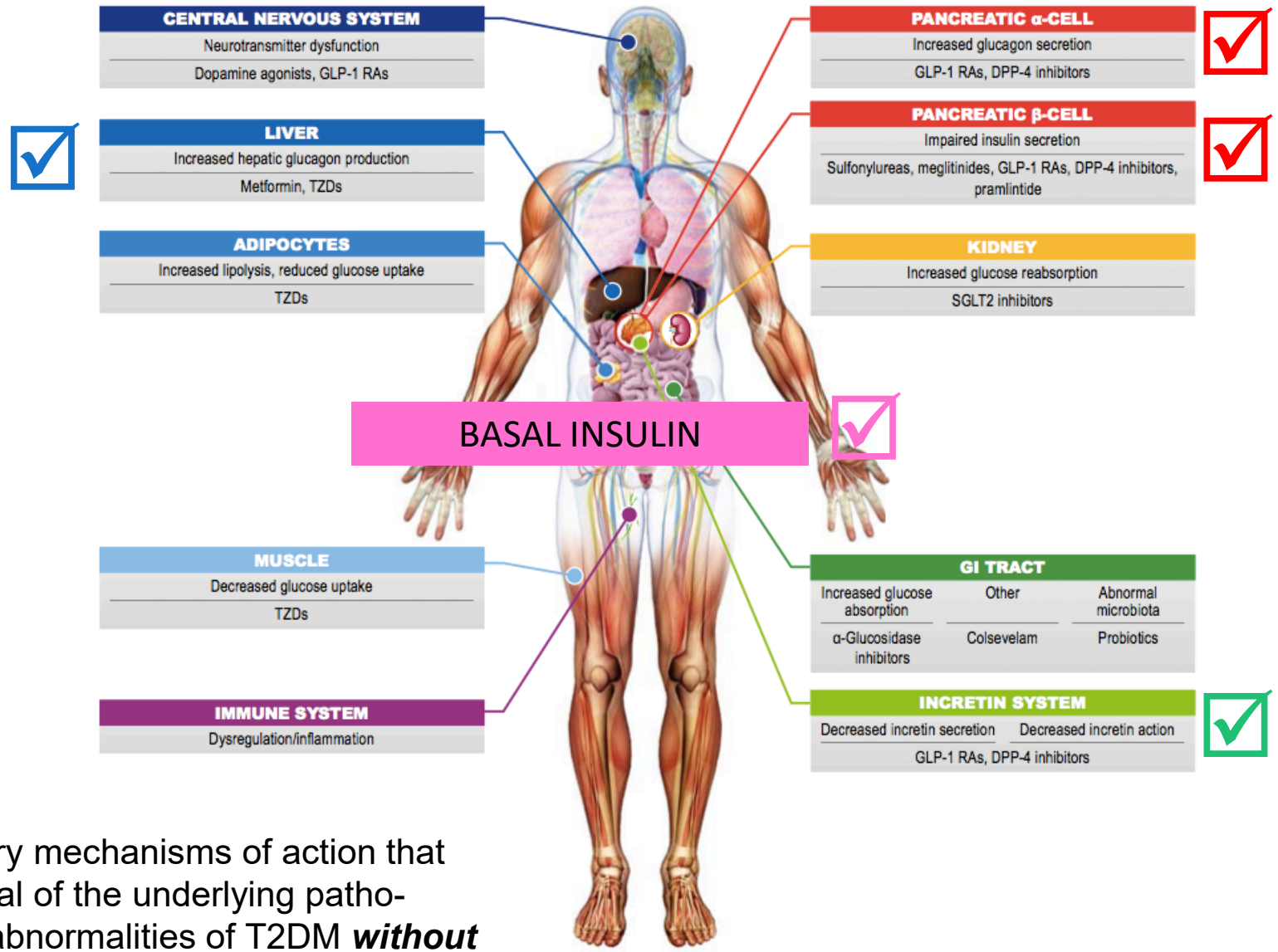
Progression of Contents

Management of Hyperglycemia in Type 2 Diabetes, 2018. A Consensus Report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD)



Devies MJ et al., Diabetologia & Diabetes Care 2018, October 5

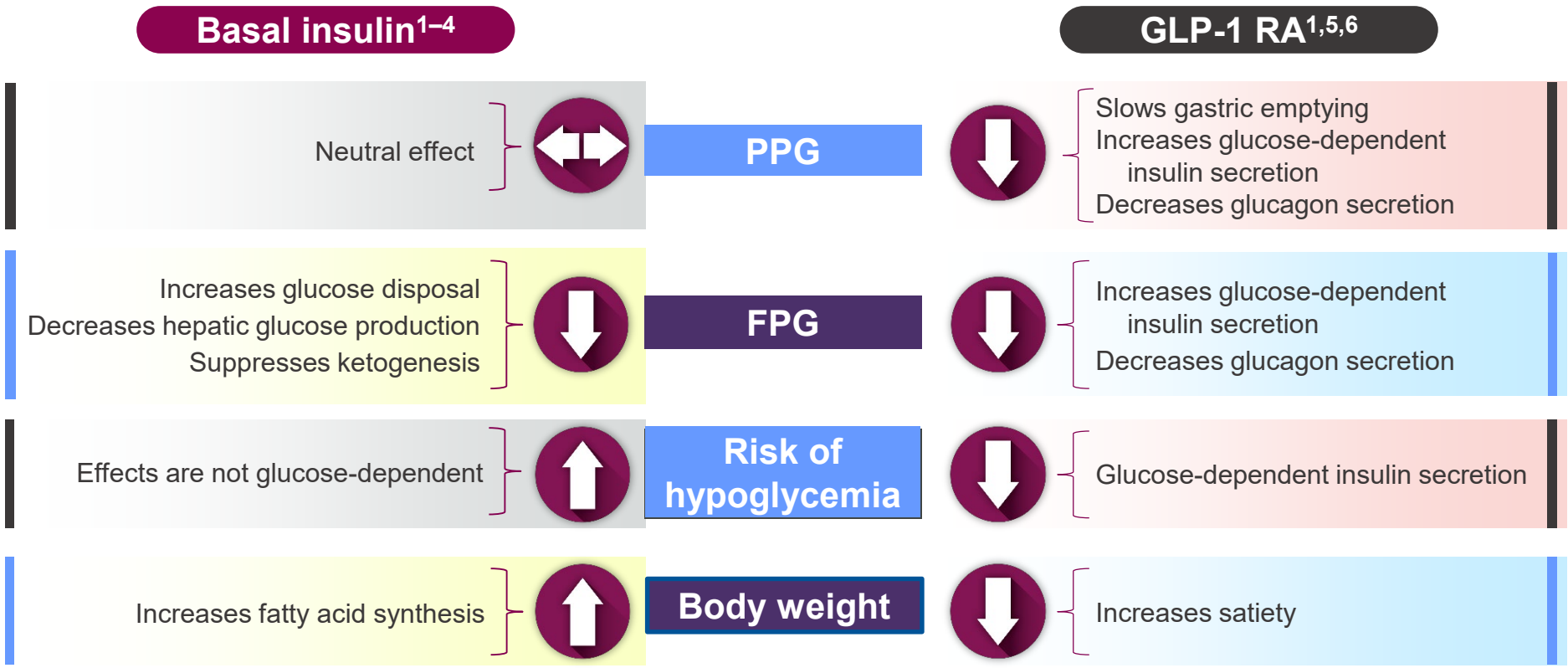
Fixed-ratio combinations: basal insulin & GLP1-RAs



Complementary mechanisms of action that address several of the underlying patho-physiological abnormalities of T2DM ***without overlapping toxicity***.

