

UPDATES IN TYPE 2 DIABETES PHARMACOTHERAPY

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CASE: MR. JONES ONE

- 68y/o male with type 2 DM dx 8 yrs ago, HTN dx 10 yrs ago, hyperlipidemia dx 5 yrs ago, and obesity since age 40. Was admitted to the hospital with an MI 2 mo ago, this is his first follow-up with you since then.
- Meds: High-intensity statin, anti-platelet therapy, ACEI, beta-blocker, metformin, sulfonylurea, DPP IV inhibitor
- BP 128/78, BMI 41
- Labs: HbA1c 7.9%, LDL 62, eGFR 70

+ASCVD/Indicators of High Risk

- Established ASCVD
- Indicators of high ASCVD risk (age ≥ 55 years with coronary, carotid, or lower-extremity artery stenosis $>50\%$, or LVH)

EITHER/
OR

GLP-1
RA with
proven
CVD
benefit¹

SGLT2i
with
proven
CVD
benefit¹

If A1C above target

If further intensification is required or patient is unable to tolerate GLP-1 RA and/or SGLT2i, choose agents demonstrating CV benefit and/or safety:

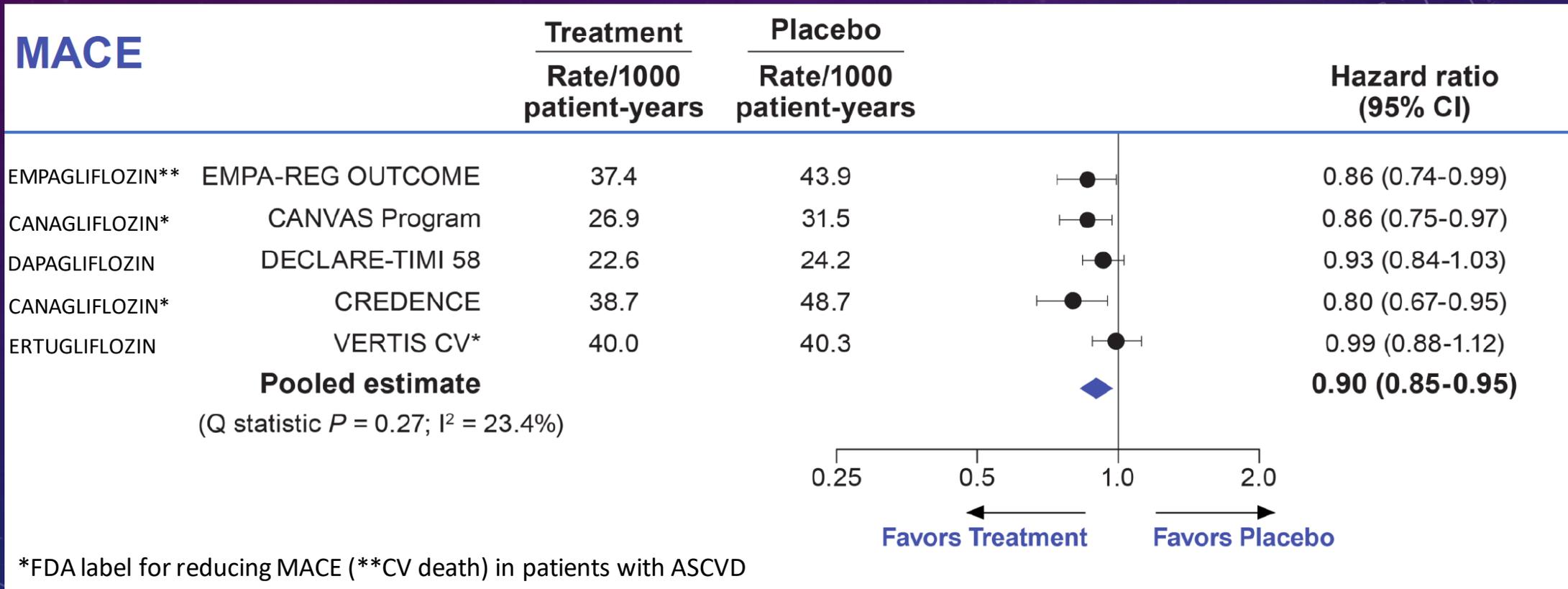
- For patients on a GLP-1 RA, consider adding SGLT2i with proven CVD benefit and vice versa¹
- TZD²
- DPP-4i if not on GLP-1 RA
- Basal insulin³
- SU⁴

TREATMENT RECOMMENDATIONS FOR PATIENTS WITH T2DM AND ASCVD

- Use GLP-1 RA* or SGLT2i* for cardio-protection
- Recommendation first noted in the 2018 ADA/EASD treatment consensus
 - Revised (and stronger) in subsequent years
- Based on results of the CVOT trials in diabetes which became a regulatory requirement starting 2008

