Update: Diabetic kidney disease

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GLMS symposium

13th February 2021

Greenlane
Medical Specialists

Aims

- Review the clinical impact of diabetic kidney disease (DKD)
- New therapies and their implications on DKD
  - GLP-1 receptor agonists
  - SGLT-2 inhibitors
  - Mineralocorticoid agonists
- Prescribing considerations of SGLT-2 inhibitors

Diabetic kidney disease

Definition

In patients with diabetes mellitus

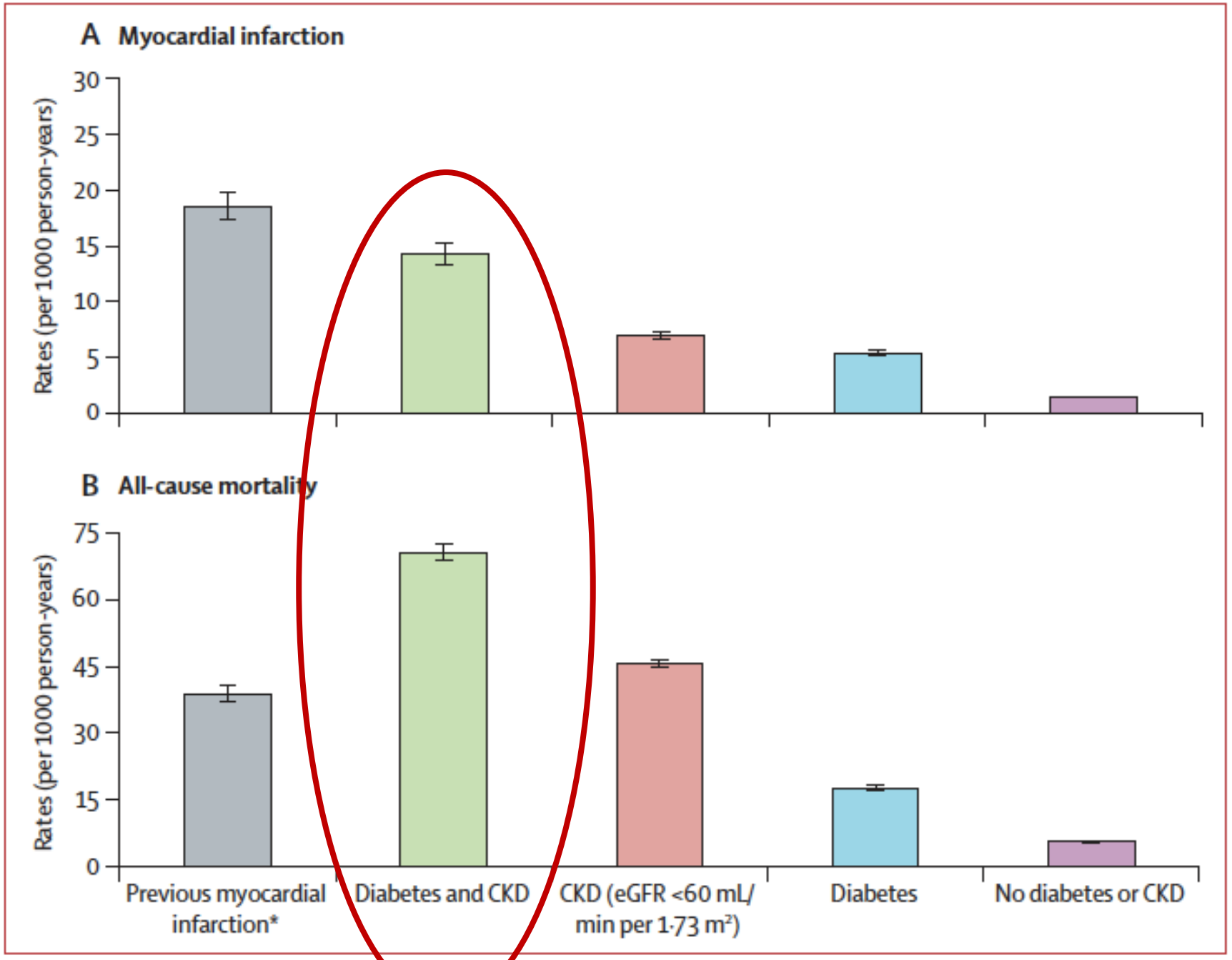
Urine ACR > 30mg/mmol

OR

eGFR < 60ml/min/1.73m^2

OR

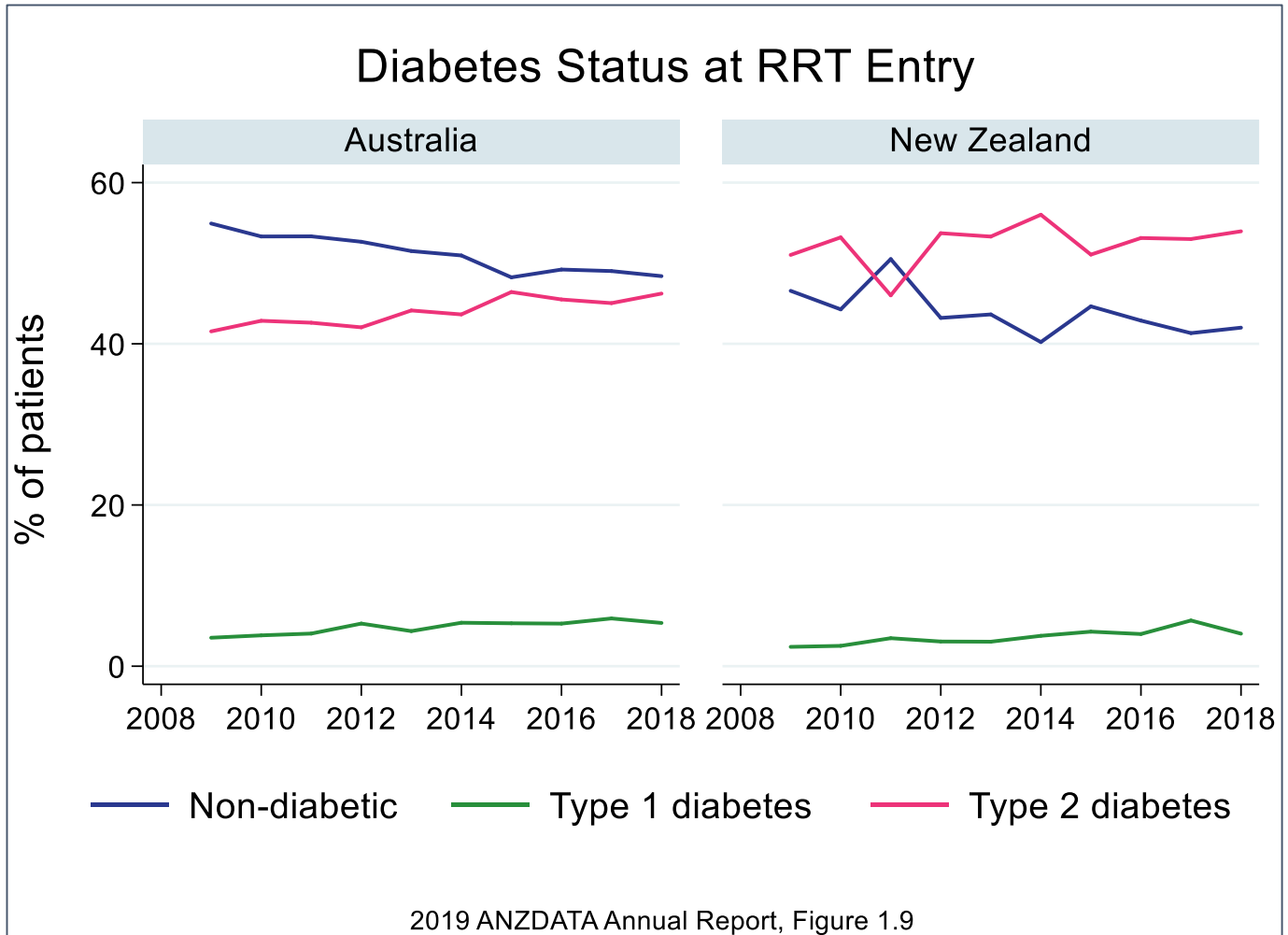
eGFR < 60ml/min/1.73m^2 & Urine ACR > 30mg/mmol



Lancet 2012; 280: 807 – 812.