Lingway I. Endocrine Practice 2017

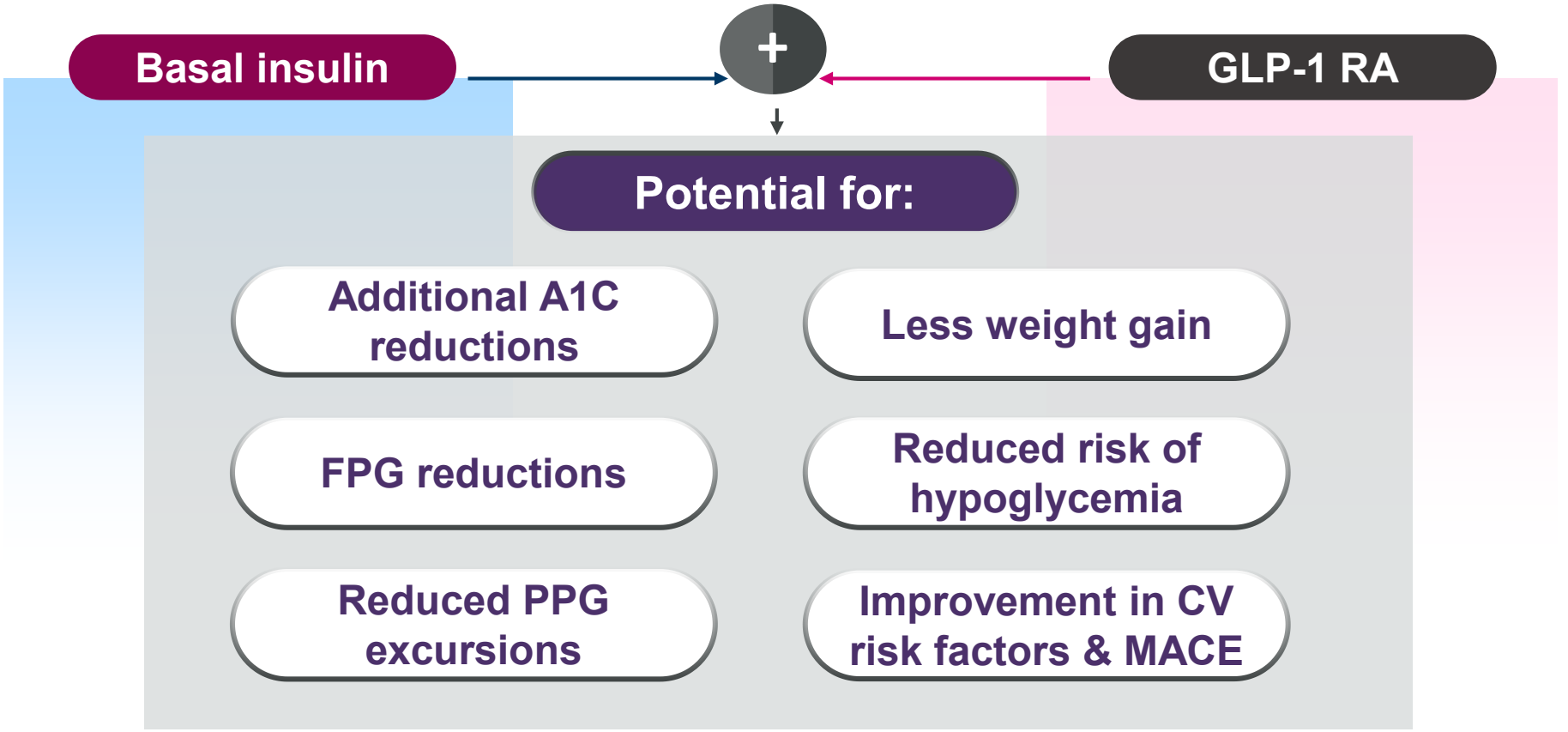
Clinical effects of basal insulin & GLP1-RAs



FPG, fasting plasma glucose; GLP-1 RA, glucagon-like peptide-1 receptor agonist; PPG, postprandial plasma glucose

1. Marathe PH et al. *J Diabetes* 2017;9:320–324; 2. Blevins T. *Postgrad Med.* 2011;123:135–147;
3. Wilcox G. *Clin Biochem Rev* 2005;26:19–39; 4. Russell-Jones D. *Diabetes Obes Metab* 2007;9:799–812;
5. Aronoff SL et al. *Diabetes Spectr* 2004;17:183–190; 6. Meier JJ. *Nat. Rev Endocrinol* 2012;8:728–742.

Potential clinical benefits of basal insulin & GLP1-RAs



A1C, glycated hemoglobin; CV, cardiovascular; FPG, fasting plasma glucose; GLP-1 RA, glucagon-like peptide-1 receptor agonist; PPG, postprandial glucose

1. Gough S et al. *Diabetes Obes Metab* 2015;17:965–973; 2. Marso SP et al. *N Eng J Med* 2016;375:311–322;
3. Marso SP et al. *N Eng J Med* 2016;375:1834–1844.

Efficacy outcomes for iGlarLixi and IDegLira

Study	Mean baseline characteristics	Background therapy	Treatment arms	Mean final basal insulin dose (units)	Baseline A1C (%)	Mean A1C change from baseline (%)	Proportion of patients achieving A1C <7% (%)	Mean body weight change from baseline (kg)
Lixi-Lan (24 weeks)	Age (years) = 56.8 BMI (kg/m²) = 32.1 Duration of T2D (years) = 6.7	Metformin	iGlarLixi (n = 161) iGlar (n = 162)	36 39	8.1 8.0	−1.82 −1.64	84 78	−1.16 +0.39
Lixi-Lan-O (30 weeks)	Age (years) = 58.4 BMI (kg/m²) = 31.8 Duration of T2D (years) = 8.8	Metformin ± 2nd OAD	iGlarLixi (n = 469) iGlar (n = 467) Lixisenatide (n = 233)	39.8 40.3 –	8.1 8.1 8.1	−1.6 −1.3 −0.9	73.7 59.4 33.0	−0.3 +1.1 −2.3
Lixi-Lan-L (30 weeks)	Age (years) = 60 BMI (kg/m²) = 31.2 Duration of T2D (years) = 12.05	Basal insulin ± up to 2 OADs	iGlarLixi (n = 367) iGlar (n = 369)	47 47	8.1 8.1	−1.1 −0.6	54.9 29.6	−0.7 +0.7
DUAL I (26 weeks)	Age (years) = 55 BMI (kg/m²) = 31.2 Duration of T2D (years) = 6.9	Metformin ± pioglitazone	IDegLira (n = 833) IDeg (n = 413) Liraglutide (n = 414)	38 53 –	8.3 8.3 8.3	−1.9 −1.4 −1.3	81 65 60	−0.5 +1.6 −3.0
DUAL II (26 weeks)	Age (years) = 57.5 BMI (kg/m²) = 33.7 Duration of T2D (years) = 10.5	Basal insulin + metformin ± sulfonylurea/ glinides	IDegLira (n = 199) IDeg (n = 199)	45 45	8.7 8.8	−1.9 −0.9	60 23	−2.7 0.0
DUAL III (26 weeks)	Age (years) = 58.4 BMI (kg/m²) = 32.95 Duration of T2D (years) = 10.4	±Metformin ± pioglitazone ± sulfonylurea	IDegLira (n = 292) GLP-1RA (n = 146)	43 –	7.8 7.7	−1.4 −0.3	75 36	+2.0 −0.8
DUAL IV (26 weeks)	Age (years) = 59.7 BMI (kg/m²) = 31.6 Duration of T2D (years) = 9.15	Sulfonylurea ± metformin	IDegLira (n = 289) Placebo (n = 146)	28 –	7.9 7.9	−1.5 −0.5	79.2 28.8	+0.5 −1.0
DUAL V (26 weeks)	Age (years) = 58.8 BMI (kg/m²) = 31.7 Duration of T2D (years) = 11.5	Metformin	IDegLira (n = 278) IGlar (n = 279)	41 66	8.4 8.2	−1.81 −1.13	71.6 47	−1.4 +1.8

Nuffer W et al., Therapeutic Advances in Endocrinology and Metabolism 9: 69-79, 2018

Fixed-ratio combinations: basal insulin & GLP1-RAs

What combinations are availables: IDegLira (up to 50 UI/1.8 mg) and iGlarLixi (up to 60 UI/20 µg);

What are the main benefits: single daily injection; robust BG-lowering beyond either insulin or GLP1-RA alone: weight neutrality/loss; similar or reduced risk of hypoglycemia compared with insulin alone;

What are the main disadvantages: patients may require amounts of insulin or GLP1-RA in a different ratio;

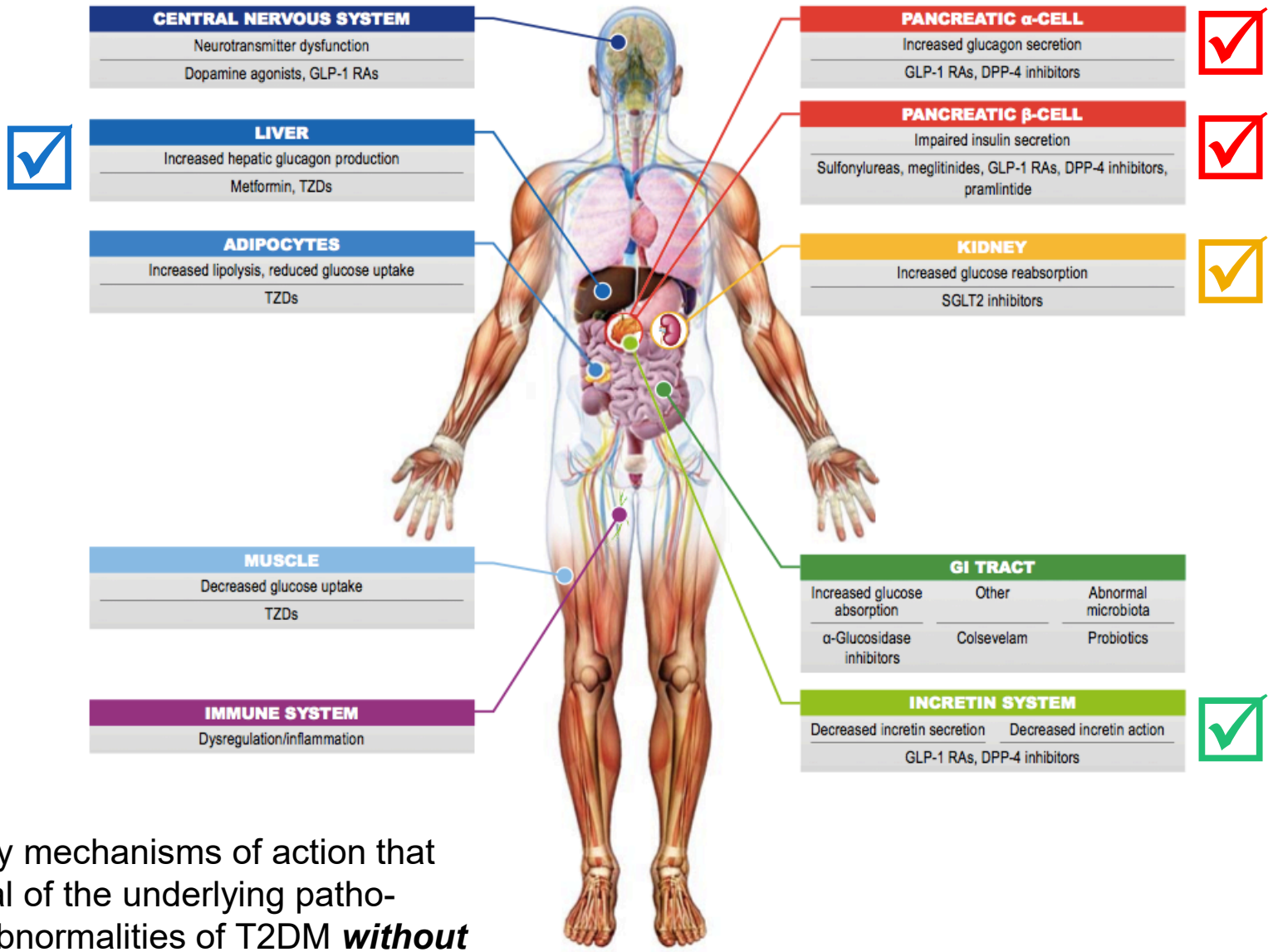
Who is a good candidate for: insufficient BG control on a combination of OHAs; insufficient BG control either on basal insulin or a GLP1-RA alone; avoiding addition of prandial insulin;