*with proven CV benefit

SGLT2 INHIBITORS ON CV EVENTS (MACE) IN PATIENTS WITH T2DM AND ASCVD



GLP-1 RECEPTOR AGONISTS ON CV EVENTS (MACE) IN PATIENTS WITH T2DM AND ASCVD

	GLP-1 receptor agonist n/N (%)	Placebo n/N (%)		Hazard ratio (95% CI)	NNT (95% CI)	p value
Three-component MACE						
ELIXA	LIXISENATIDE 400/3034 (13%)	392/3034 (13%)		1.02 (0.89-1.17)		0.78
LEADER	LIRAGLUTIDE* 608/4668 (13%)	694/4672 (15%)		0.87 (0.78-0.97)		0.015
SUSTAIN-6	SEMAGLUTIDE QW* 108/1648 (7%)	146/1649 (9%)		0.74 (0.58-0.95)		0.016
EXSCEL	EXENATIDE QW 839/7356 (11%)	905/7396 (12%)		0.91 (0.83-1.00)		0.061
Harmony	ALBIGLUTIDE 338/4731 (7%)	428/4732 (9%)		0.78 (0.68-0.90)		<0.0001
REWIND	DULAGLUTIDE* 594/4949 (12%)	663/4952 (13%)		0.88 (0.79-0.99)		0.026
PIONEER 6	SEMAGLUTIDE po 61/1591 (4%)	76/1592 (5%)		0.79 (0.57-1.11)		0.17
Overall ($I^2=40.9%$, $p=0.118$)	2948/27 977 (11%)	3304/28 027 (12%)		0.88 (0.82-0.94)	75 (50-151)	<0.0001

*FDA indication for prevention of MACE in patients with ASCVD

CASE: MR. JONES TWO

- 68y/o male with type 2 DM dx 8 yrs ago, HTN dx 10 yrs ago, hyperlipidemia dx 5 yrs ago, and obesity since age 40. Was admitted to the hospital with an MI 2 mo ago, this is his first follow-up with you since then.
- Meds: High-intensity statin, anti-platelet therapy, ACEI, beta-blocker, metformin, sulfonylurea, DPP IV inhibitor
- BP 128/78, BMI 41
- Labs: **HbA1c 6.1%**, LDL 62, eGFR 70

CARDIO (OR RENAL)-PROTECTIVE AGENTS SHOULD BE USED INDEPENDENT OF HBA1C (OR METFORMIN USE)

INDICATORS OF HIGH-RISK OR ESTABLISHED ASCVD, CKD, OR HF†

**CONSIDER INDEPENDENTLY OF BASELINE A1C,
INDIVIDUALIZED A1C TARGET, OR METFORMIN USE***

- If indicated for cardio- or renal-protection, these agents should be used irrespective of HbA1c
- Risk of hypoglycemia with these agents (both GLP-1 RA and SGLT2i) is very low (in the absence of SU or INS co-treatment)

PRACTICAL APPROACH FOR INITIATING CARDIO-PROTECTIVE AGENTS IN PATIENTS ALREADY AT HBA1C TARGET

- If on SU: substitute SU for new agent
- If on INS: half insulin dose at initiation of new agent
 - Monitor closely and down-titrate insulin further if hypoglycemia
- If not on SU or INS: add new agent
 - De-escalate treatment as follows:
 - stop agents that are not cardioprotective (DPP IV, etc)
 - hypoglycemia occurs (rare) – de-escalate gradually to SGLT2i or GLP-1 RA mono-therapy

CASE: MR. JONES THREE

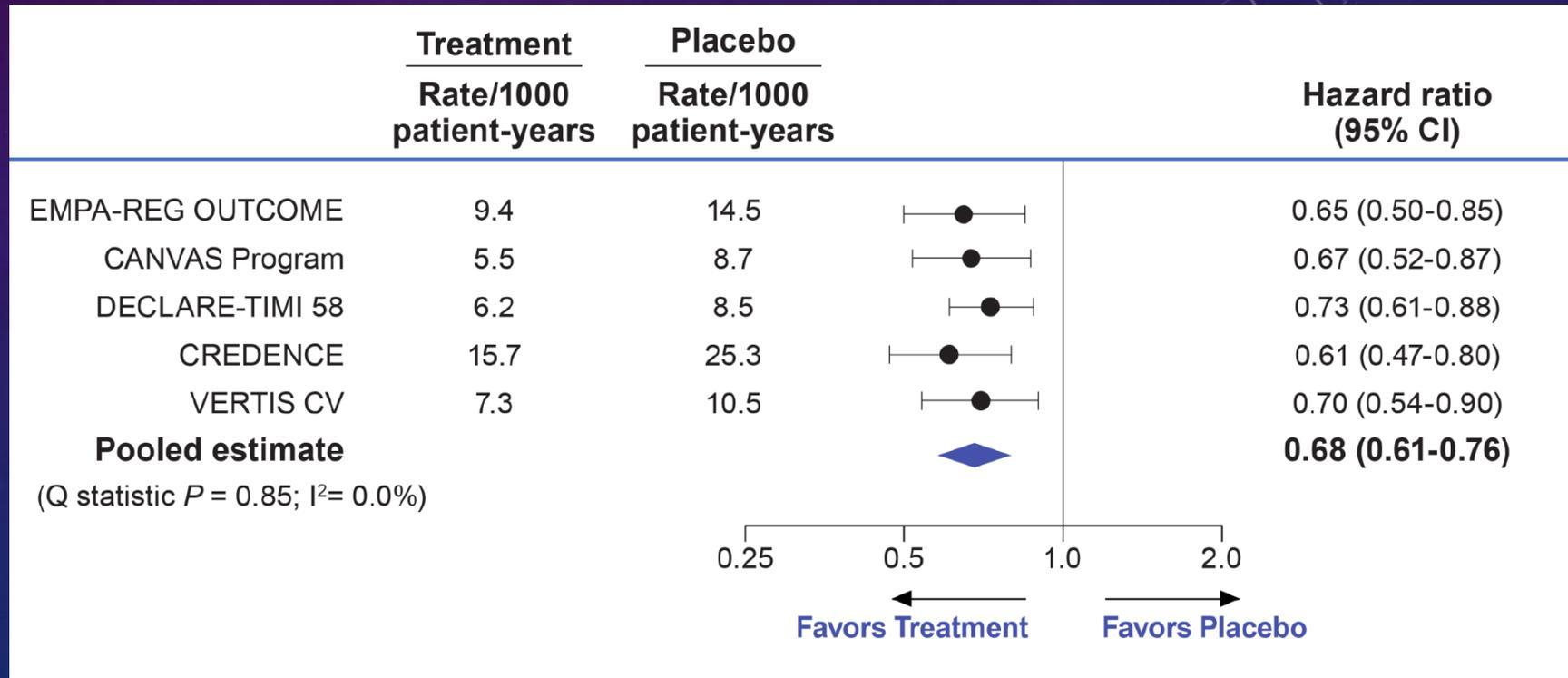
- 68y/o male with type 2 DM dx 8 yrs ago, HTN dx 10 yrs ago, hyperlipidemia dx 5 yrs ago, and obesity since age 40. Was admitted to the hospital with **congestive heart failure with EF of 25%** 2 mo ago, this is his first follow-up with you since then.
- Meds: High-intensity statin, **furosemide**, ACEI, beta-blocker, metformin, sulfonylurea, DPP IV inhibitor
- BP 128/78, BMI 41
- Labs: HbA1c 7.9%, LDL 62, eGFR 70