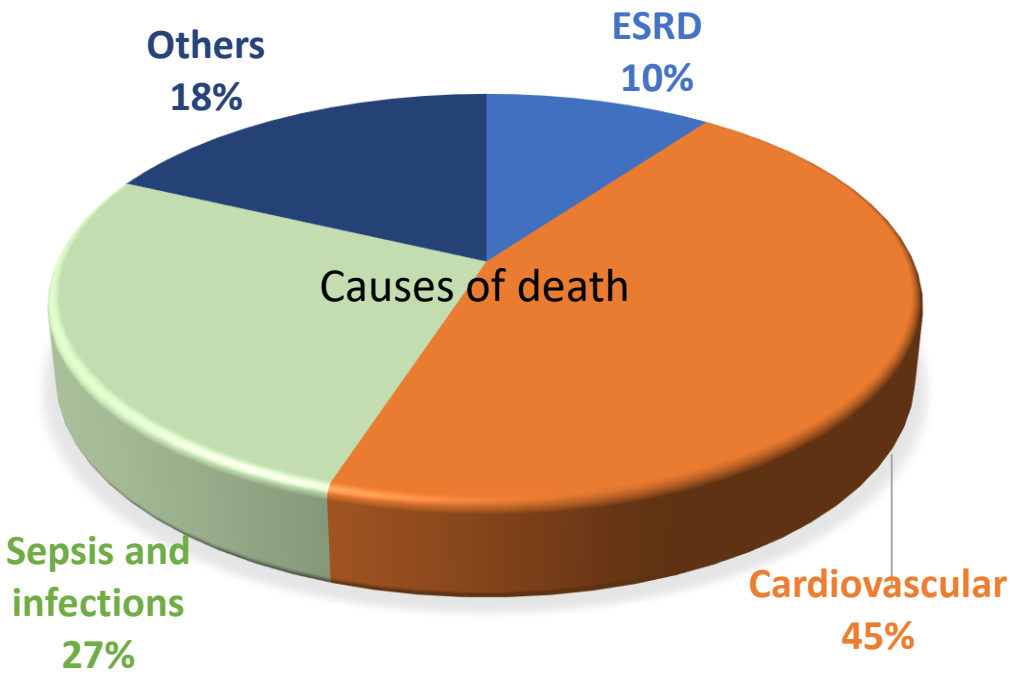
Diabetic kidney disease

- Leading cause of end-stage renal disease (ESRD) worldwide



2019 ANZDATA Annual Report, Figure 1.9

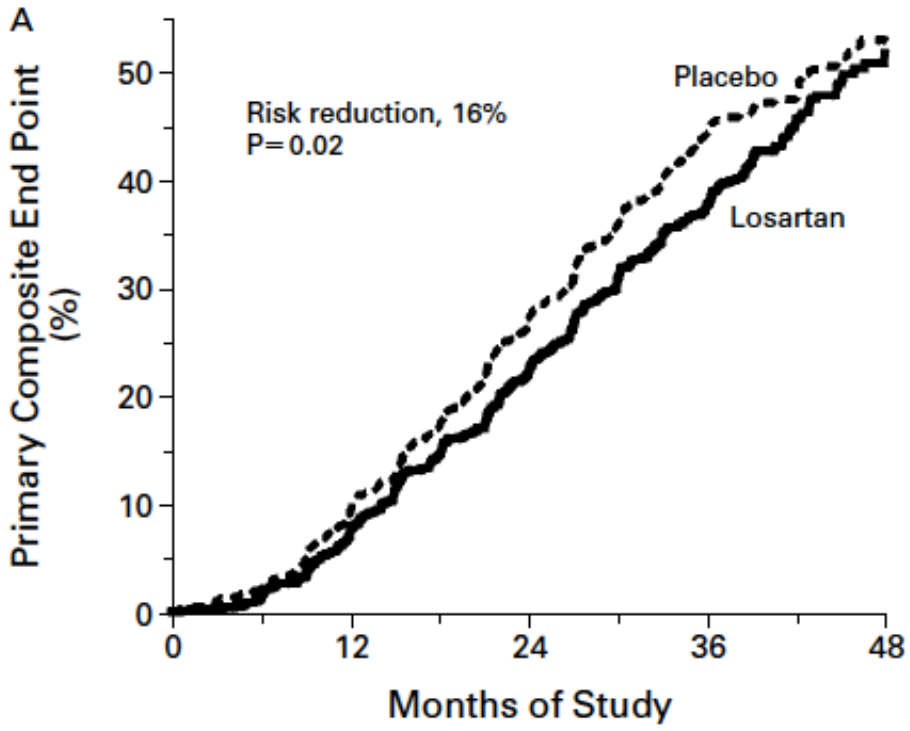
30 – 40% will develop DKD



CJASN 2017; 12: 2032 - 2045

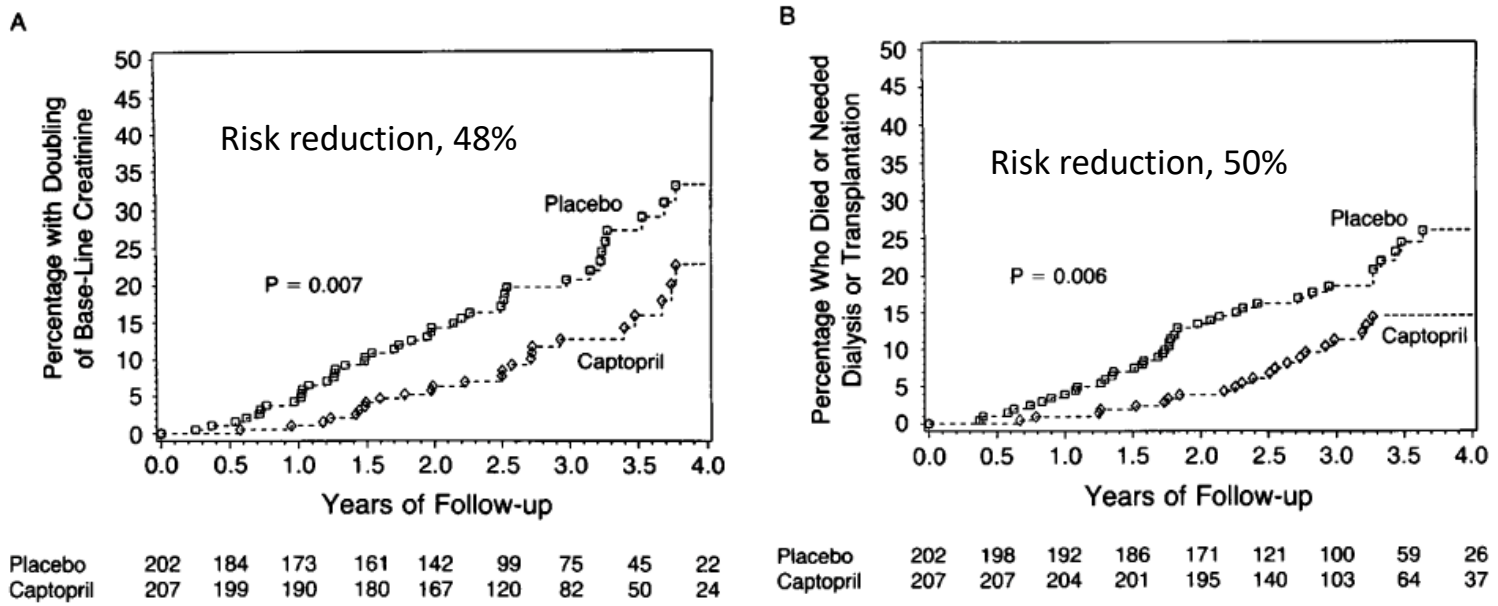
Renal benefit with AT II inhibition (doubling of sCr, ESRD or all-cause mortality)

RENAAL



NEJM 2001; 345:861-869

Captopril

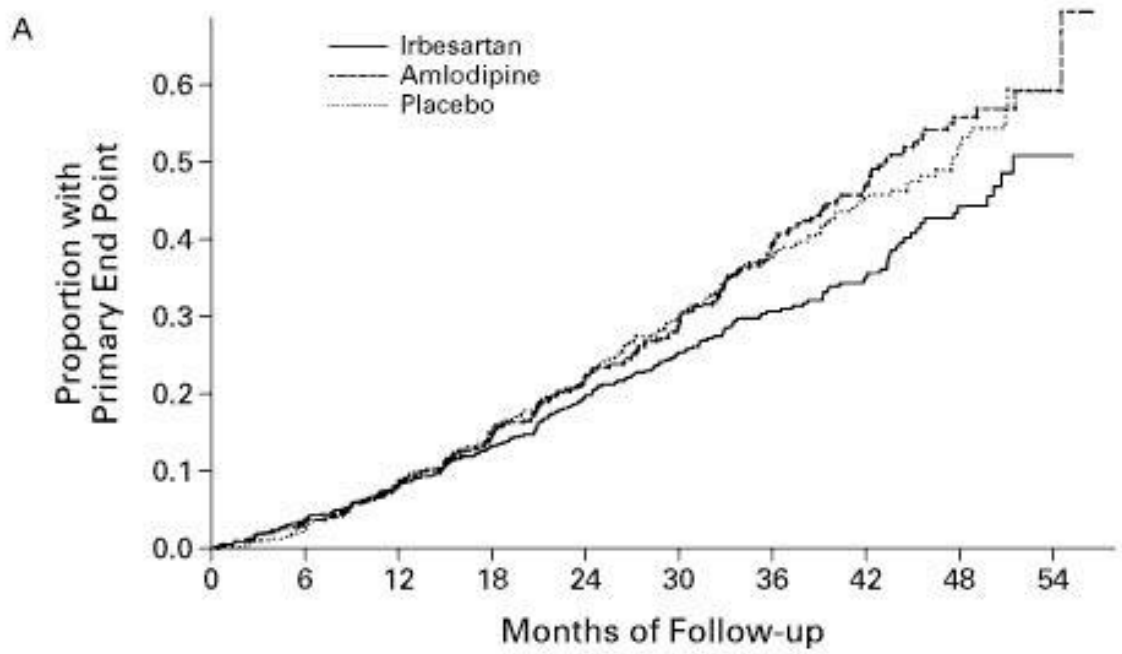


Risk reduction, 50% for composite renal outcome.
Greater benefit in those with eGFR <60 ml/min/1.73m^2

NEJM 1993; 329: 1456 -1462.