Who is a poor candidate for: patients with history of pancreatitis; family history of medullary thyroid cancer;

Starting: IDegLira 16 steps; iGlarLixi 15 or 30 steps (if basal insulin < or >30 UI)

Adjustment/titration: IDegLira ±2 steps every 3-4 days; iGlarLixi 2-4 steps weekly; adjustments are made based on the insulin, not the GLP1-RA component;

Rationale for the combination of DPP-4 and SGLT2 inhibition

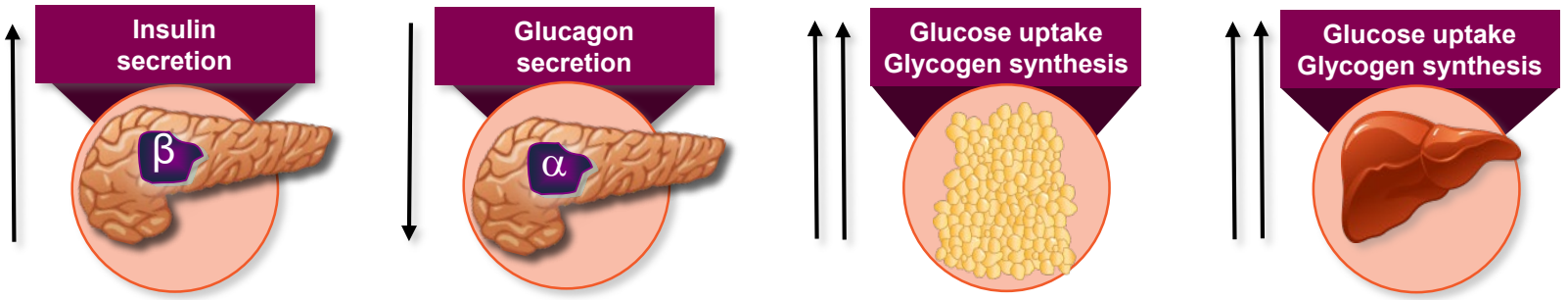


Complementary mechanisms of action that address several of the underlying patho-physiological abnormalities of T2DM ***without overlapping toxicity***.

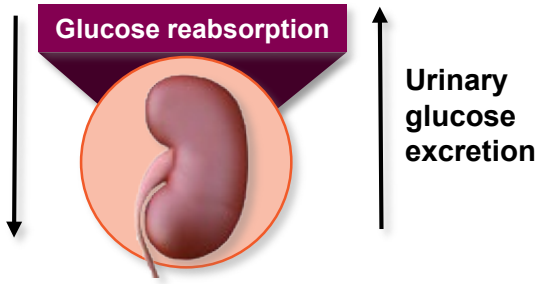
Lingway I. Endocrine Practice 2017

DPP4i/SGLT2i + Metformin Provides a Logical Approach to T2DM Treatment Through Complementary Mechanisms

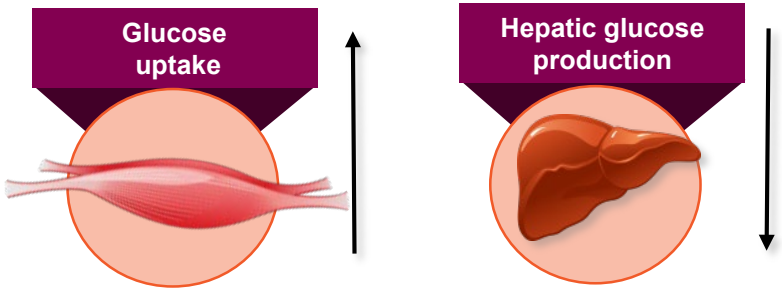
- **DPP4i/SGLT2i combination** is differentiated from other therapies due to its **complementary mechanisms** that target multiple disease pathways[1]
- DPP4i slow the deactivation of GLP-1 in the circulation, resulting in[2,3]:



- **SGLT2i** exert effects on the kidneys to[4]:



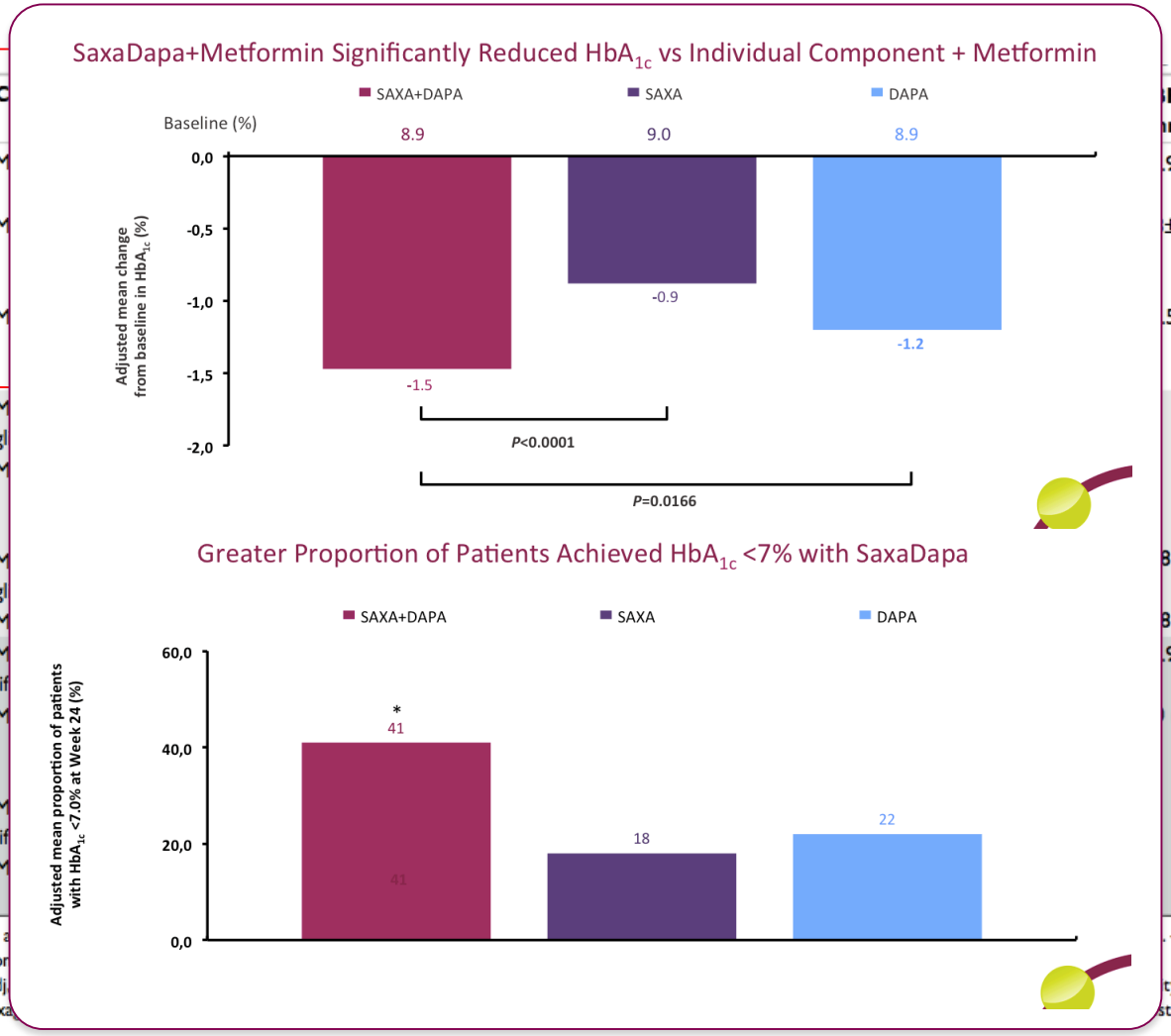
- **Metformin** exerts its effects to[4]:



1. DeFronzo RA. *Diabetes* 2009;58:773–795. 2. Wang A, et al. *BMC Pharmacology* 2012 Apr 4;12:2.
3. Drucker DJ, Nauck MA. *Lancet* 2006;368:1696–1705. 4. Paisley AN, et al. *Expert Opin Investig Drugs* 2013;22:131–140.