TREATMENT OF PATIENTS WITH T2DM AND HF

+HF

Particularly HFrEF
(LVEF <45%)

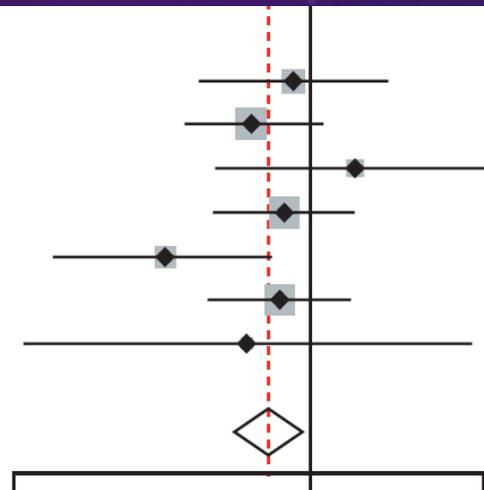
SGLT2i with proven
benefit in this
population^{5,6,7}



HHF WITH GLP-1 RA

Hospital admission for heart failure

ELIXA	122/3034 (4%)	127/3034 (4%)
LEADER	218/4668 (5%)	248/4672 (5%)
SUSTAIN-6	59/1648 (4%)	54/1649 (3%)
EXSCEL	219/7356 (3%)	231/7396 (3%)
Harmony Outcomes	79/4731 (2%)	111/4732 (2%)
REWIND	213/4949 (4%)	226/4952 (5%)
PIONEER 6	21/1591 (1%)	24/1592 (2%)



0.96 (0.75-1.23)	0.75
0.87 (0.73-1.05)	0.14
1.11 (0.77-1.61)	0.57
0.94 (0.78-1.13)	0.51
0.71 (0.53-0.94)	<0.0001
0.93 (0.77-1.12)	0.46
0.86 (0.48-1.44)	0.59
Overall ($I^2=0.0\%$, $p=0.595$)	0.91 (0.83-0.99)
312 (165 to 2810)	0.028

CASE: MR. JONES FOUR

- 68y/o male with type 2 DM dx 8 yrs ago, HTN dx 10 yrs ago, hyperlipidemia dx 5 yrs ago, obesity since age 40, and **diabetic nephropathy** dx 1 yr ago.
- Meds: High-intensity statin, anti-platelet therapy, ACEI, **diuretic**, beta-blocker, metformin, sulfonyleurea, DPP IV inhibitor
- BP 128/78, BMI 41
- Labs: HbA1c 7.9%, LDL 62, **eGFR 50, UACR 570**

+CKD

DKD and
Albuminuria⁸

PREFERABLY

SGLT2i with
primary evidence
of reducing CKD
progression

OR

SGLT2i with
evidence of
reducing CKD
progression in
CVOTs^{5,6,8}

OR

GLP-1 RA with
proven CVD
benefit¹ if SGLT2i
not tolerated or
contraindicated

For patients with T2D
and CKD⁸ (e.g., eGFR
<60 mL/min/1.73 m²) and
thus at increased risk of
cardiovascular events

