UPDATES IN TYPE 2 DIABETES PHARMACOTHERAPY

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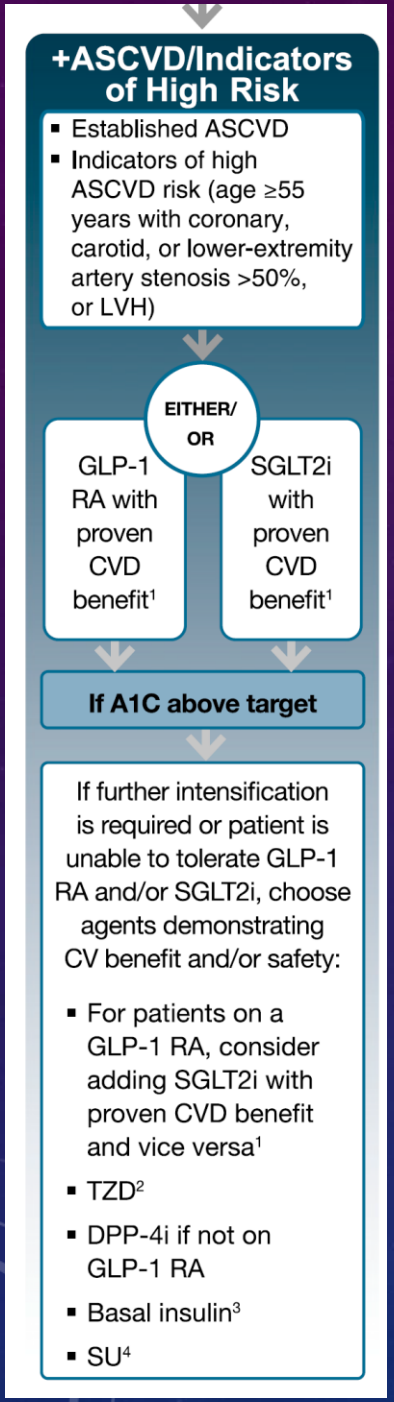
CASE: MR. JONES ONE

- 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



TREATMENT RECOMMENDATIONS FOR PATIENTS WITH T2DM AND ASCVD

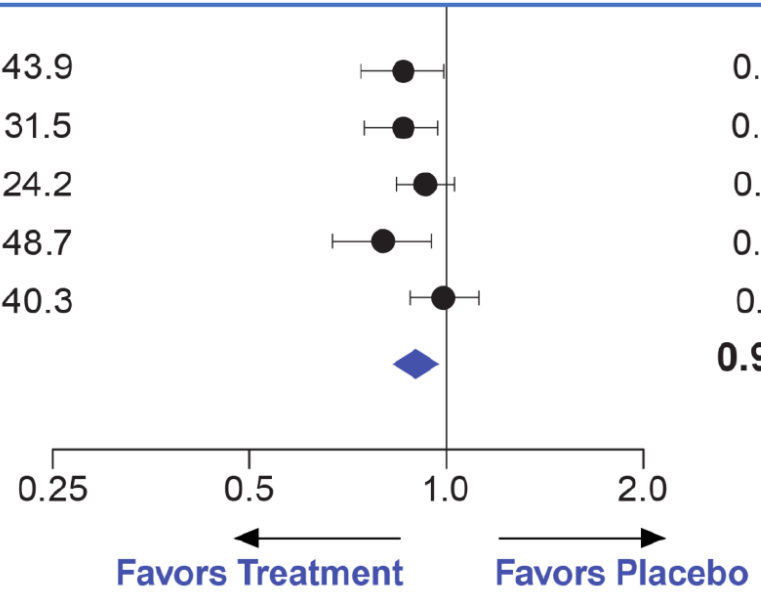
- Use GLP-1 RA* or SGLT2i* for cardio-protection
- Recommendation first noted in the 2018 ADA/EASD treatment consensus
  - Revised (and stronger) in subsequent years
- Based on results of the CVOT trials in diabetes which became a regulatory requirement starting 2008

**with proven CV benefit*

American Diabetes Association. Standards of Medical Care 2021

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

MACE		Treatment Rate/1000 patient-years	Placebo Rate/1000 patient-years	Hazard ratio (95% CI)
EMPAGLIFLOZIN**	EMPA-REG OUTCOME	37.4	43.9	0.86 (0.74-0.99)
CANAGLIFLOZIN*	CANVAS Program	26.9	31.5	0.86 (0.75-0.97)
DAPAGLIFLOZIN	DECLARE-TIMI 58	22.6	24.2	0.93 (0.84-1.03)
CANAGLIFLOZIN*	CREDENCE	38.7	48.7	0.80 (0.67-0.95)
ERTUGLIFLOZIN	VERTIS CV*	40.0	40.3	0.99 (0.88-1.12)
	Pooled estimate			**0.90 (0.85-0.95)**
	(Q statistic $P = 0.27$; $I^2 = 23.4\%$)			

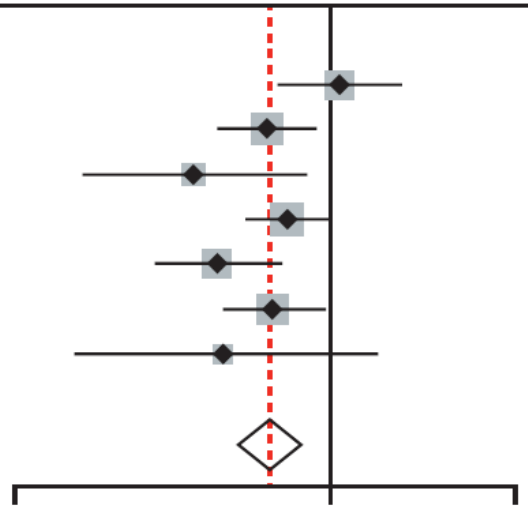


*FDA label for reducing MACE (**CV death) in patients with ASCVD

McGuire DK. JAMA Cardiology 2020

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

Kristensen SL. LancetD&E 2019

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)