Emerging use of combination therapies for the management of type 2 diabetes – focus on saxagliptin and dapagliflozin

Five completed phase III trials, and at least seven trials ongoing



Trial, year	C	P Δ[b] (mmHg)	DBP Δ[b] (mmHg)	LDL[b] (%)	HDL[b] (%)
Rosenstock et al,[99] 2015	M	.9±12.0	−1.0±8.0	3.7 (−0.9, 8.6)	5.4 (3.0, 7.8)
	M	±10.2	−0.4±7.0	−0.6 (−5.1, 4.1), p=0.20	0.9 (−1.4, 3.3), p=0.009
	M	.5±12.9	−1.4±8.4	1.5 (−3.1, 6.4), p=0.52	7.7 (5.2, 10.2), p=0.19
Matthaei et al,[100] 2015	M		–	−1.0 (−5.1, 3.4)	1.3 (−1.1, 3.8)
	gl		–	1.5 (−2.7, 5.9)	0.1 (−2.3, 2.5)
	M				
Matthaei et al,[101] 2016	M	8 (−)	0.3 (−)	–	–
	gl				
	M	8 (−)	0.3 (−)	–	–
Mathieu et al,[102] 2015	M	.9 (−)	−1.7 (−)	4.7 (0.9, 8.7)	6.2 (3.4, 9.0)
	lif				
	M	) (−)	0.3 (−)	2.8 (−0.9, 6.6)	2.8 (0.2, 5.5)
Mathieu et al,[103] 2016	M		–	–	–
	lif				
	M		–	–	–

Notes: Paired trials a – denotes where data were not reported or could not be obtained from authors. To cor

Abbreviations: Adj ty lipoprotein; CI, confidence interval; SD, standard deviation; Metf, metformin; Saxa, saxa sting procedure of the respective studies.

Yu H et al., Diabetes, Metabolic Syndrome and Obesity: Targets and Therapy 10: 337-332, 2017

Pharmacokinetic drug evaluation of empagliflozin plus linagliptin for the treatment of type 2 diabetes

Four completed phase III trials, others ongoing

Study, duration (primary outcome)	Combination[a]	Background therapy	N	Treatment and dose (mg/day)	Efficacy parameters (change from baseline)[b]			
					HbA_{1c} (%)	FPG (mg/dL)[c]	Body weight (kg)	SBP (mmHg)
Lewin et al[72] 24 weeks; study duration 52 weeks	EMPA 10 or 25 mg/day + LINA 5 mg/day	Treatment-naïve		Single-pill combination[d]	(Week 24)	(Week 24)	(Week 24)	(Week 52)
			134	EMPA 25/LINA 5	−1.08	−29.55	−2.0	−2.5
			135	EMPA 10/LINA 5	−1.24	−28.21	−2.7	−2.1
			133	EMPA 25	−0.95	−24.24	−2.1	−2.1
			132	EMPA 10	−0.83	−22.39	−2.3	−2.2
			133	LINA 5	−0.67	−5.92	−0.8	−0.4
DeFronzo et al[73] 24 weeks; study duration 52 weeks	EMPA 10 or 25 mg/day + LINA 5 mg/day as add-on to MET	MET IR ≥1,500 mg/day, MTD, or maximum dose per local label		Single-pill combination[d]	(Week 24)	(Week 24)	(Week 24)	(Week 52)
			134	EMPA 25/LINA 5 + MET	−1.19	−35.3	−3.0	−3.6
			135	EMPA 10/LINA 5 + MET	−1.08	−32.2	−2.6	−2.8
			140	EMPA 25 + MET	−0.62	−18.8	−3.2	−2.8
			137	EMPA 10 + MET	−0.66	−20.8	−2.5	−3.5
			128	LINA 5 + MET	−0.70	−13.1	−0.7	0.3

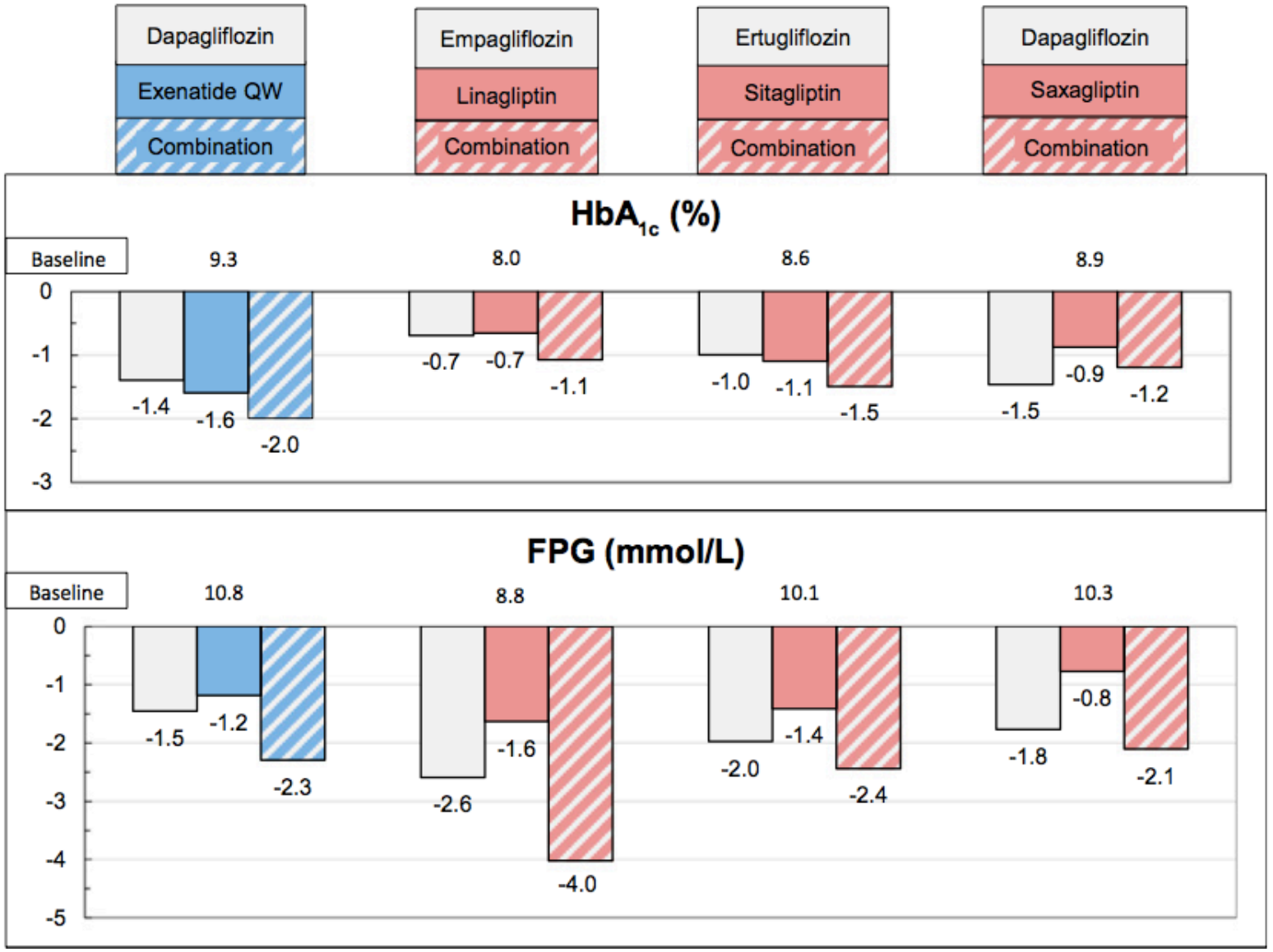
Rizos CV et al., Exper Opinion on Drug Metabolism & Toxicology [Epub ahead of print], 2018