EITHER/
OR

GLP-1
RA with
proven
CVD
benefit¹

SGLT2i
with
proven
CVD
benefit^{1,7}

TREATMENT OF T2DM WITH DKD

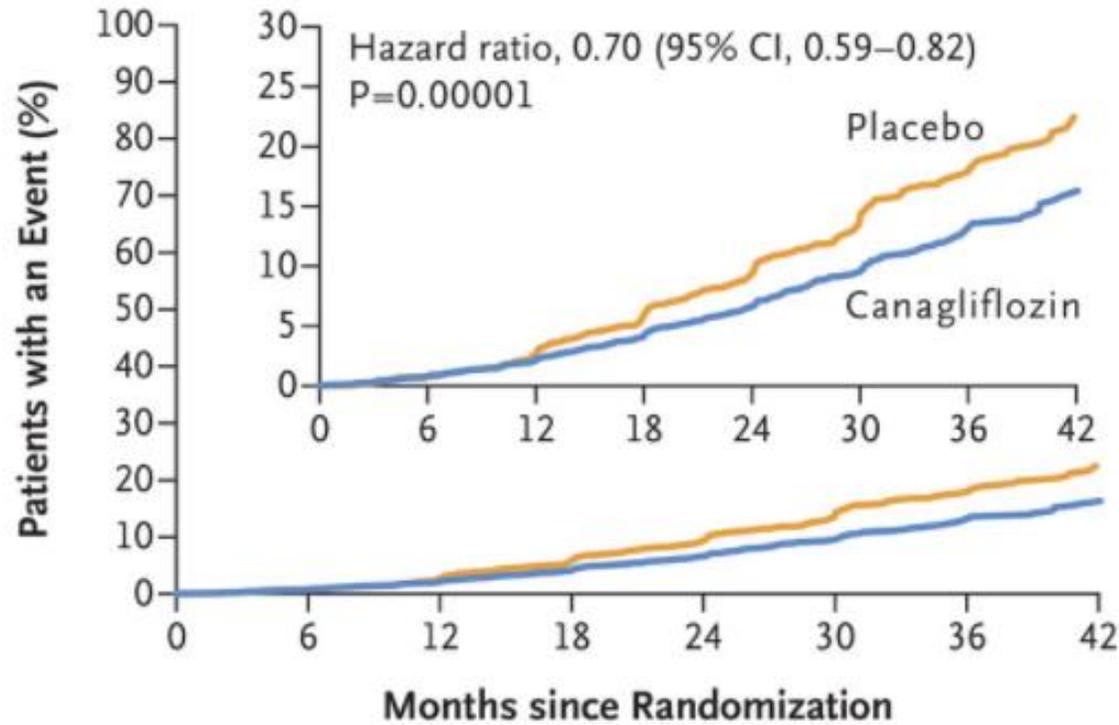
- Goals of treatment are:
 - reduce CKD progression
 - prevent MACE
- Treatment recommendations:
 - Use SGLT2i if eGFR >30 AND ACR >300*
 - Use SGLT2i or GLP-1 RA if CKD with normoalbuminuria
 - Use GLP-1 RA if eGFR <30

*FDA label for canagliflozin

CREDENCE

DAPA-CKD

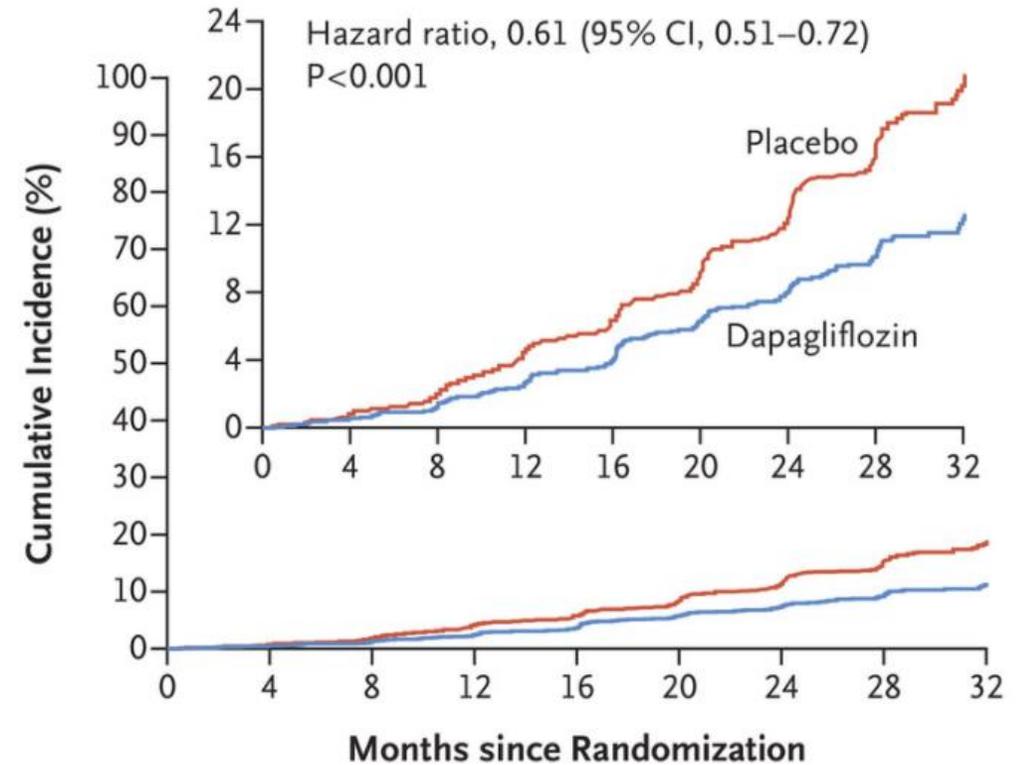
A Primary Composite Outcome



No. at Risk

Placebo	2199	2178	2132	2047	1725	1129	621	170
Canagliflozin	2202	2181	2145	2081	1786	1211	646	196