- 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)

American Diabetes Association. Standards of Medical Care 2021

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-escalatate 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

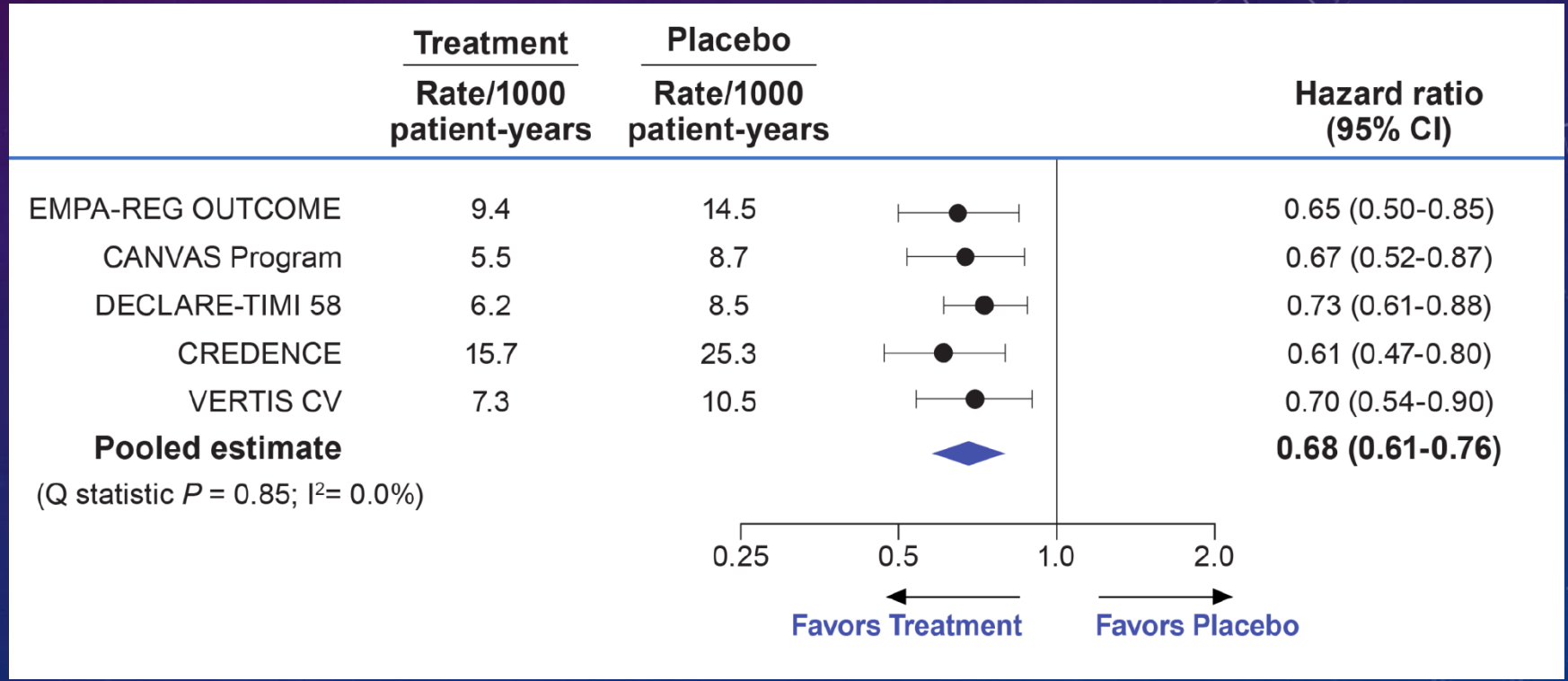
- 68y/o male with type 2 DM dx 8 yrs ago, HTN dx 10 yrs ago, hyperlipidemia dx 5 yrs ago, and obesity since age 40. Was admitted to the hospital with **congestive heart failure with EF of 25%** 2 mo ago, this is his first follow-up with you since then.
- Meds: High-intensity statin, **furosemide**, ACEI, 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]