Ertugliflozin and Sitagliptin: the VERTIS Program

Three completed phase III trials, others ongoing

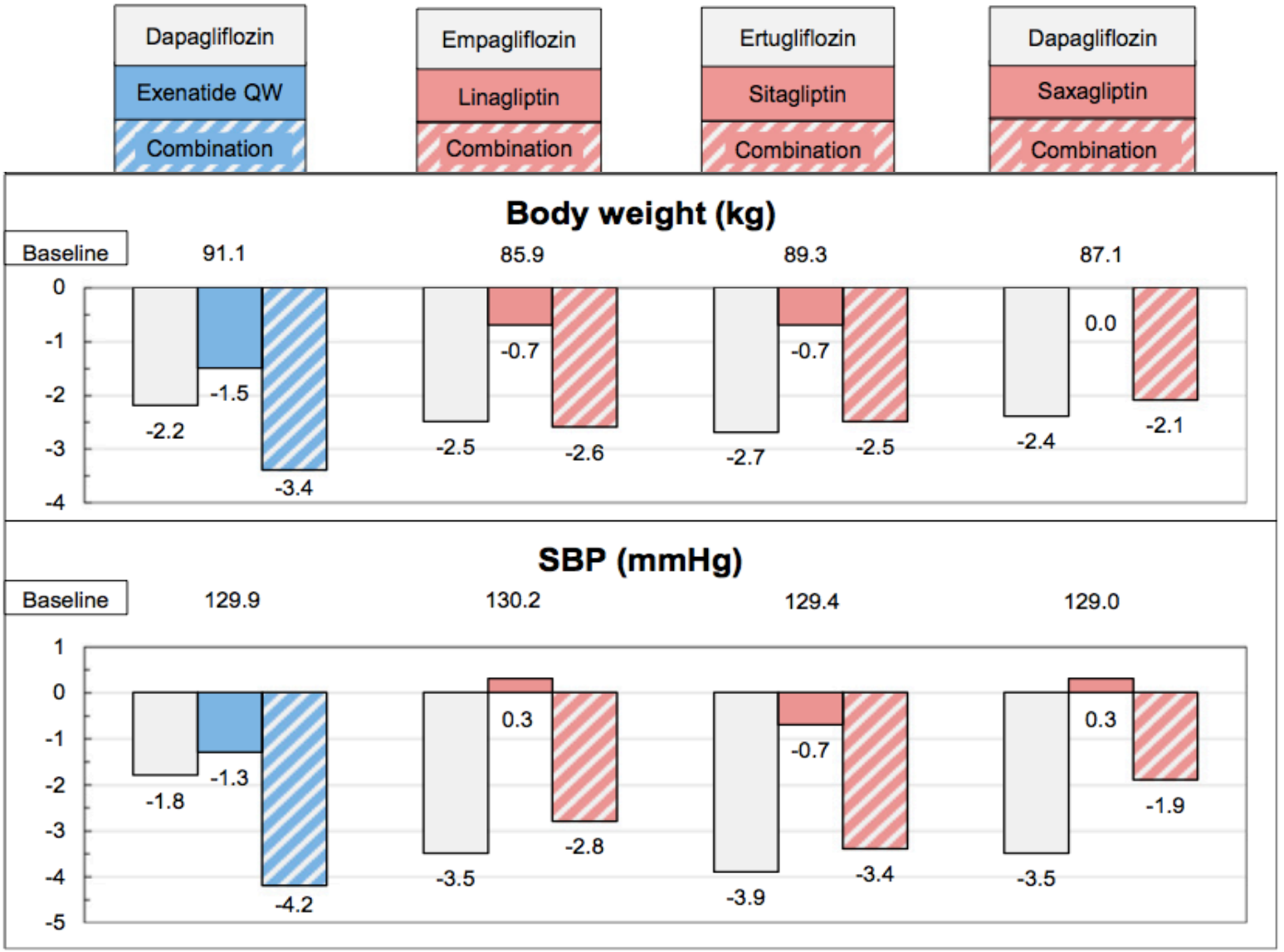
	Reductions from baseline in HbA1c		
	Placebo	E5/S100	E15/S100
Ertugliflozin and Sitagliptin Co-initiation in Patients with Type 2 Diabetes: The VERTIS SITA Randomized Study	-0.4%	-1.6%	-1.7%
	E5, E15, S100	E5/S100	E15/S100
Ertugliflozin plus sitagliptin versus either individual agent over 52 weeks in patients with T2DM inadequately controlled with metformin: The VERTIS FACTORIAL randomized trial.	-1.0% -1.1% -1.1%	-1.5%	-1.5%
	Placebo	E5	E15
Efficacy and safety of the addition of ertugliflozin in patients with T2DM inadequately controlled with metformin and sitagliptin: The VERTIS SITA2 placebo-controlled randomized study.	0.0	-0.7	-0.8

Additivity in glycemic and pleiotropic effects. Reductions from baseline in combination therapy vs. either agent alone



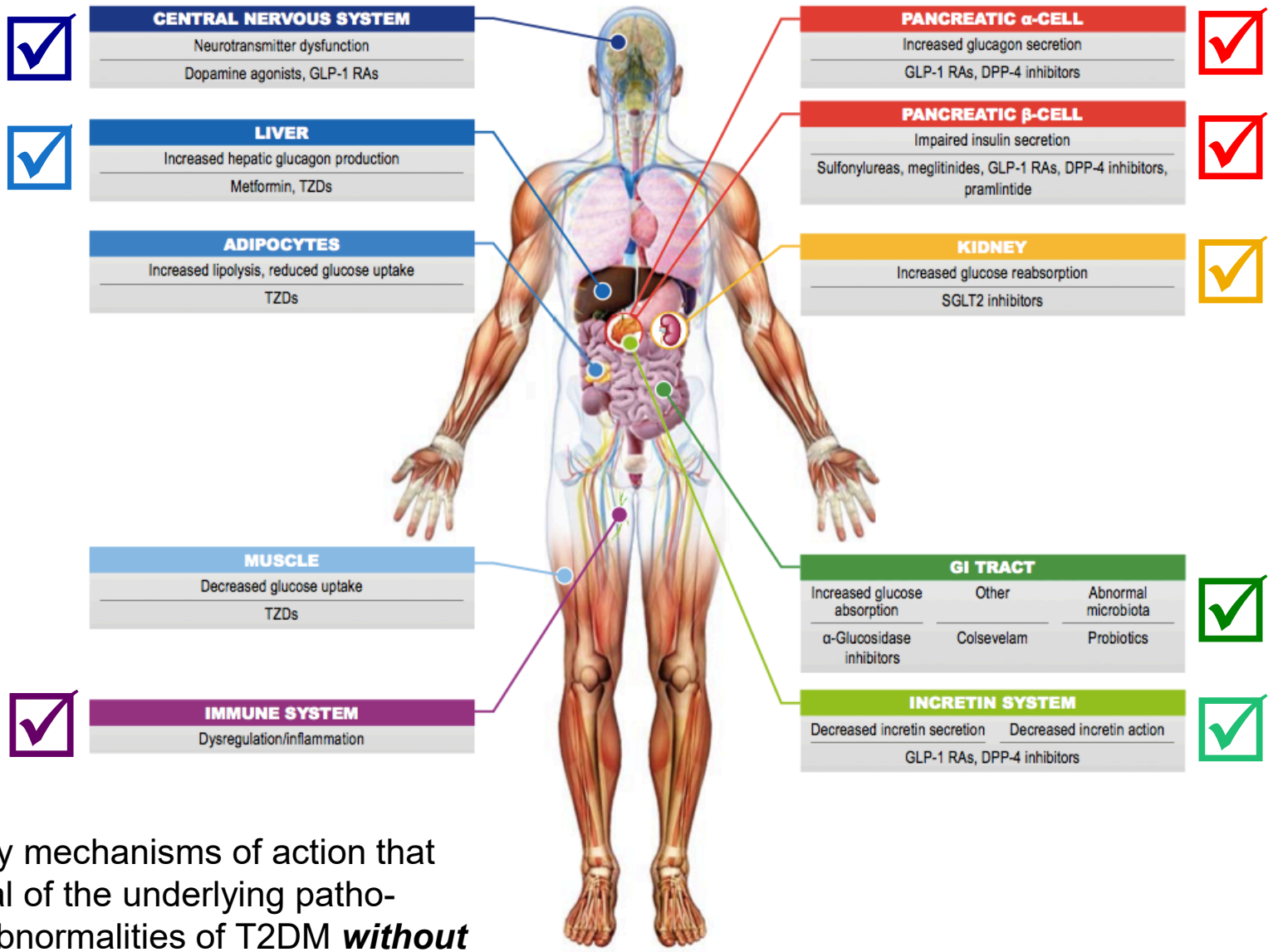
Van Baar MJB et al., Diabetes Care 41: 1543-1556, 2018

Additivity in glycemic and pleiotropic effects. Reductions from baseline in combination therapy vs. either agent alone



Van Baar MJB et al., Diabetes Care 41: 1543-1556, 2018

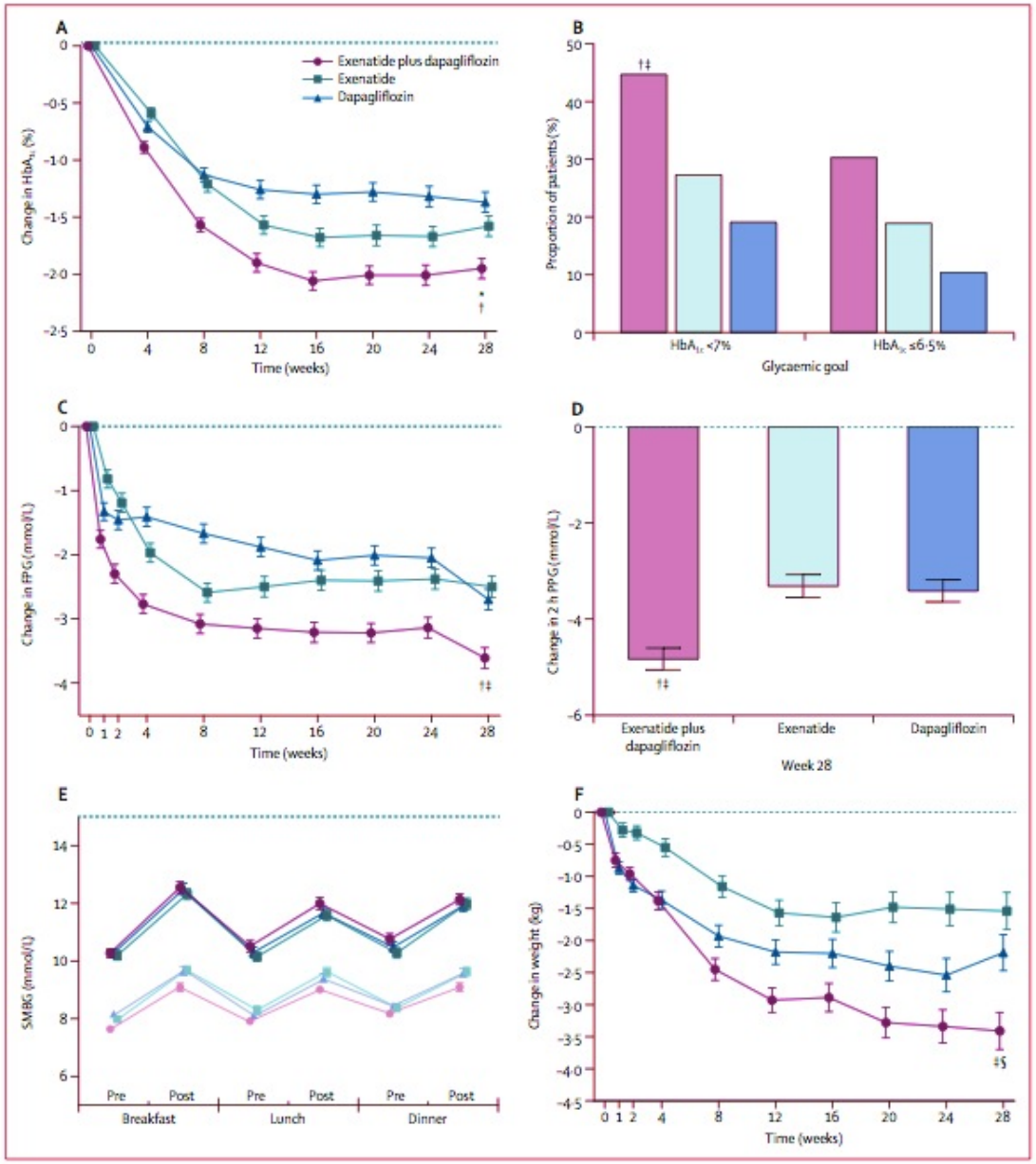
Rationale for the combination of SGLT2i and GLP1-RA