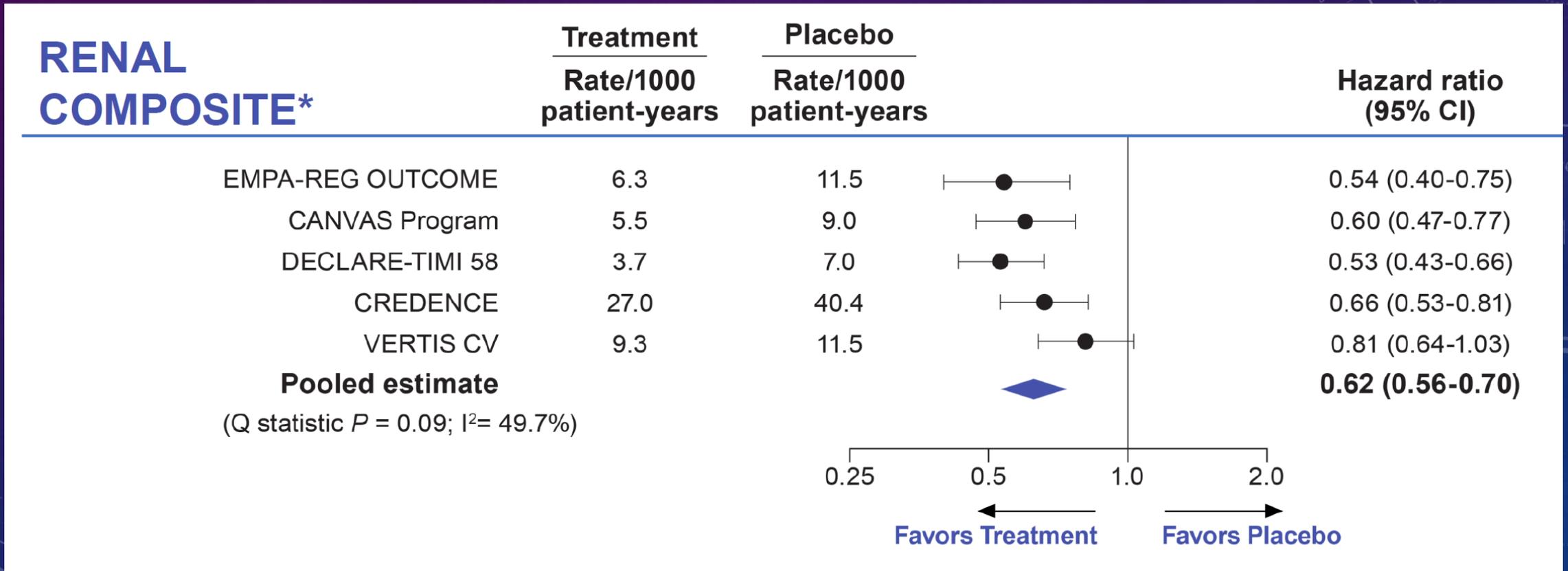
A Primary Composite Outcome



No. at Risk

Placebo	2152	1993	1936	1858	1791	1664	1232	774	270
Dapagliflozin	2152	2001	1955	1898	1841	1701	1288	831	309

RENAL OUTCOMES WITH SGLT2 INHIBITORS



RENAL OUTCOMES WITH GLP-1 RA

Composite kidney outcome including macroalbuminuria

ELIXA	172/2639 (6%)	203/2647 (6%)		0.84 (0.68-1.02)	0.083	
LEADER	268/4668 (6%)	337/4672 (7%)		0.78 (0.67-0.92)	0.003	
SUSTAIN-6	62/1648 (4%)	100/1649 (6%)		0.64 (0.46-0.88)	0.006	
EXSCEL	366/6256 (6%)	407/6222 (7%)		0.88 (0.76-1.01)	0.065	
REWIND	848/4949 (17%)	970/4952 (20%)		0.85 (0.77-0.93)	0.0004	
Overall ($I^2=0.0\%$, $p=0.413$)	1716/20160 (9%)	2017/20142 (10%)		0.83 (0.78-0.89)	62 (48 to 96)	<0.0001

Worsening of kidney function

ELIXA	35/3032 (1%)	41/3031 (1%)		1.16 (0.74-1.83)	0.51	
LEADER	87/4668 (2%)	97/4672 (2%)		0.89 (0.67-1.19)	0.43	
SUSTAIN-6	18/1648 (1%)	14/1649 (1%)		1.28 (0.64-2.58)	0.48	
EXSCEL	246/6456 (4%)	273/6458 (4%)		0.88 (0.74-1.05)	0.16	
REWIND	169/4949 (3%)	237/4952 (5%)		0.70 (0.57-0.85)	0.0004	
Overall ($I^2=42.7\%$, $p=0.137$)	555/20753 (3%)	662/20762 (3%)		0.87 (0.73-1.03)	245 (118 to -1064†)	0.098