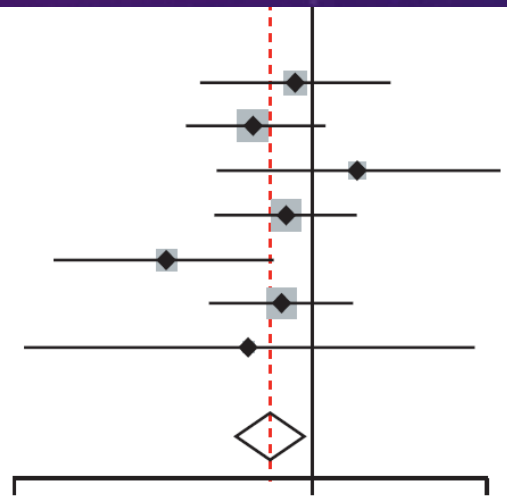


McGuire DK. JAMA Cardiology 2020

American Diabetes Association. Standards of Medical Care 2021

HHF WITH GLP-1 RA

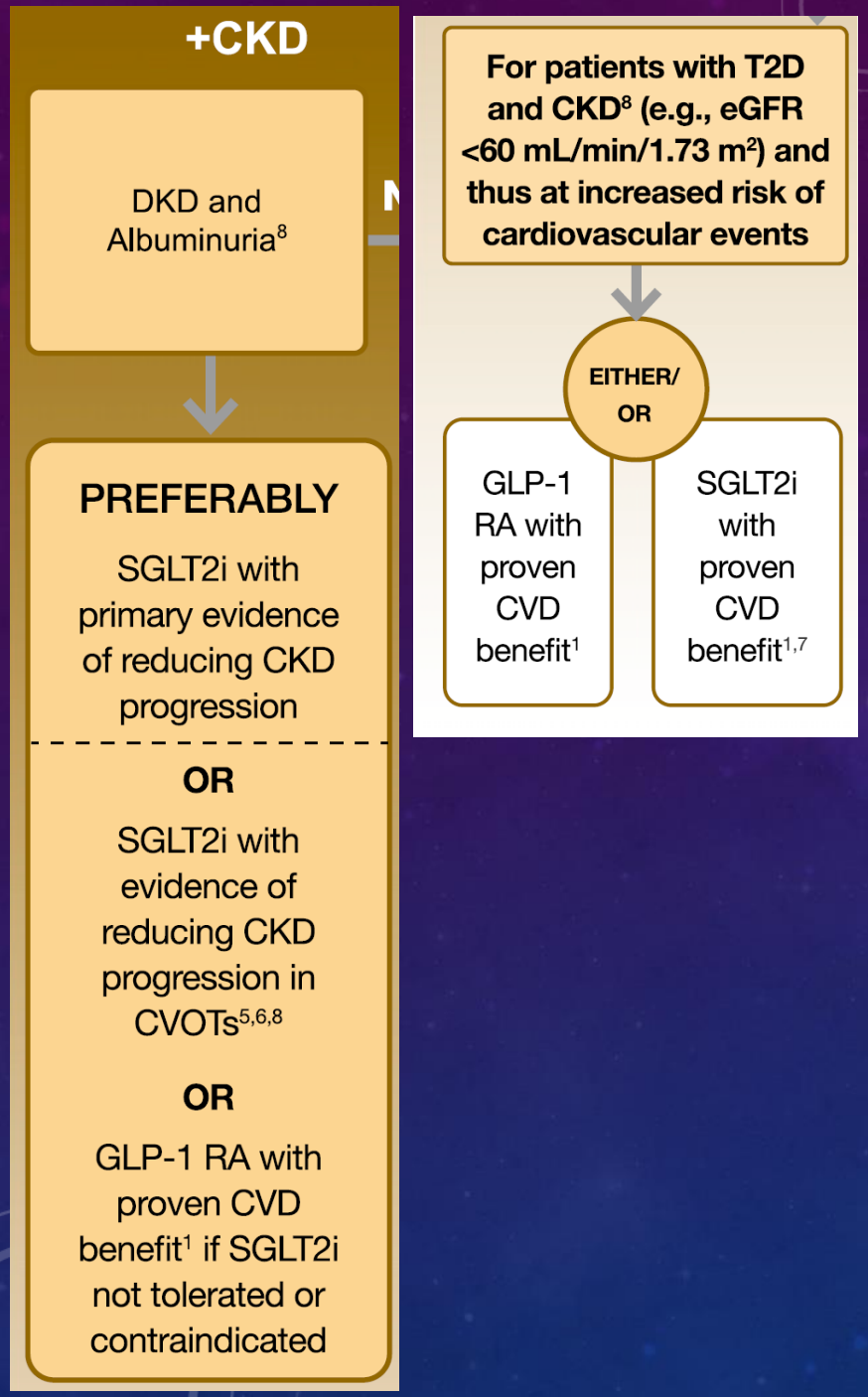
Hospital admission for heart failure					
ELIXA	122/3034 (4%)	127/3034 (4%)	0·96 (0·75–1·23)		0·75
LEADER	218/4668 (5%)	248/4672 (5%)	0·87 (0·73–1·05)		0·14
SUSTAIN-6	59/1648 (4%)	54/1649 (3%)	1·11 (0·77–1·61)		0·57
EXSCEL	219/7356 (3%)	231/7396 (3%)	0·94 (0·78–1·13)		0·51
Harmony Outcomes	79/4731 (2%)	111/4732 (2%)	0·71 (0·53–0·94)		<0·0001
REWIND	213/4949 (4%)	226/4952 (5%)	0·93 (0·77–1·12)		0·46
PIONEER 6	21/1591 (1%)	24/1592 (2%)	0·86 (0·48–1·44)		0·59
Overall (I^2=0·0%, p=0·595)	**936/27 977 (3%)**	**1016/28 027 (4%)**	**0·91 (0·83–0·99)**	**312 (165 to 2810)**	**0·028**



Kristensen SL. LancetD&E 2019

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, sulfonylurea, DPP IV inhibitor
- BP 128/78, BMI 41
- Labs: HbA1c 7.9%, LDL 62, **eGFR 50, UACR 570**