Complementary mechanisms of action that address several of the underlying patho-physiological abnormalities of T2DM ***without overlapping toxicity***.

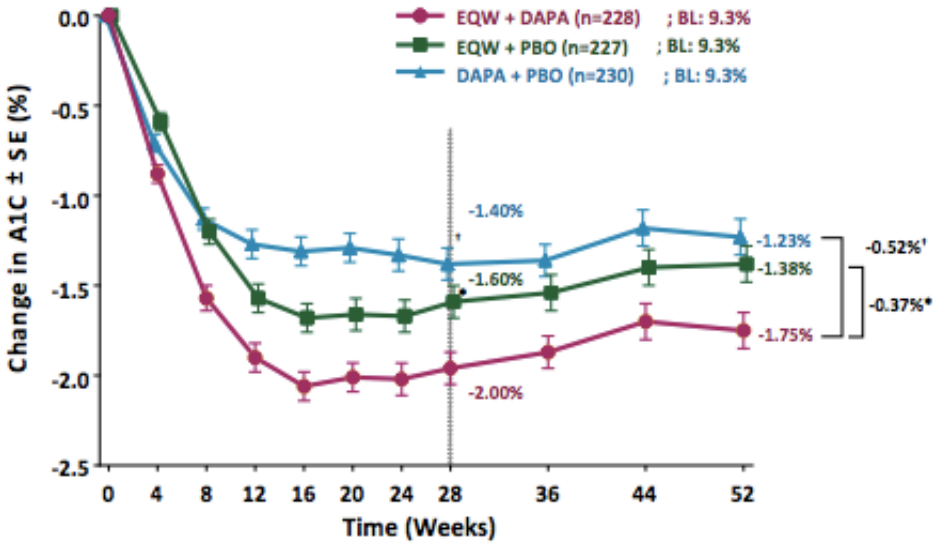
Lingway I. Endocrine Practice 2017

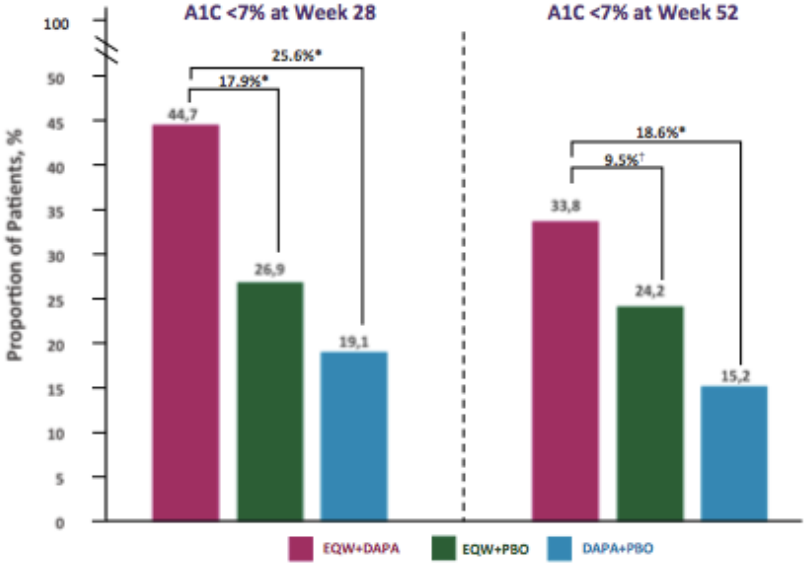
Exenatide once weekly plus dapagliflozin once daily versus exenatide or dapagliflozin alone in patients with T2DM inadequately controlled with metformin monotherapy (DURATION-8): a 28 week, multicentre, double-blind, phase 3, randomised trial

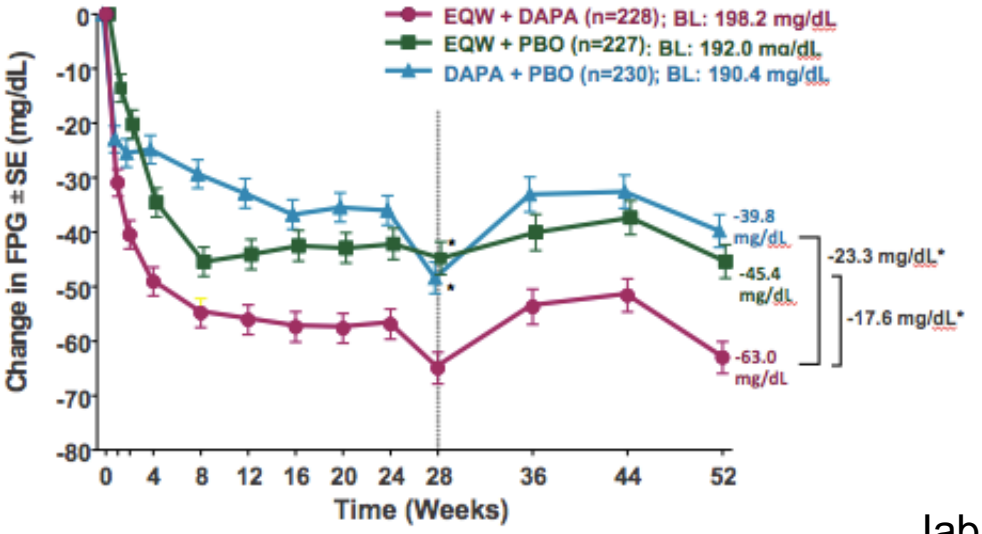


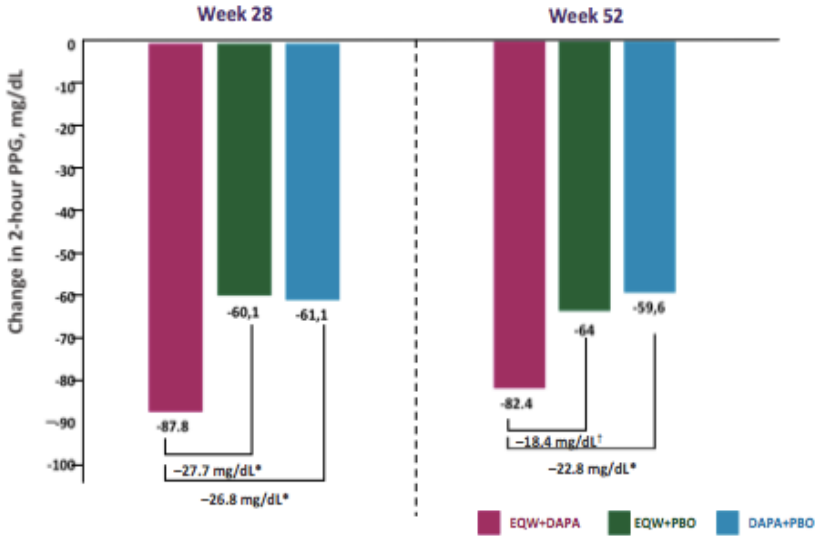
Frias JP et al., Lancet Diabetes Endocrinol, September 6, 2016

Safety and Efficacy of Exenatide Once Weekly Plus Dapagliflozin Once Daily Versus Exenatide or Dapagliflozin Alone in Patients With Type 2 Diabetes Inadequately Controlled With Metformin Monotherapy: 52-Week Results of the DURATION-8 Randomized Controlled Trial