RAS blockers superior to other antihypertensive agents for renoprotection

- IDNT



No. at Risk

Irbesartan	579	555	528	496	400	304	216	146	65
Amlodipine	565	542	508	474	385	287	187	128	46
Placebo	568	551	512	471	401	280	190	122	53

NEJM 2001; 345:851-860

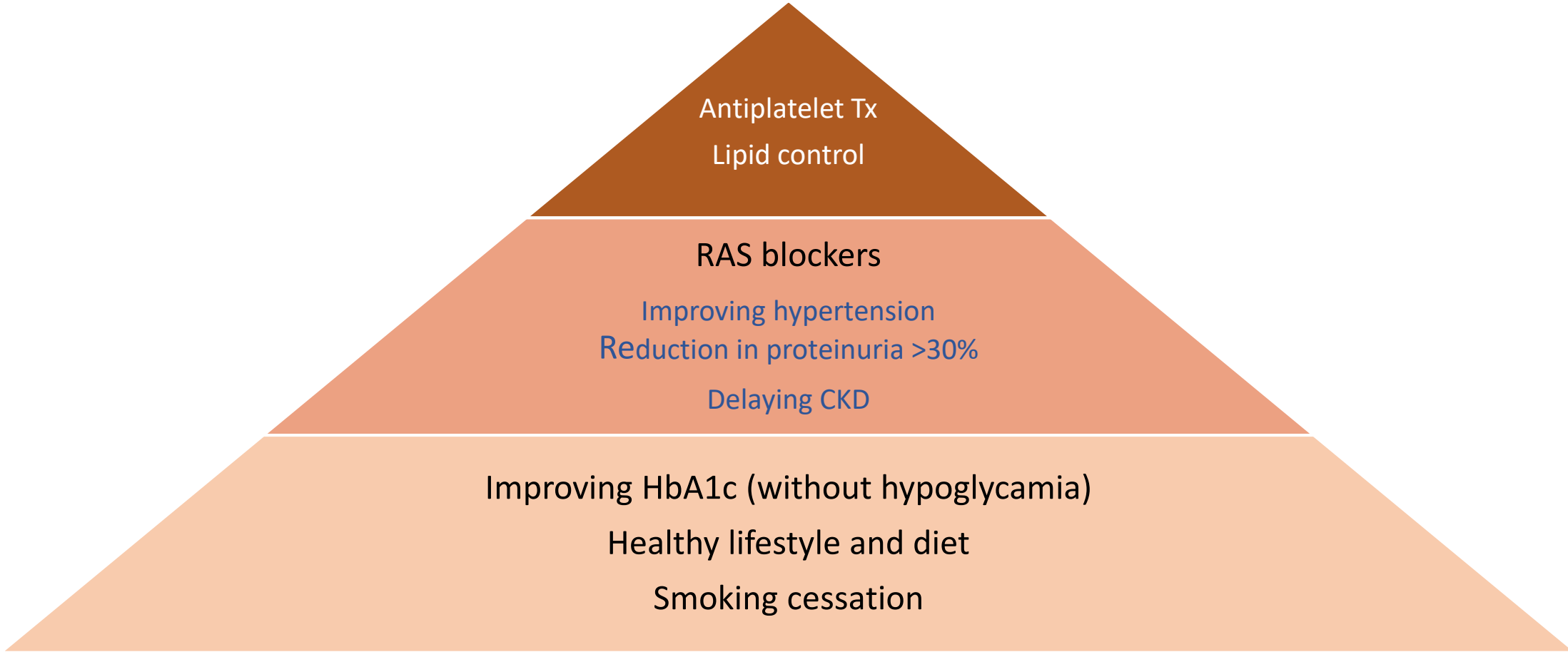
Risk reduction of primary outcome

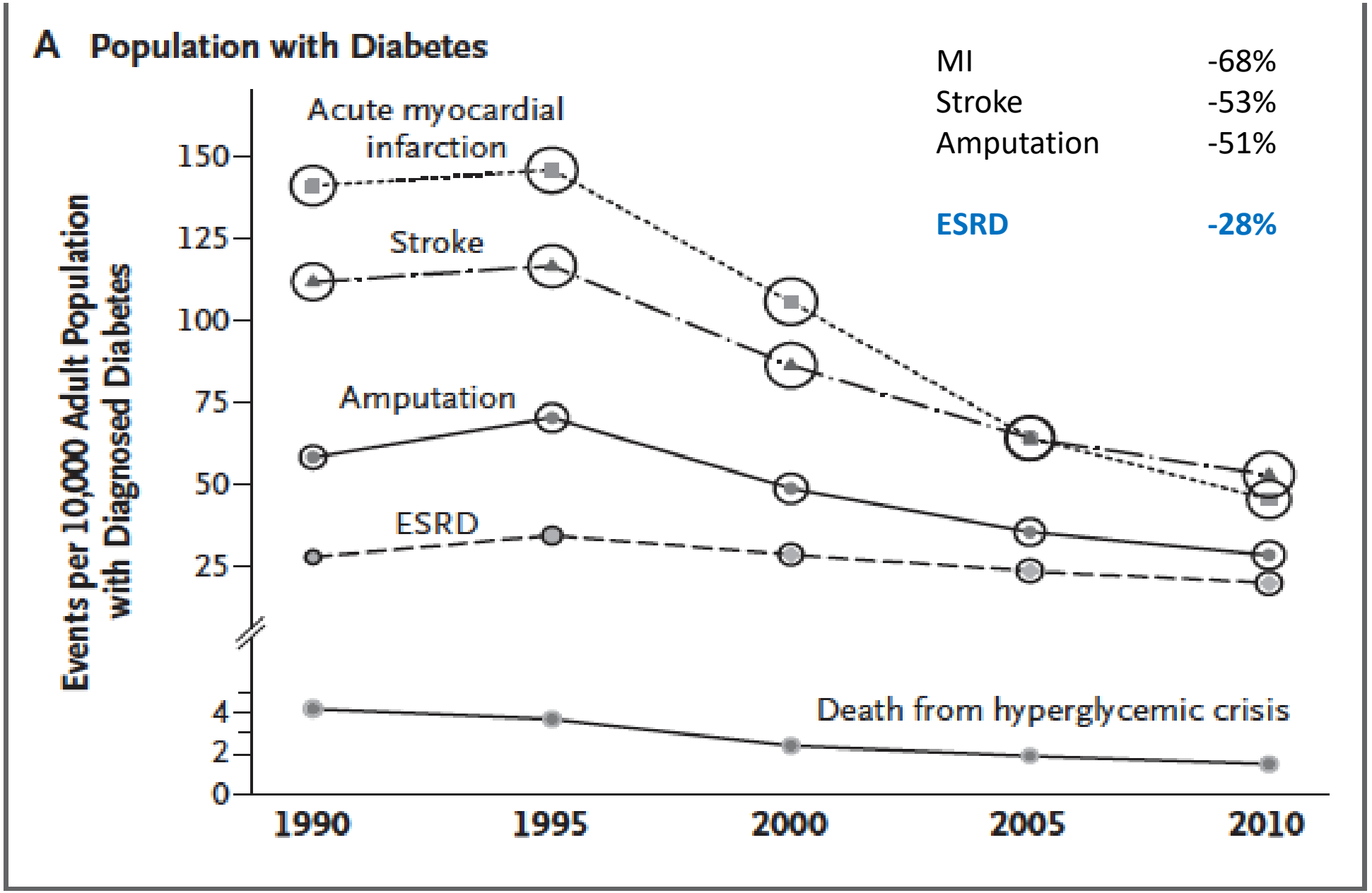
(ESRD, doubling sCR, death)

- Amlodipine: 23% (p = 0.006)
- Placebo: 20% (p=0.02)

BP similar in groups

Standard of care in DKD





NEJM 2014; 370: 1514 – 1523.