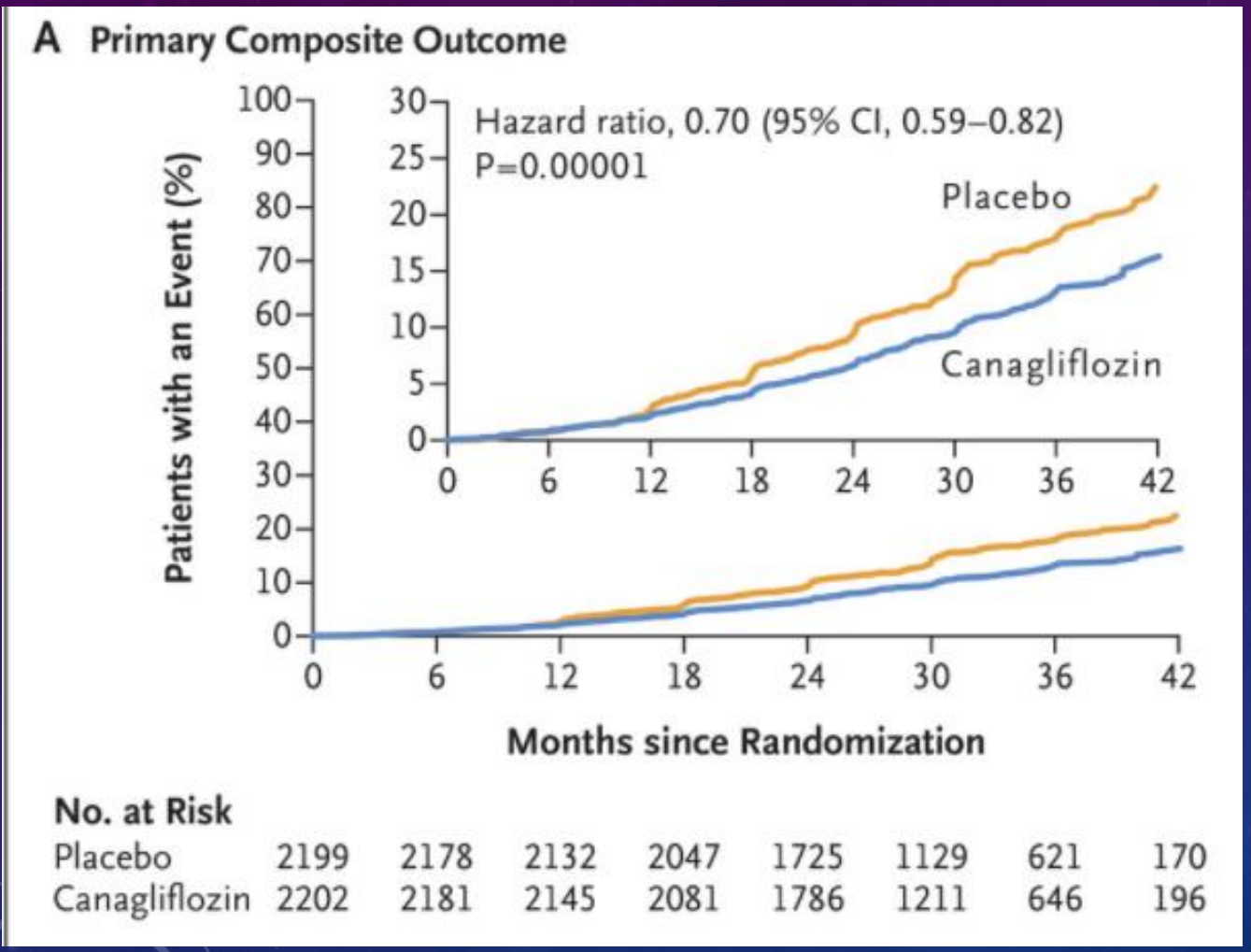
TREATMENT OF T2DM WITH DKD

- 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

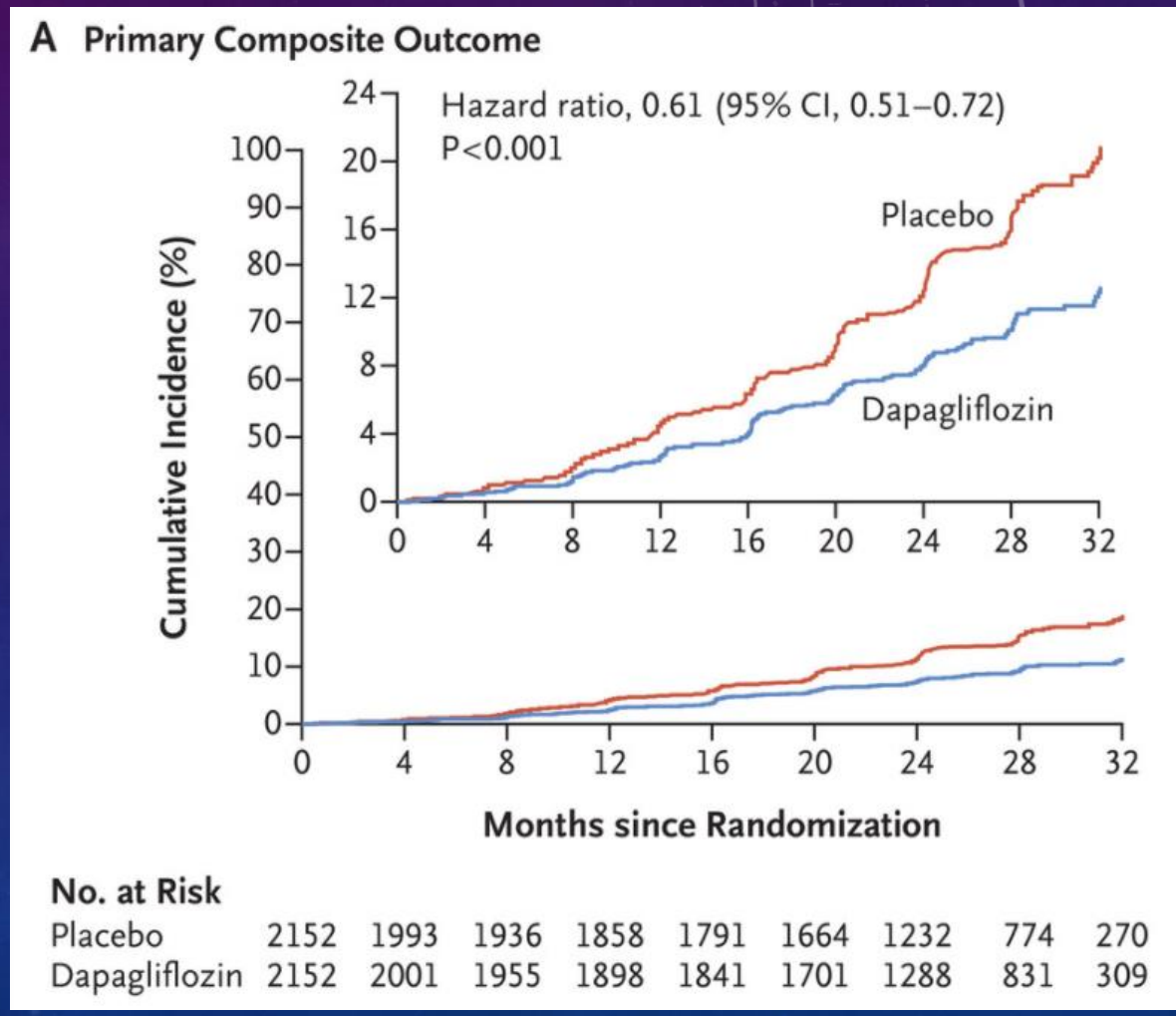
American Diabetes Association. Standards of Medical Care 2021