Jabbour SA et al., Diabetes Care August 6, 2018

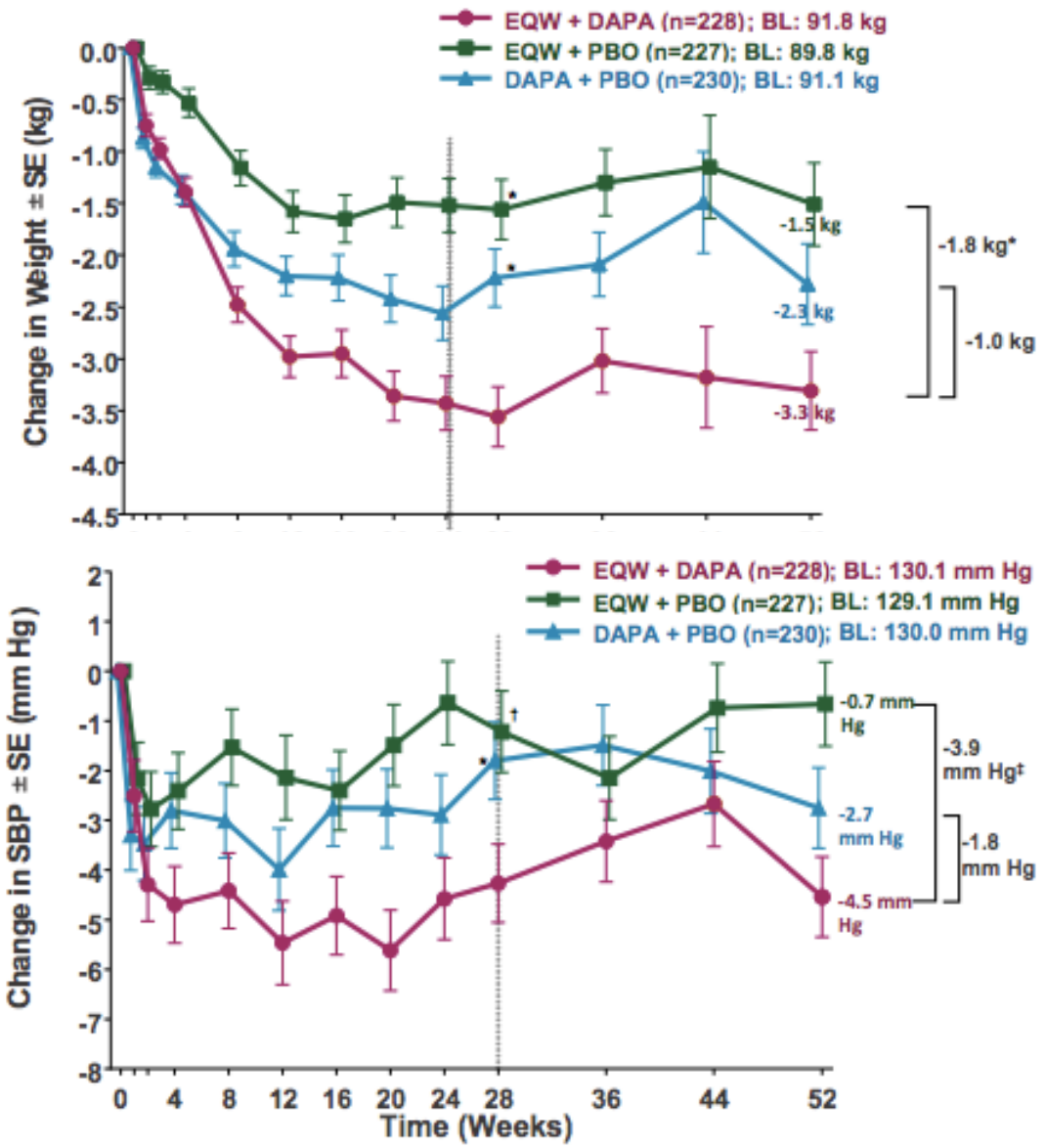
Safety and Efficacy of Exenatide Once Weekly Plus Dapagliflozin Once Daily Versus Exenatide or Dapagliflozin Alone in Patients With Type 2 Diabetes Inadequately Controlled With Metformin Monotherapy: 52-Week Results of the DURATION-8 Randomized Controlled Trial

Weight loss ≥5%:

EQW + PBO: 14%

DAPA + PBO: 20%

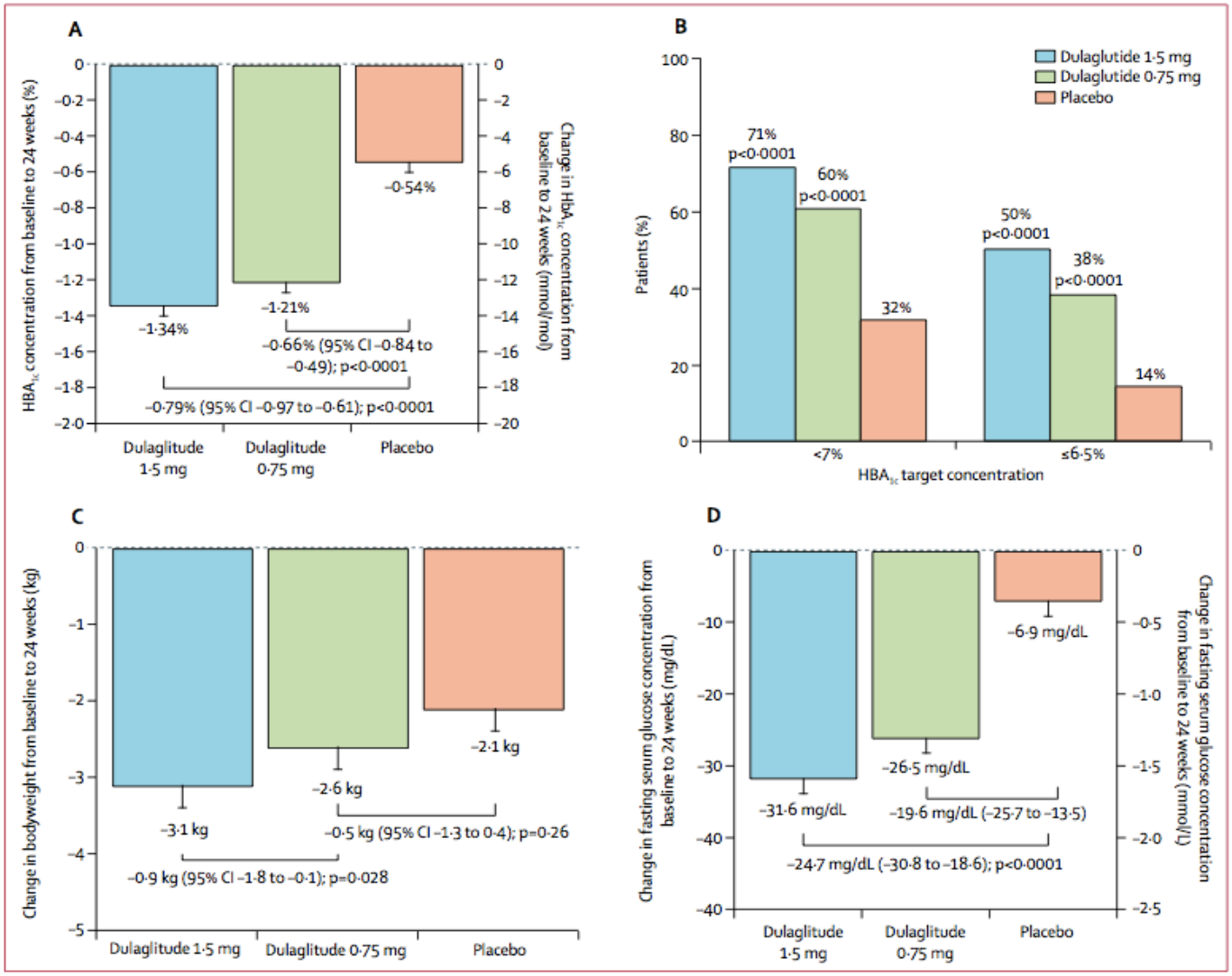
EQW + DAPA: 33%



Jabbour SA et al., Diabetes Care August 6, 2018

Dulaglutide as add-on therapy to SGLT2 inhibitors in patients with inadequately controlled type 2 diabetes (AWARD-10): a 24-week, randomised, double-blind, placebo-controlled trial

dulaglutide given as add-on treatment to any of the three available SGLT2 inhibitors (±metformin)