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GLP-1 R agonists trials in T2D

In addition to standard practice

ELIXA (2015)

Once weekly Lixisenatide

LEADER (2016)

Liraglutide

SUSTAIN-6 (2016)

Semagluitde

EXSCEL (2017)

Long-acting Exanatide

Cardiovascular safety & outcome trials
Secondary macroalbuminuria onset & renal outcomes

T2D
eGFR ≥ 30 ml/min/1.73m^2
¾ eGFR ≥ 60 ml/min/1.73m^2
> 80% RAS blockade

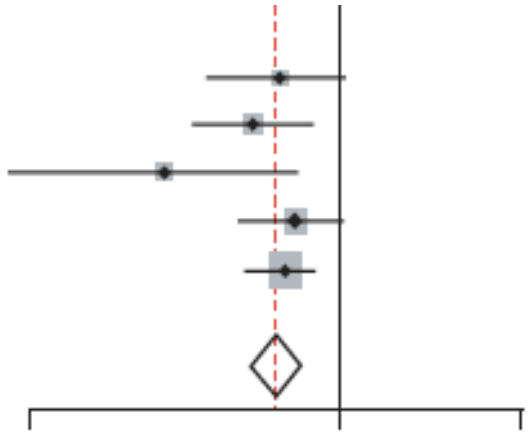
AWARD-7 (2018)

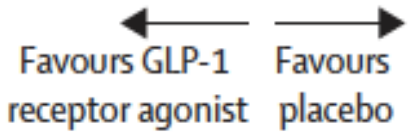
Dulaglutide vs Glargine

Non-inferiority trial
Secondary eGFR and uACR change

T2D
eGFR 15-59 ml/min/1.73m^2
45% ≥ 0.5 g proteinuria/day
> 90% RAS blockade

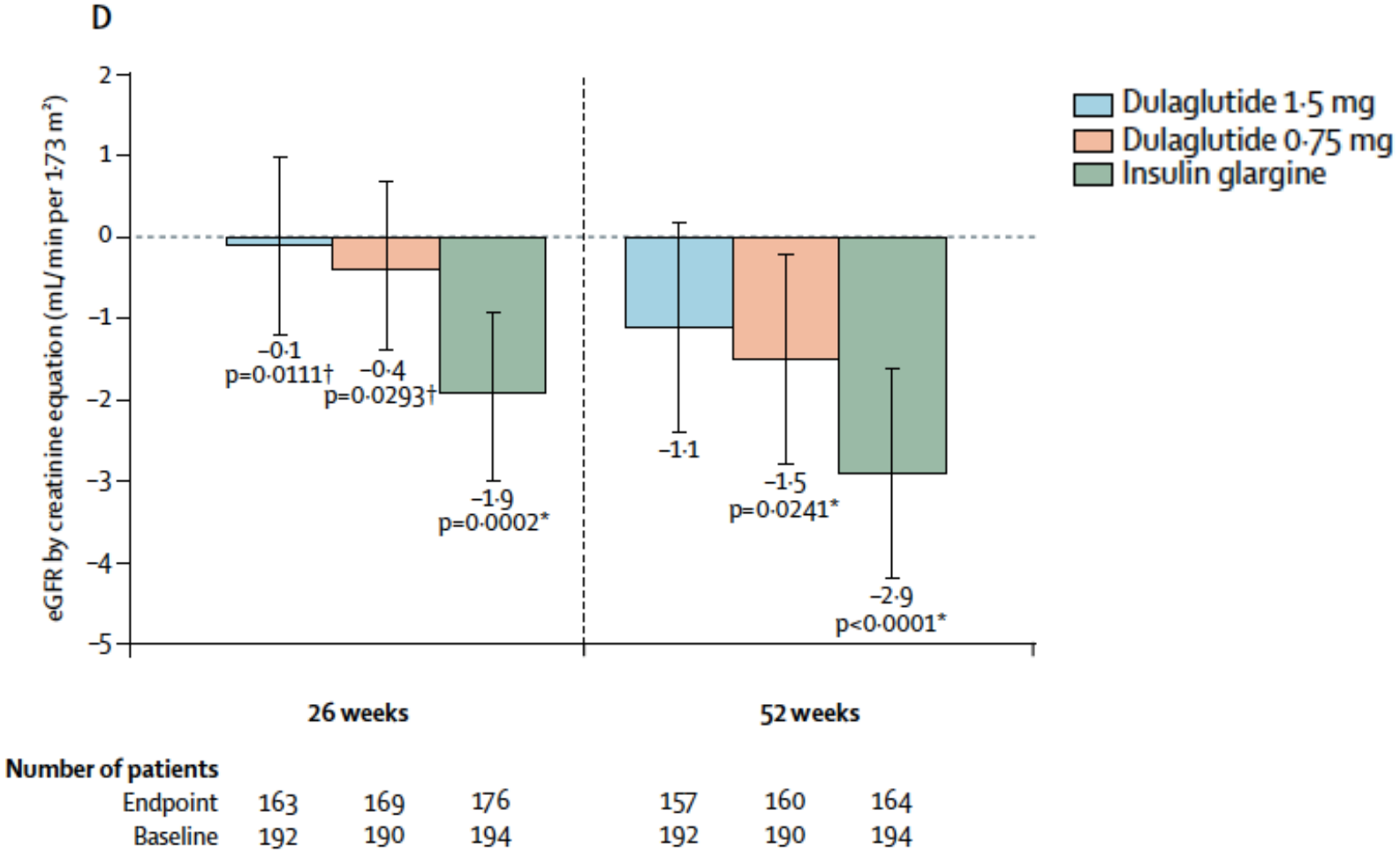
Composite kidney outcome including macroalbuminuria					
ELIXA	172/2647 (6%)	203/2639 (8%)	0·84 (0·68–1·02)		0·083
LEADER	268/4668 (6%)	337/4672 (7%)	0·78 (0·67–0·92)		0·003
SUSTAIN-6	62/1648 (4%)	100/1649 (6%)	0·64 (0·46–0·88)		0·006
EXSCEL	366/6256 (6%)	407/6222 (7%)	0·88 (0·76–1·01)		0·065
REWIND	848/4949 (17%)	970/4952 (20%)	0·85 (0·77–0·93)		<0·001
Overall (I^2=0·0%, p=0·413)	**1716/20168 (9%)**	**2017/20134 (10%)**	**0·83 (0·78–0·89)**	**62 (48 to 96)**	**<0·001**