CREDENCE



Perkovic V. NEJM 2019

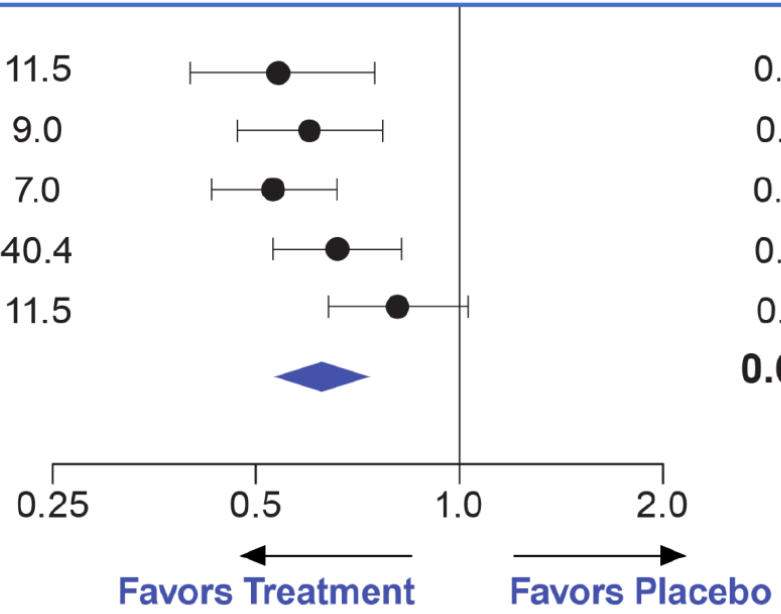
DAPA-CKD



Heerspink HJL. NEJM 2020

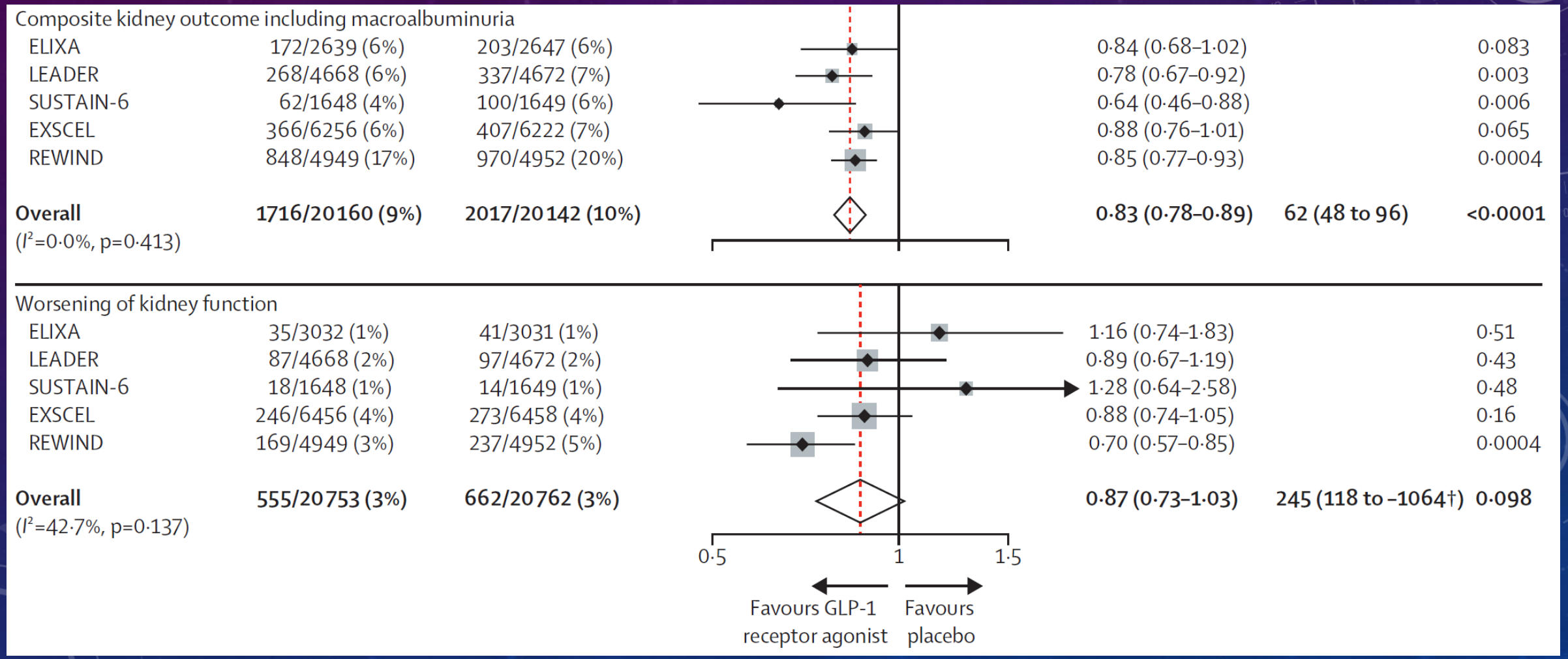
RENAL OUTCOMES WITH SGLT2 INHIBITORS

RENAL COMPOSITE*	Treatment Rate/1000 patient-years	Placebo Rate/1000 patient-years	Hazard ratio (95% CI)
EMPA-REG OUTCOME	6.3	11.5	0.54 (0.40-0.75)
CANVAS Program	5.5	9.0	0.60 (0.47-0.77)
DECLARE-TIMI 58	3.7	7.0	0.53 (0.43-0.66)
CREDENCE	27.0	40.4	0.66 (0.53-0.81)
VERTIS CV	9.3	11.5	0.81 (0.64-1.03)
Pooled estimate			**0.62 (0.56-0.70)**
(Q statistic P = 0.09; I^2= 49.7%)			