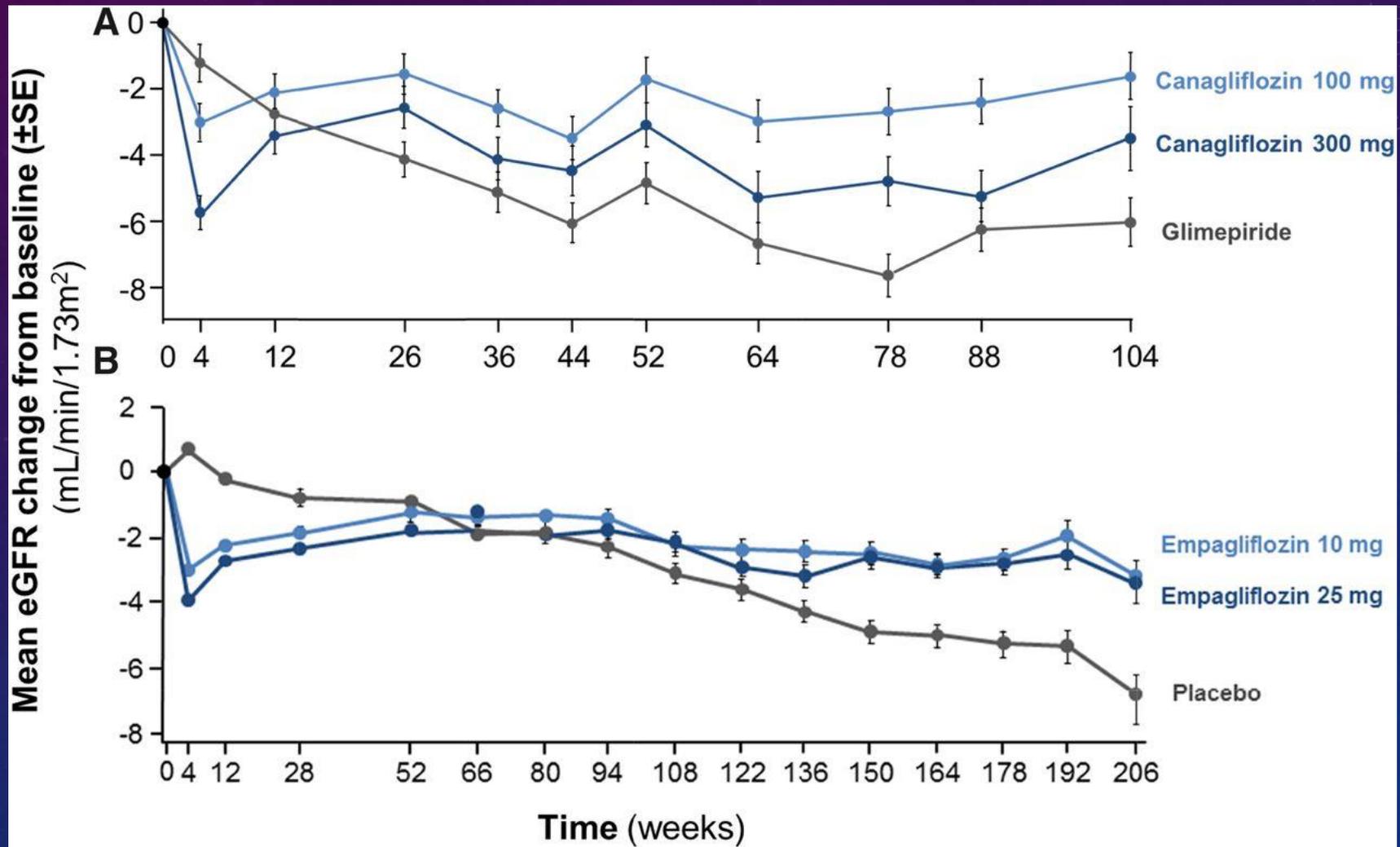
SGLT2 INHIBITORS AND RENAL FUNCTION

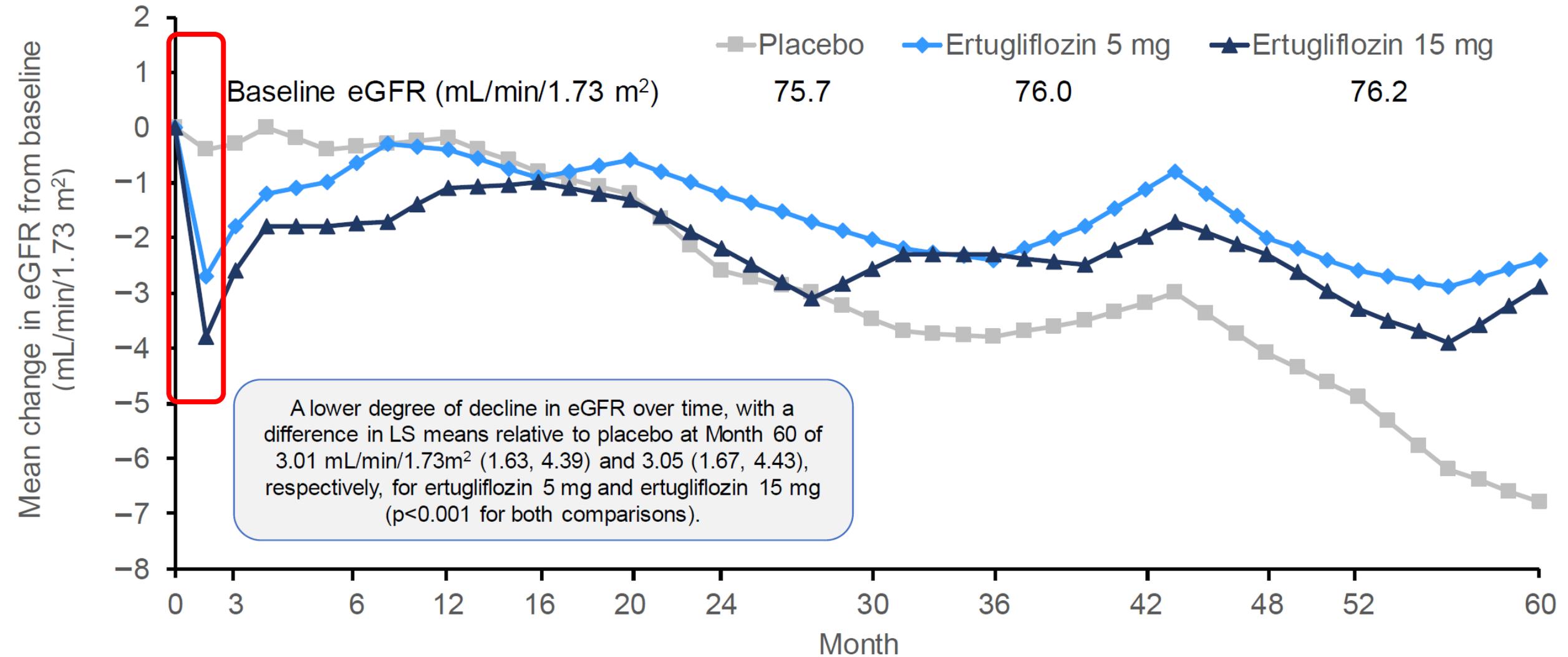
- All SGLT2 inh: not indicated when eGFR <45, contraindicated when eGFR <30 **when used for glycemic control**
- Canagliflozin:
 - Indicated for CKD (eGFR>30) with ACR>300
 - Use 100 mg if eGFR<60
- Empa and dapa submitted for CKD indication, review pending