Lancet Diab Endocrinol 2019; 7: 776–85

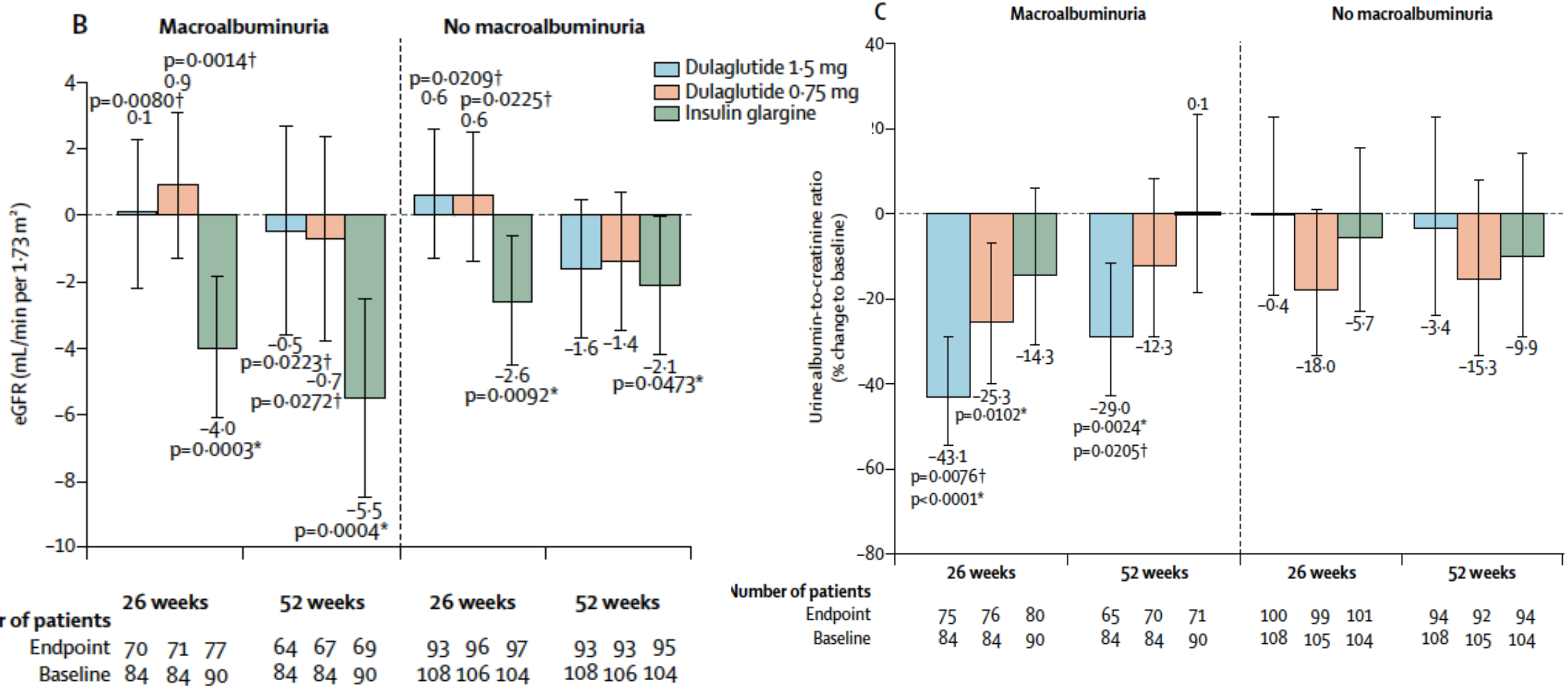
AWARD-7



Independent of HbA1c change, BP and RAS use

Lancet Diab Endocrinol 2018; 6: 605–17

AWARD-7



Lancet Diab Endocrinol 2018; 6: 605–17

SGLT 2 inhibitor trials

In addition to standard practice

EMPA-REG Outcome (2016)
- Empagliflozin

CANVAS (2017)
- Canagliflozin

DECLARE-TIMI 58 (2019)
- Dapagliflozin

Cardiovascular safety and outcome trials
Secondary renal outcome

T2D
Mild CKD; <20% nephropathy
80-85% RAS blockade

CREDENCE (2019)
- Canagliflozin

DAPA-CKD (2020)
- Dapagliflozin

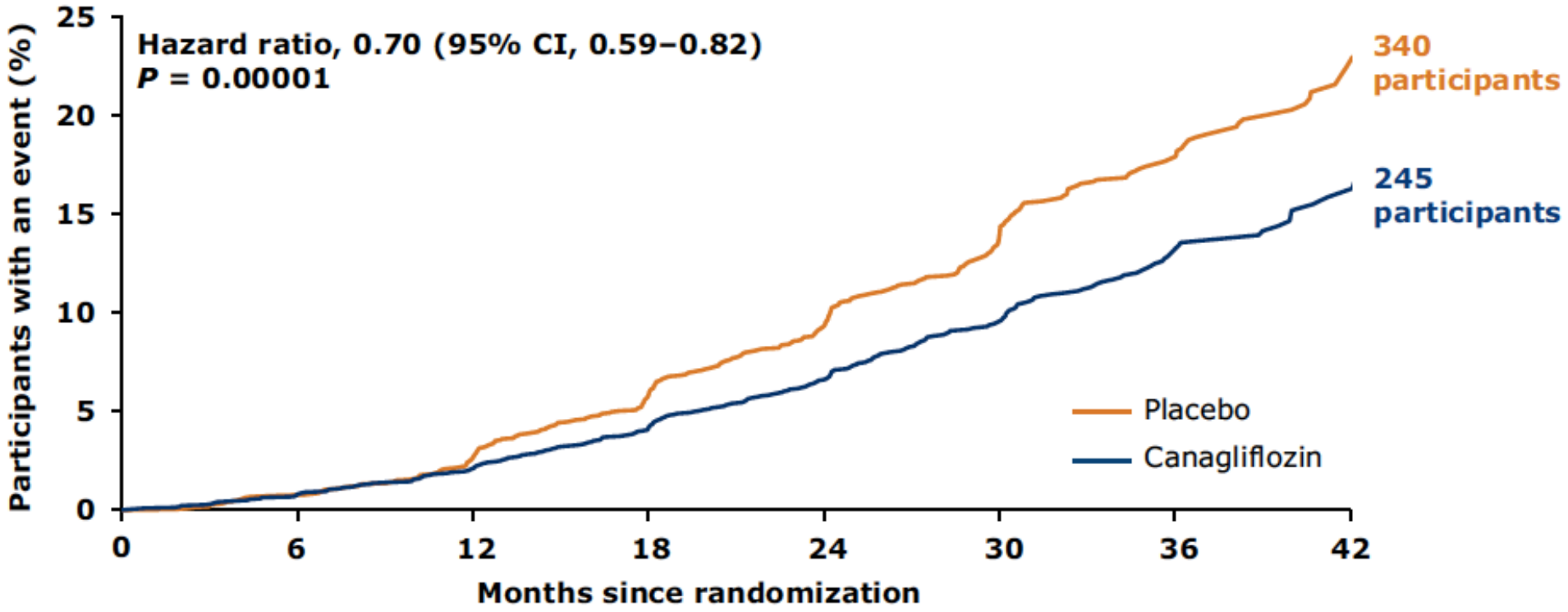
Primary renal outcome trials
Diabetic kidney disease
CKD, no diabetes (DAPA-CKD)

T2D & no diabetes*
* DAPA-CKD: 33% without T2D
DKD/CKD
eGFR 25 to 60 ml/min/1.73m^2
Significant albuminuria
90% RAS blockade

EMPA-REG Outcome DKD (2020)
- Empagliflozin

Post hoc analysis
Cardiovascular & renal outcomes
DKD subgroups

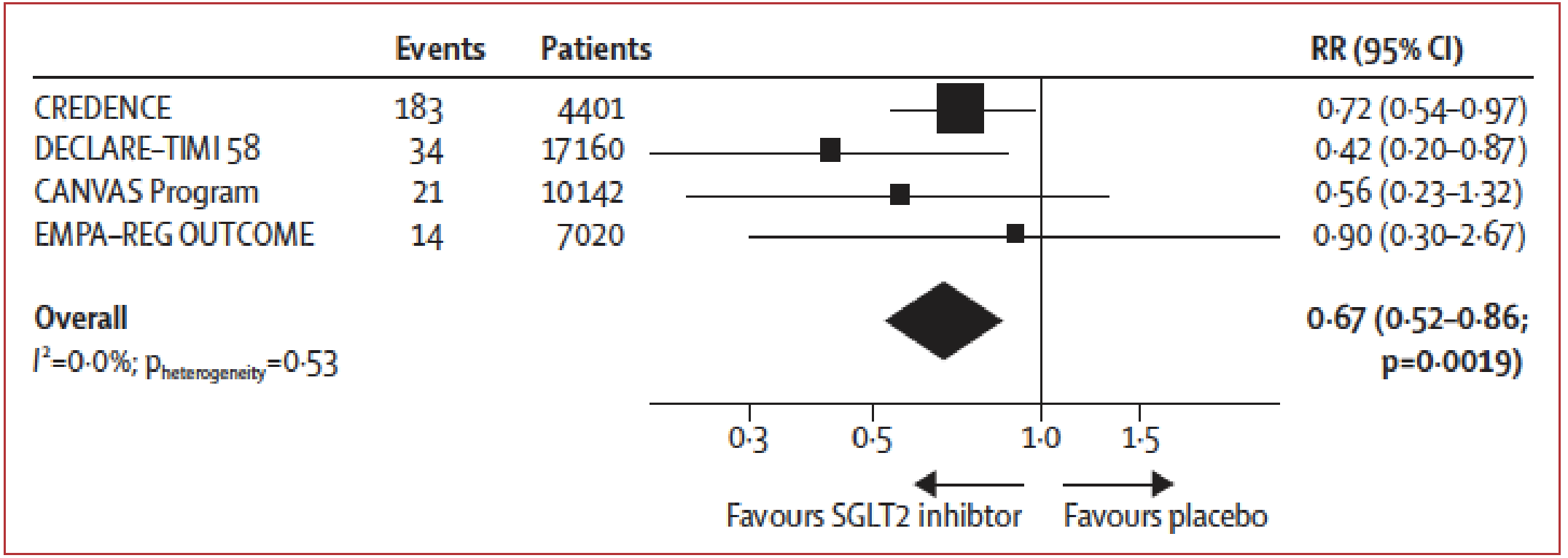
CREDENCE



No. at risk								
Placebo	2199	2178	2132	2047	1725	1129	621	170
Canagliflozin	2202	2181	2145	2081	1786	1211	646	196