McGuire DK. JAMA Cardiology 2020

RENAL OUTCOMES WITH GLP-1 RA



Kristensen SL. LancetD&E 2019

SGLT2 INHIBITORS AND RENAL FUNCTION

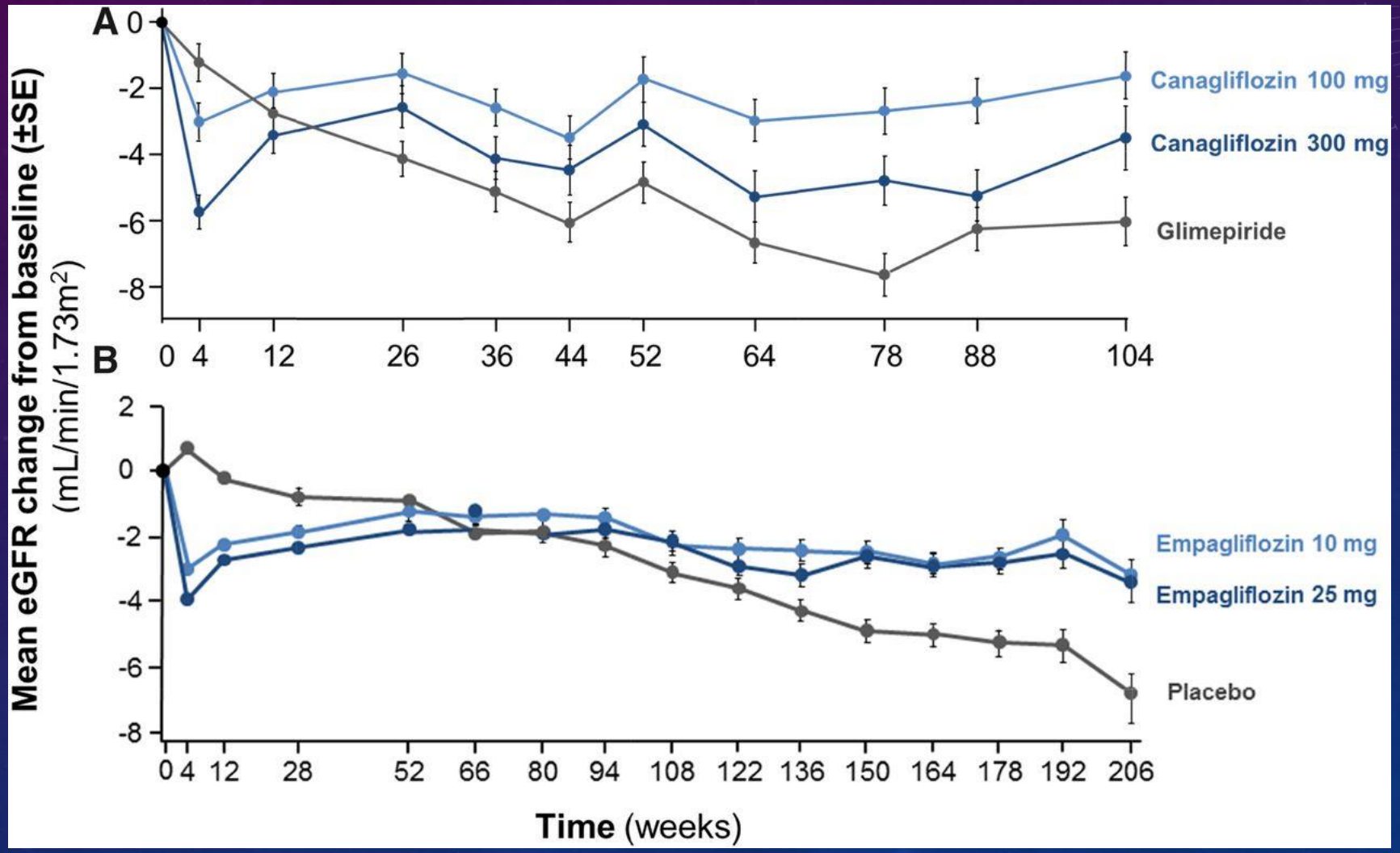
- All SGLT2 inh: not indicated when eGFR <45, contraindicated when eGFR <30 **when used for glycemic control**
- Canagliflozin:
  - Indicated for CKD (eGFR>30) with ACR>300
  - Use 100 mg if eGFR<60
- Empa and dapa submitted for CKD indication, review pending