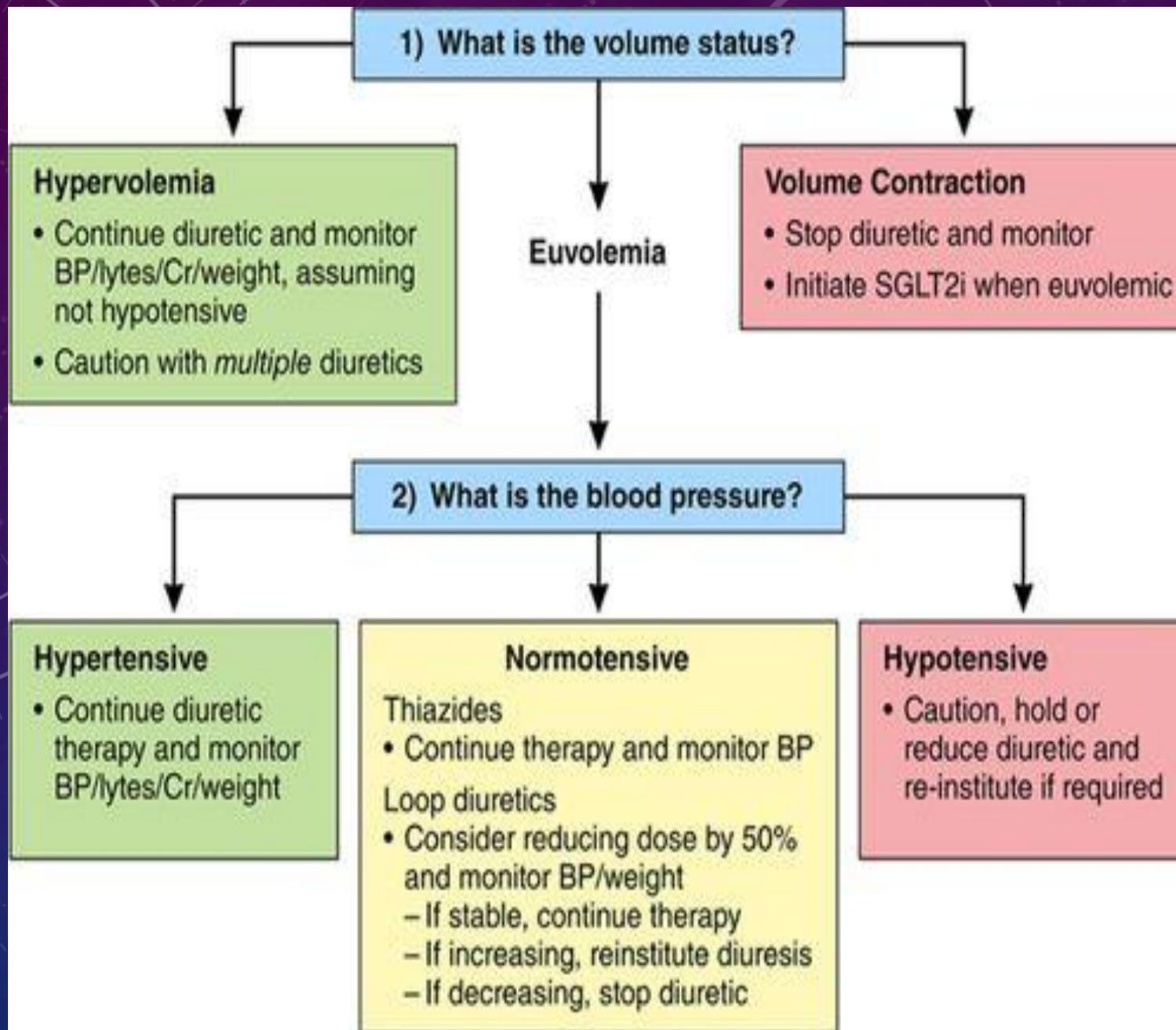
CASE: MR. JONES FIVE

- 68y/o male with type 2 DM dx 8 yrs ago, HTN dx 10 yrs ago, hyperlipidemia dx 5 yrs ago, obesity since age 40, and **diabetic nephropathy** dx 1 yr ago.
- Meds: High-intensity statin, anti-platelet therapy, ACEI, **diuretic**, beta-blocker, metformin, sulfonyleurea, DPP IV inhibitor
- BP 128/78, BMI 41, **no pedal edema**
- Labs: HbA1c 8.1%, LDL 62, **eGFR 50, ACR 570**
- **You started him on an SGLT2 inhibitor and rechecked his labs in 10 days – eGFR decreased to 39. What do you do?**