Ludvik B et al., Lancet Diabetes Endocrinol, February 23, 2018

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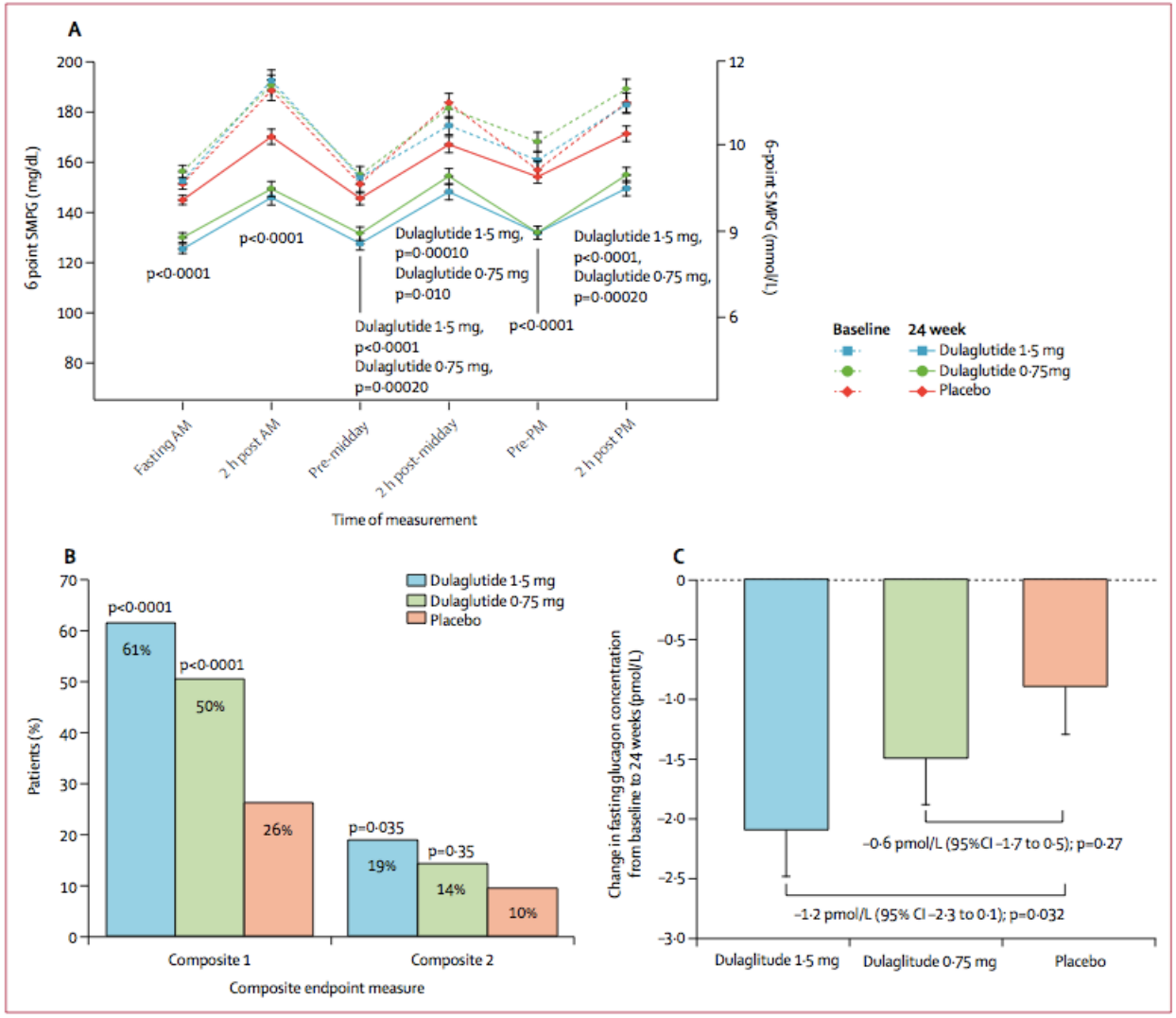


Ludvik B et al., Lancet Diabetes Endocrinol, February 23, 2018

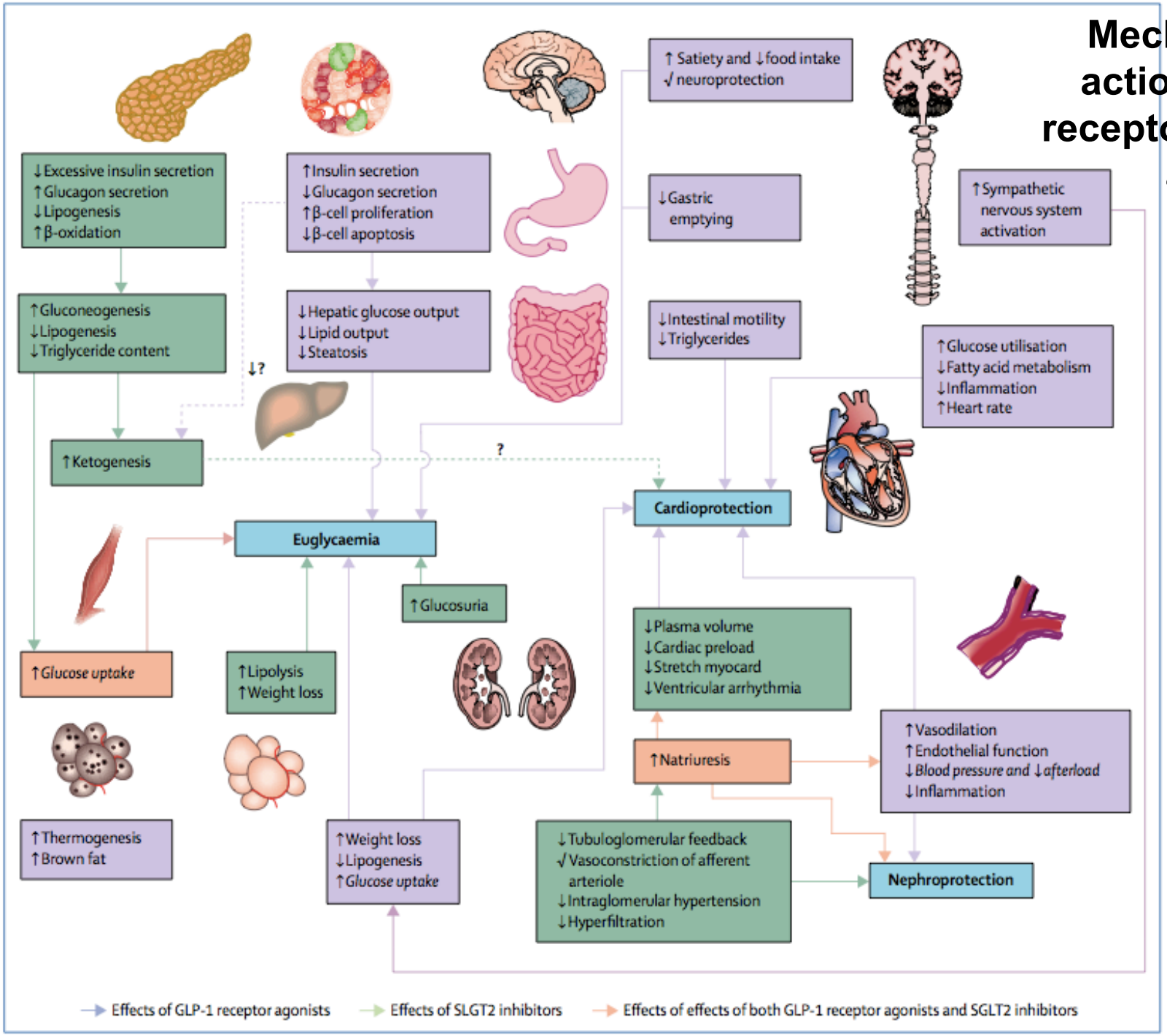
Expected and demonstrated net effects in combination therapy with SGLT2is in T2DM

			MET + SGLT2i				
	MET	SGLT2i	+GLP-1RA	+DPP-4i	+TZD	+SU	+Insulin
Insulin secretion	=	↓	↑	↑	↓	↑	↓
Glucagon secretion	↓	↑	=*	=	↑?	↓	↓
HGP	↓	↑	↑*	↑	↑	↓?	↓
Insulin sensitivity	↑	↑	↑↑	↑/↑↑	↑↑	↑	↑
Body weight	=/↓	↓	↓↓*	↓*	↑*	↓*	=*
Food intake	=/↓	↑	↓	↑?	↑?	↑?	↑?
SBP	=	↓	↓↓*	↓*	↓↓*	↓/=*	↓*
HDL/LDL ratio	=	=	↓*	=*	=/↑*	= *	=/↑*
Diuresis (osmotic and natriuretic)	=?	↑	↑↑	↑↑	↑/=	↑?	↑/=
Cardiovascular events	=	↓	↓↓	↓	↓	↓?	↓?
HF events	=	↓	↓	↓/=	↓/=	↓?	↓?
New or worsening of nephropathy	=?	↓	↓↓	↓	↓	↓?	↓?

All combined effects are expected effects based on single-drug effects, except for *, which are demonstrated net effects in combination studies.

Van Baar MJB et al., Diabetes Care 41: 1543-1556, 2018

Mechanisms of action of GLP-1 receptor agonists and SGLT2 inhibitors



The effects of GLP-1 receptor agonists are shown in purple boxes,

those of SGLT2 inhibitors in green boxes,

and those of both classes in orange boxes.

Progression of Contents

- DIABETES BURDEN TODAY
- CONSENSUS ADA-EASD 2018
- GLP-1 RA: AN UPDATING
- SGLT2i: AN UPDATING
- COMBINATION OF INNOVATIVES
- WHAT THE NEXT FUTURE HOLDS TO US

CREDENCE, Canagliflozin

Canagliflozin Renal Outcomes Study – Halted Early for Efficacy

•CREDENCE – Canagliflozin and Renal Events in Diabetes with Established Nephropathy Clinical Evaluation

•4,400 patients with T2DM and eGFR between 30 to 90 ml/min/1.73 mq on ACE inhibitors or ARBs

•Study halted nearly a year sooner = the primary composite endpoint (ESRD, doubling of serum creatinine, or Cv death) has been achieved

•SGLT2-i as the first therapy to treat patients with DKD and T2DM in more than 15 years

•CVD and DKD are inextricably linked in diabetes

REWIND, Dulaglutide

Superiority in reduction of cardiovascular events for broad range of T2DM

•REWIND – Researching cardiovascular Events with a Weekly INcretin in Diabetes

•A clinical trial (n. 9,901) that included a majority of participants who did not have established CV disease in a median follow-up period of more than 5 years.

•Only 31% of participants had established CVD at baseline.

•Dulaglutide significantly reduces major adverse cardiovascular events (MACE) across a broad range of people with T2DM

•The 9.901 participants had a mean duration of diabetes of 10 years and a mean baseline HbA1c of 7.3%.

unite for diabetes