American Diabetes Association. Standards of Medical Care 2021

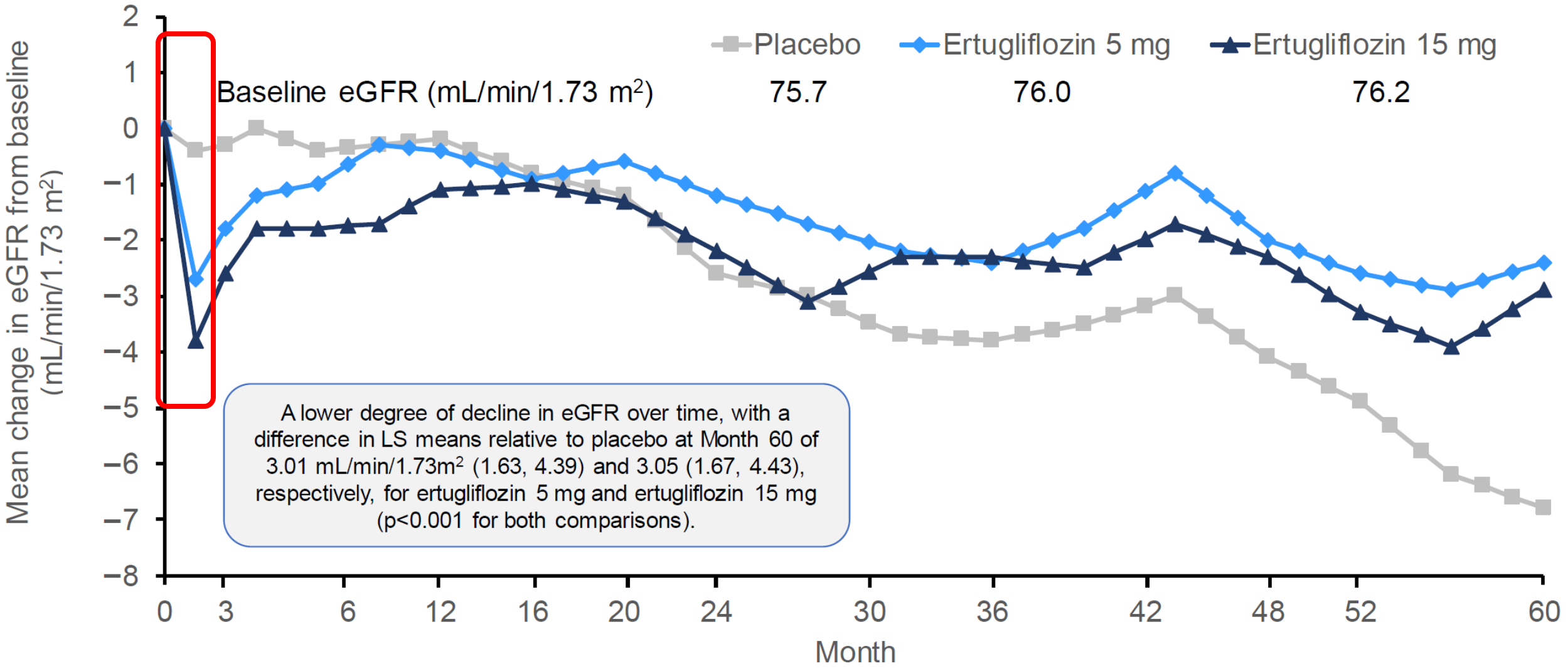
CASE: MR. JONES FIVE

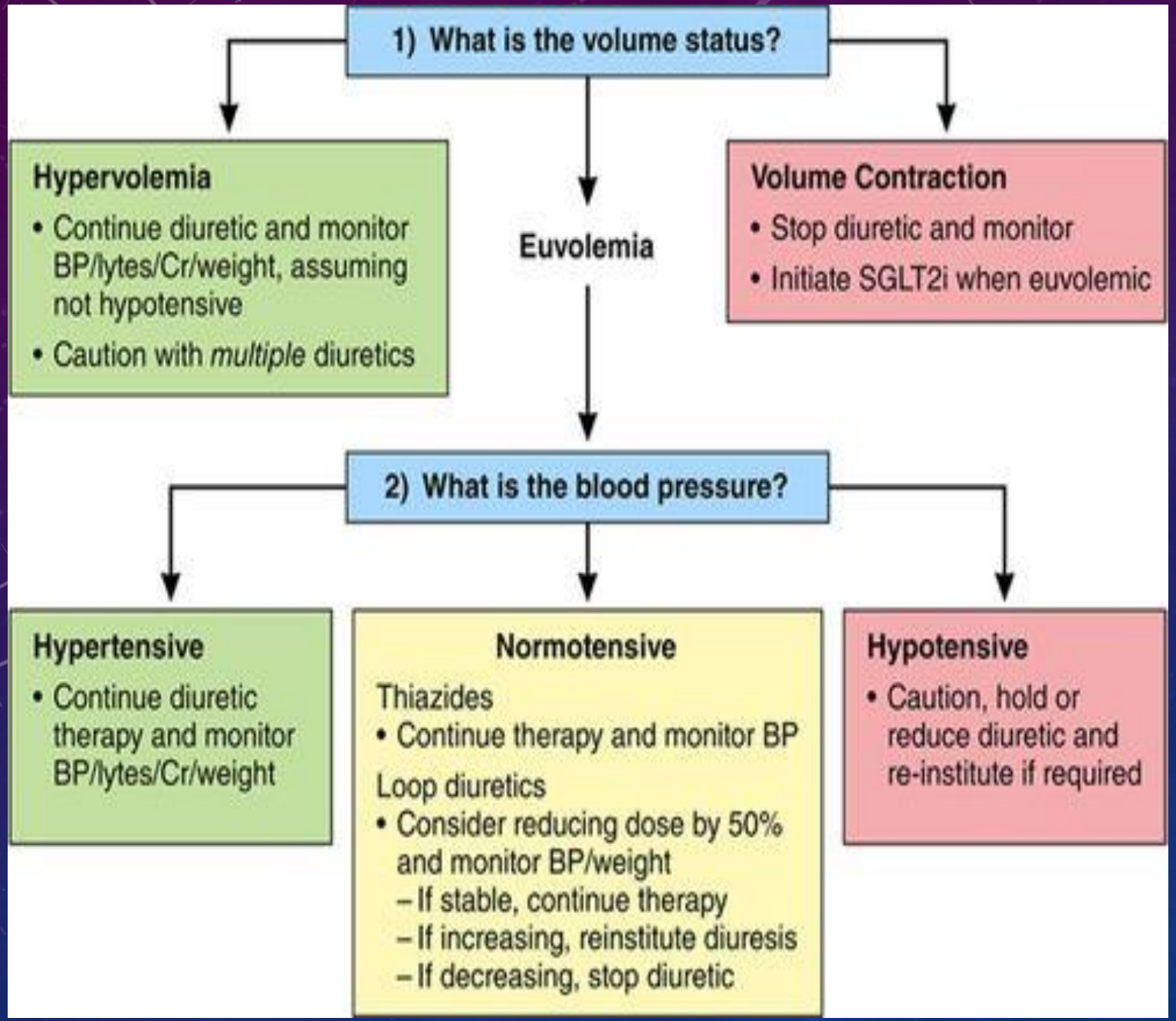
- 68y/o male with type 2 DM dx 8 yrs ago, HTN dx 10 yrs ago, hyperlipidemia dx 5 yrs ago, obesity since age 40, and **diabetic nephropathy** dx 1 yr ago.
- Meds: High-intensity statin, anti-platelet therapy, ACEI, **diuretic**, beta-blocker, metformin, sulfonylurea, DPP IV inhibitor
- BP 128/78, BMI 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