EGFR COURSE WITH SGLT2 INHIBITORS

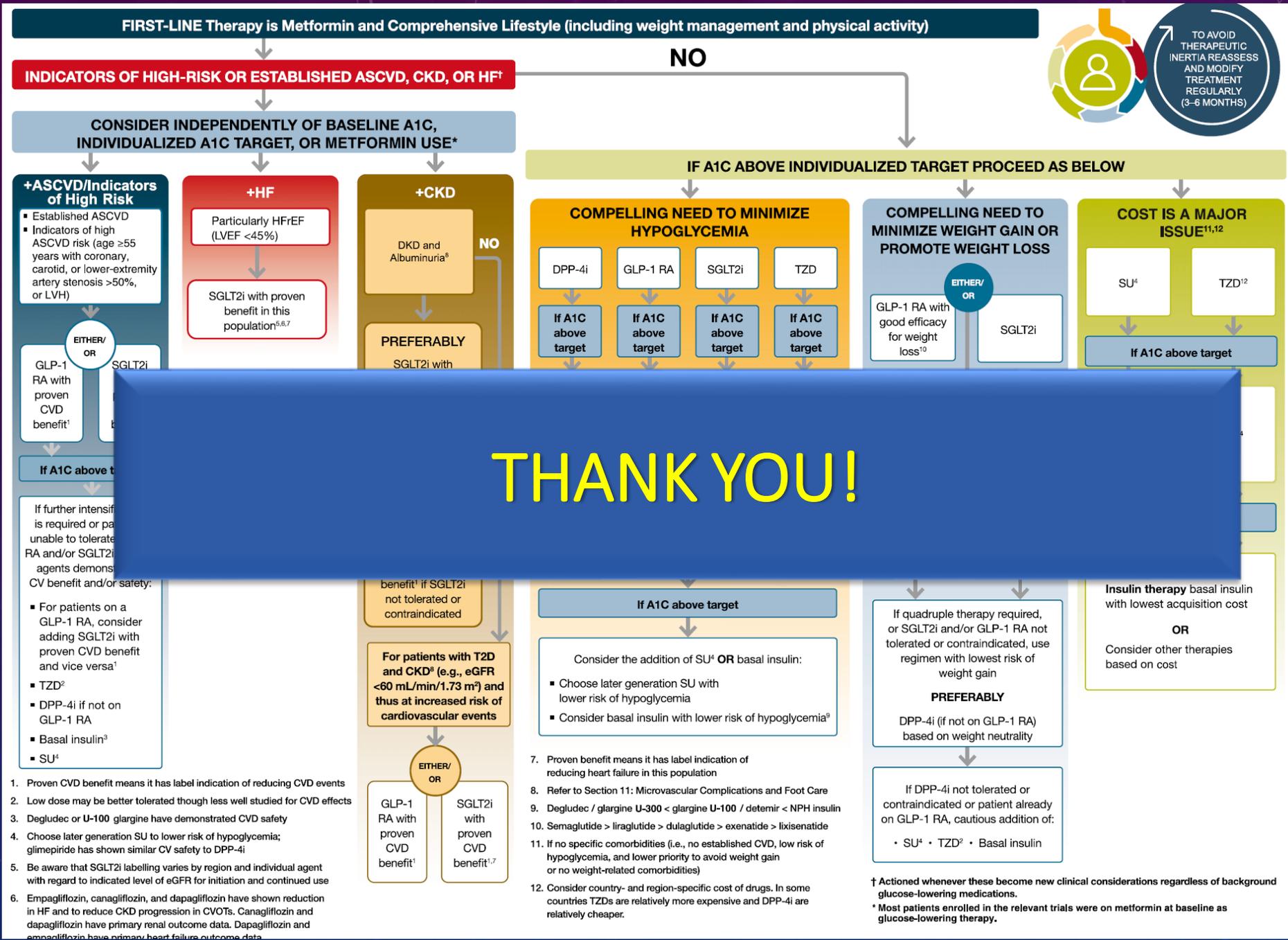






TAKE HOME MESSAGES

- In patients with type 2 diabetes and:
 - ASCVD: ensure use of GLP-1 RA or SGLT2i **IRRESPECTIVE** of HbA1c → reduce MACE
 - HF: ensure use of SGLT2i → reduced HHF and CV death
 - eGFR 30-60 AND ACR>300: use SGLT2i → reduce progression of CKD
 - eGFR<30: use GLP-1 RA → reduce MACE
- SGLT2i lead to a transient decrease in eGFR which should NOT prompt drug discontinuation
 - Consider fluid status & BP before starting an SGLT2i, especially if already on diuretic



- Proven CVD benefit means it has label indication of reducing CVD events
- Low dose may be better tolerated though less well studied for CVD effects
- Degludec or U-100 glargine have demonstrated CVD safety
- Choose later generation SU to lower risk of hypoglycemia; glimepiride has shown similar CV safety to DPP-4i
- Be aware that SGLT2i labelling varies by region and individual agent with regard to indicated level of eGFR for initiation and continued use
- Empagliflozin, canagliflozin, and dapagliflozin have shown reduction in HF and to reduce CKD progression in CVOTs. Canagliflozin and dapagliflozin have primary renal outcome data. Dapagliflozin and empagliflozin have primary heart failure outcome data

- Proven benefit means it has label indication of reducing heart failure in this population
- Refer to Section 11: Microvascular Complications and Foot Care
- Degludec / glargine U-300 < glargine U-100 / detemir < NPH insulin
- Semaglutide > liraglutide > dulaglutide > exenatide > lixisenatide
- If no specific comorbidities (i.e., no established CVD, low risk of hypoglycemia, and lower priority to avoid weight gain or no weight-related comorbidities)
- Consider country- and region-specific cost of drugs. In some countries TZDs are relatively more expensive and DPP-4i are relatively cheaper.

† Actioned whenever these become new clinical considerations regardless of background glucose-lowering medications.

* Most patients enrolled in the relevant trials were on metformin at baseline as glucose-lowering therapy.