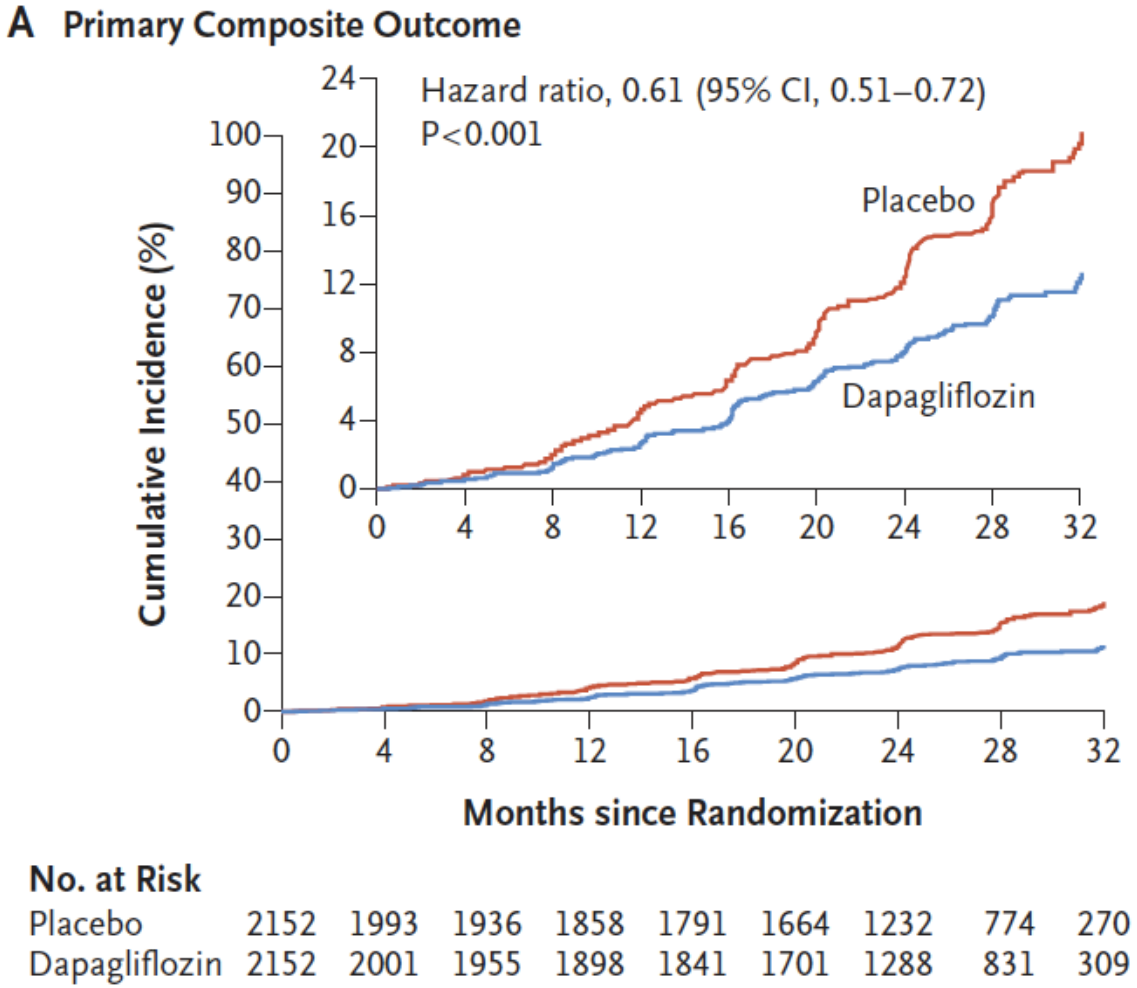
N Engl J Med 2019; 380:2295-2306

Class effect of SGLT2 inhibitors on dialysis, transplant or renal death



Lancet Diab Endocrinol 2019; 7: 845–54

DAPA-CKD



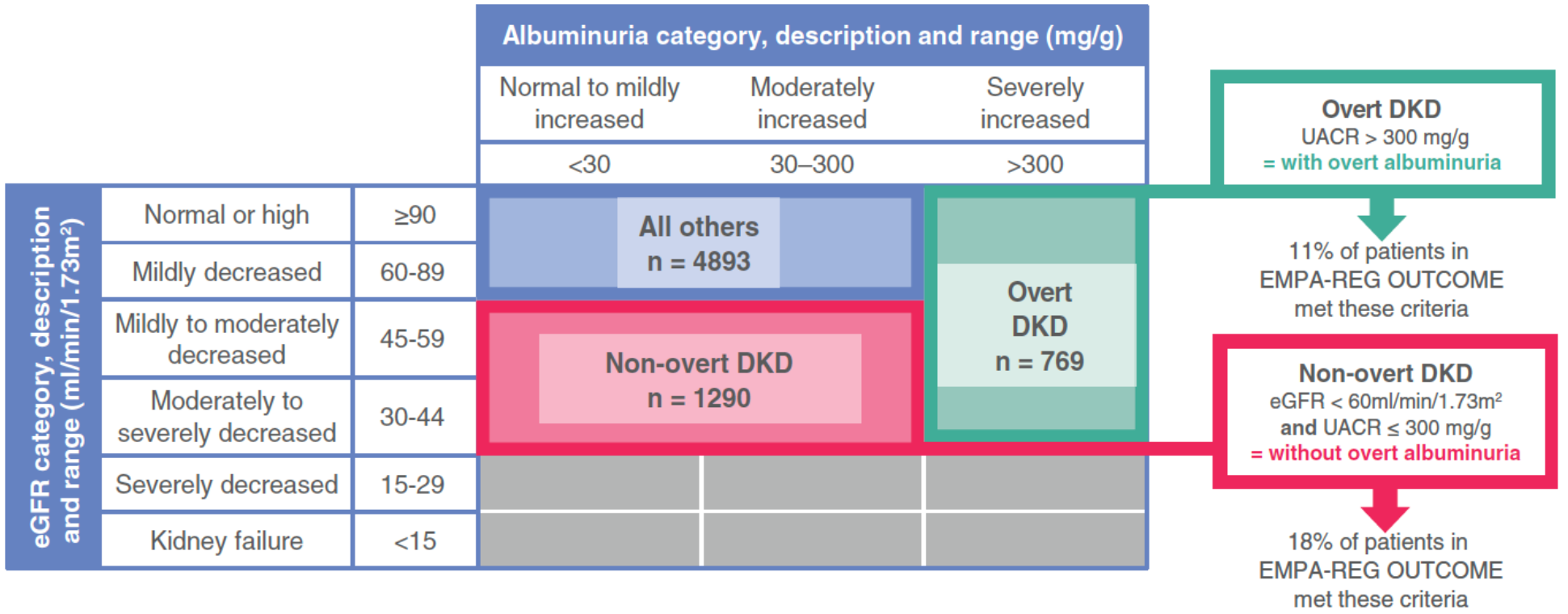
N Engl J Med 2020. 383(13):1436-1446

Dapagliflozin

33% without T2D
eGFR 25 – 75 (15% with < 30 ml/min/1.73m^2)
Significant nephropathy
ACEi/ARB use 98%
Diuretic use 43%

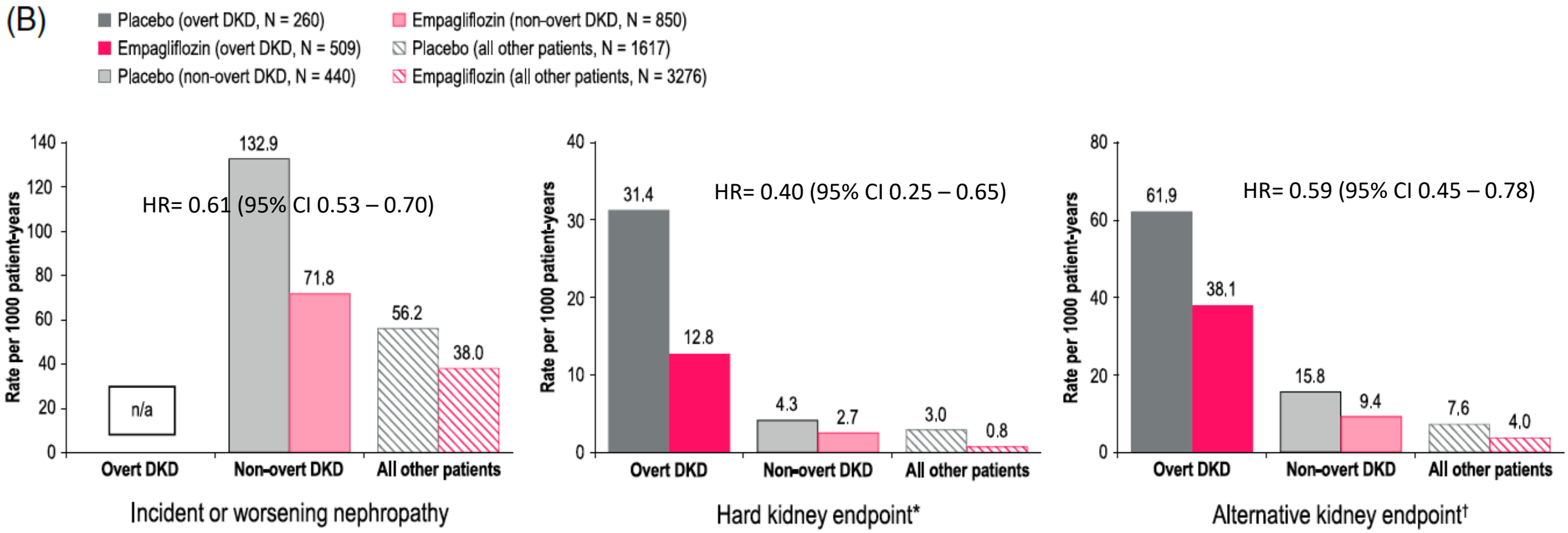
Risk reduction observed across subgroups of renal function, proteinuria and presence of T2D

EMPA-REG OUTCOME DKD



Diabetes Obes Metab. 2020;22:2335–2347.