van Bommel, CJASN 2017

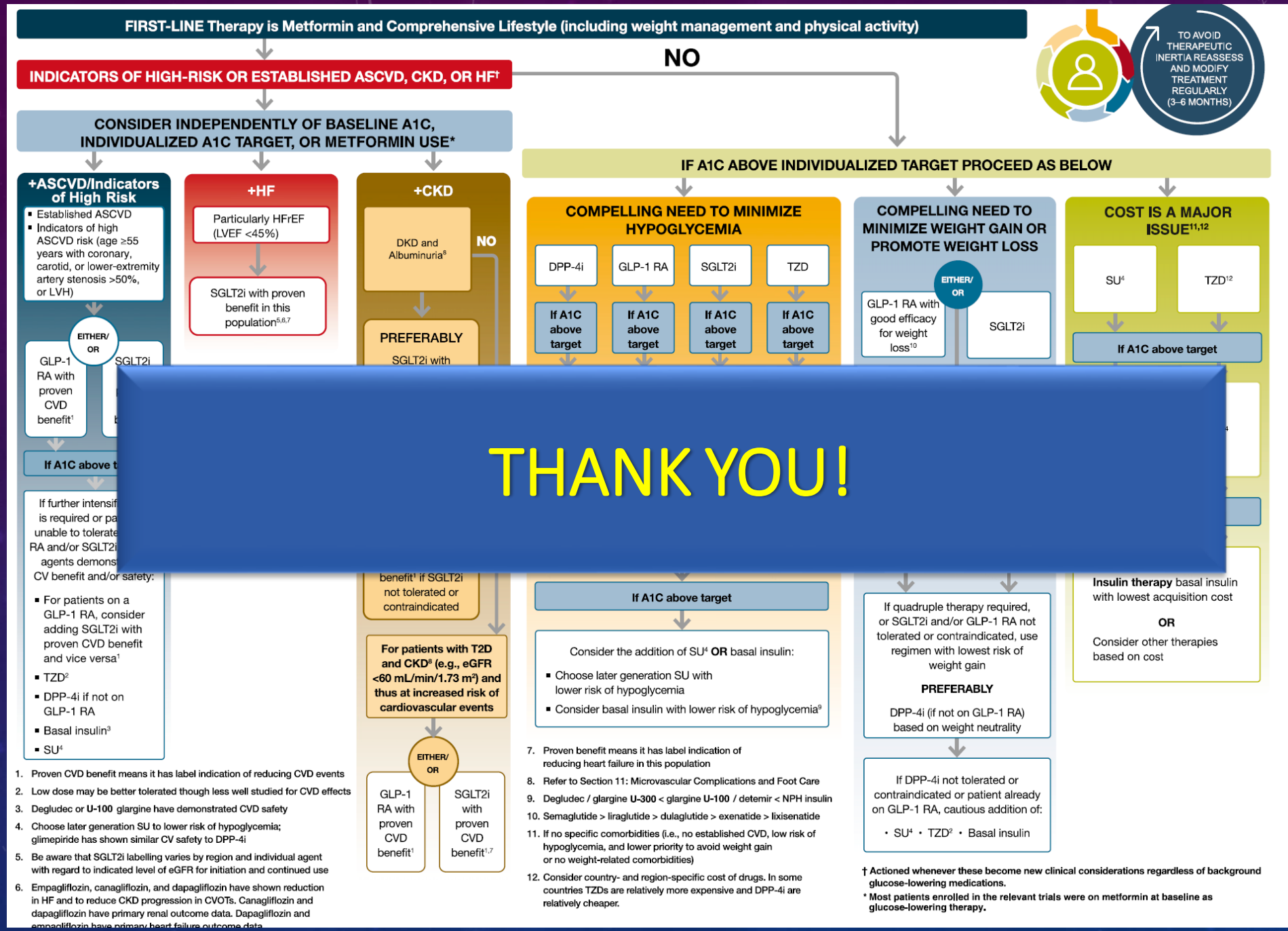

Placebo
Ertugliflozin 5 mg
Ertugliflozin 15 mg
Baseline eGFR (mL/min/1.73 m²)
75.7
76.0
76.2
Mean change in eGFR from baseline (mL/min/1.73 m²)
2
1
0
−1
−2
−3
−4
−5
−6
−7
−8
0
3
6
12
16
20
24
30
36
42
48
52
60
Month
A lower degree of decline in eGFR over time, with a difference in LS means relative to placebo at Month 60 of 3.01 mL/min/1.73m² (1.63, 4.39) and 3.05 (1.67, 4.43), respectively, for ertugliflozin 5 mg and ertugliflozin 15 mg (p<0.001 for both comparisons).



Cherney DZ. Circulation. 134(24):1915

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



THANK YOU!

American Diabetes Association. Standards of Medical Care 2021