EMPA-REG OUTCOME DKD



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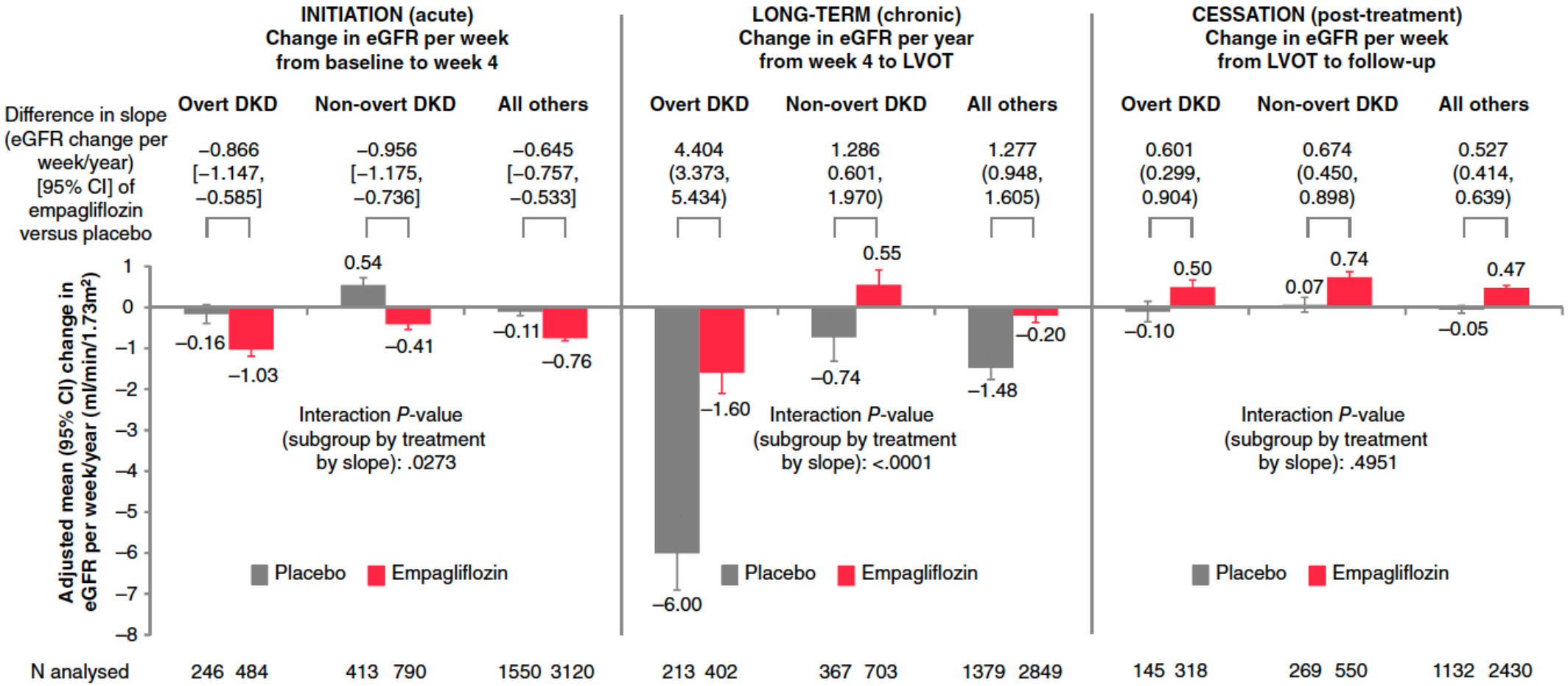
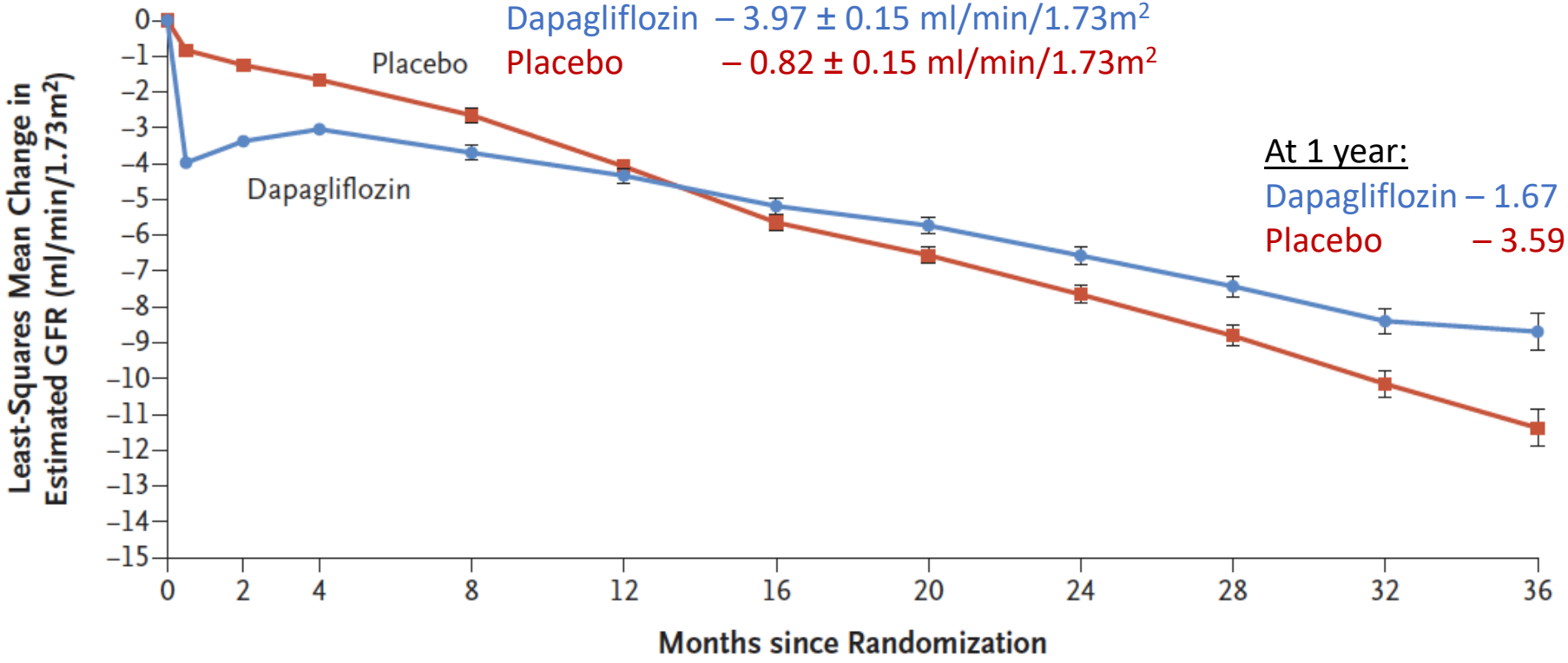
EMPA-REG OUTCOME DKD



Diabetes Obes Metab. 2020;22:2335–2347.

Initial eGFR dip



First 2 weeks:

Dapagliflozin – 3.97 ± 0.15 ml/min/1.73m^2

Placebo – 0.82 ± 0.15 ml/min/1.73m^2

At 1 year:

Dapagliflozin – 1.67 ± 0.11 ml/min/1.73m^2

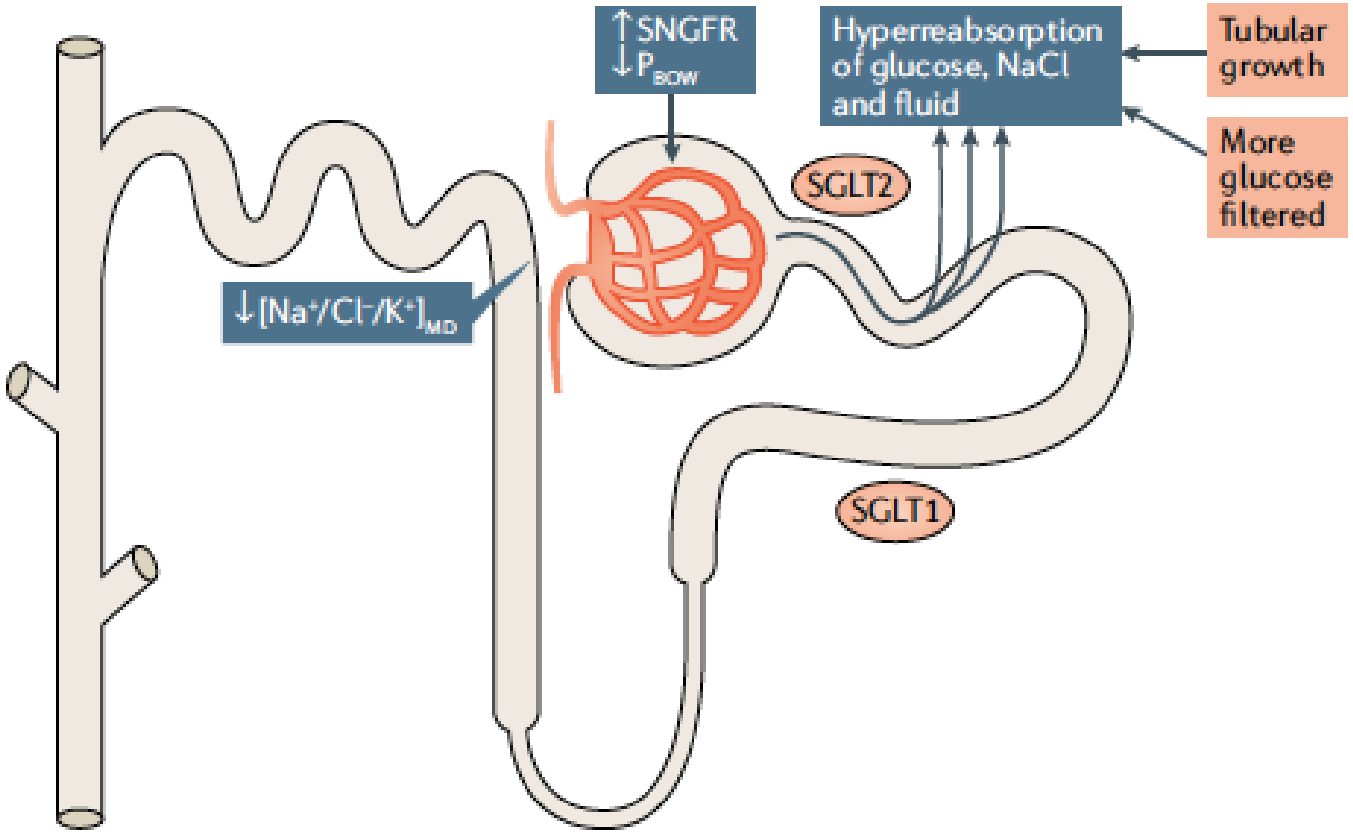
Placebo – 3.59 ± 0.11 ml/min/1.73m^2

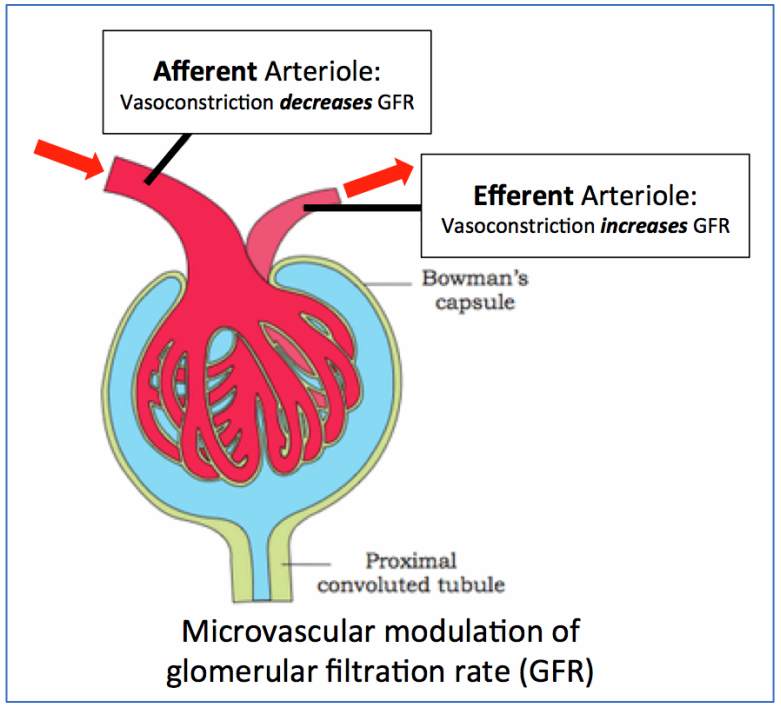
No. of Participants

Placebo	2152	2029	1981	1866	1795	1753	1672	1443	935	447	157
Dapagliflozin	2152	2031	2001	1896	1832	1785	1705	1482	978	496	157

N Engl J Med 2020. 383(13):1436-1446

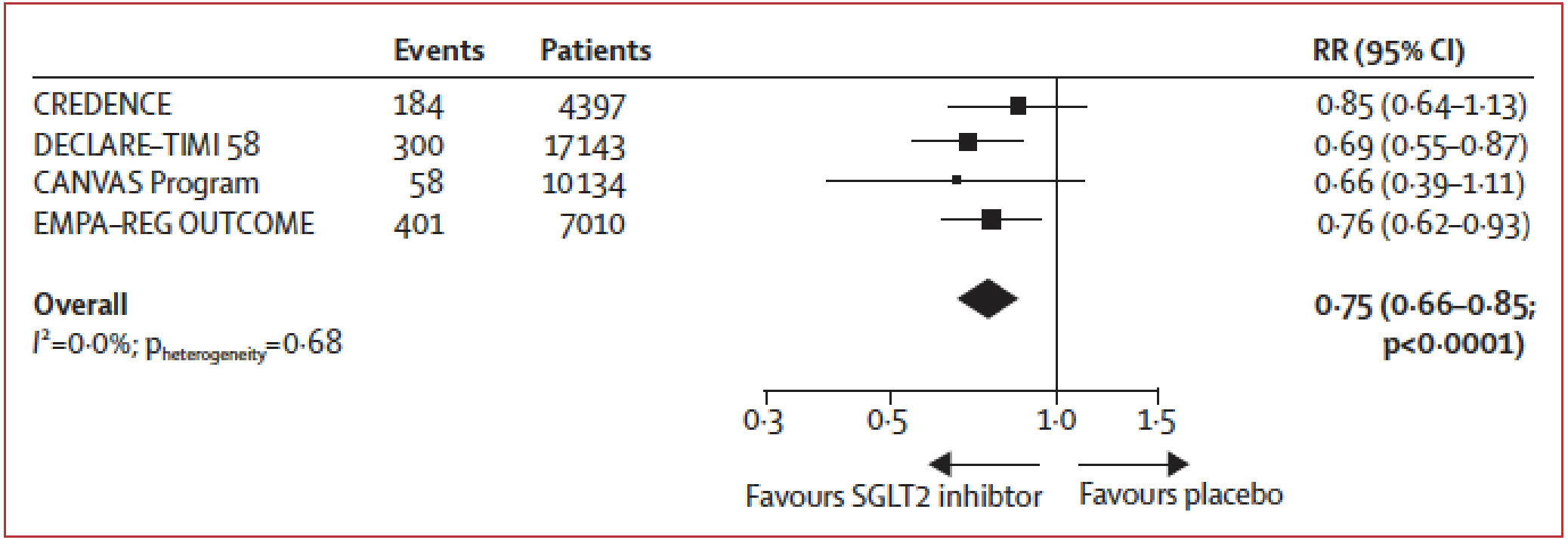
Effect of glomerular filtration with SGLT2 and RAS inhibition





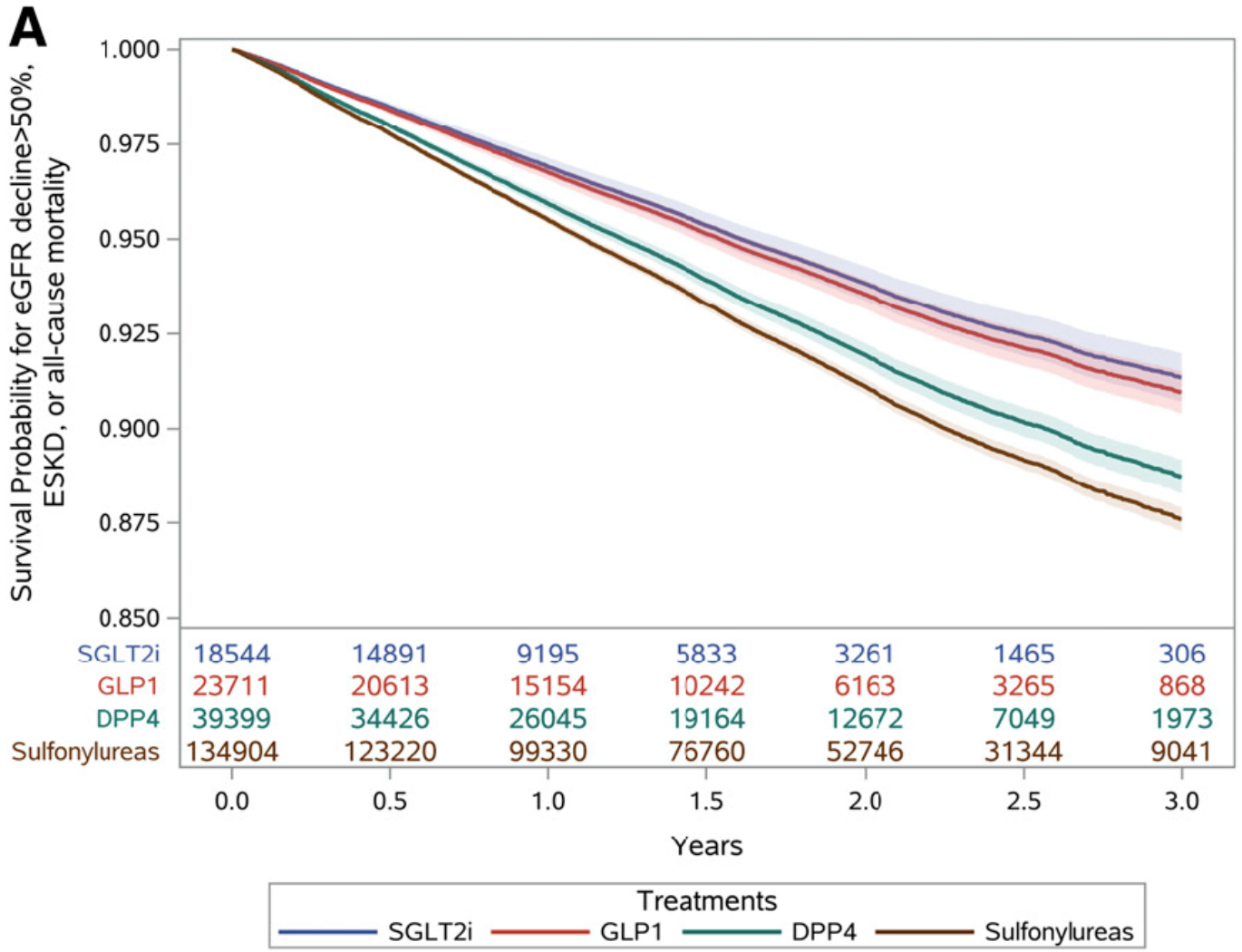
Microvascular modulation of glomerular filtration rate (GFR)

Effect of SGLT2 inhibitors on acute kidney injury



Lancet Diab Endocrinol 2019; 7: 845–54

SGLT2i vs GLP1R agonists vs DDP4i



DPP4 i vs SU:
Observed risk difference is small
Lower risk in people with eGFR ≥ 60

Compared with DDP4 i, SGLT2i and GLP-1R agonists are associated with lower risk of composite outcome across all eGFR levels

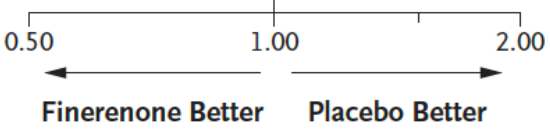
Diabetes Care 2020;43:2859–2869

Finerone (FIDELIO-DKD)

55% with baseline eGFR <45 ml/min/1.73 m^2

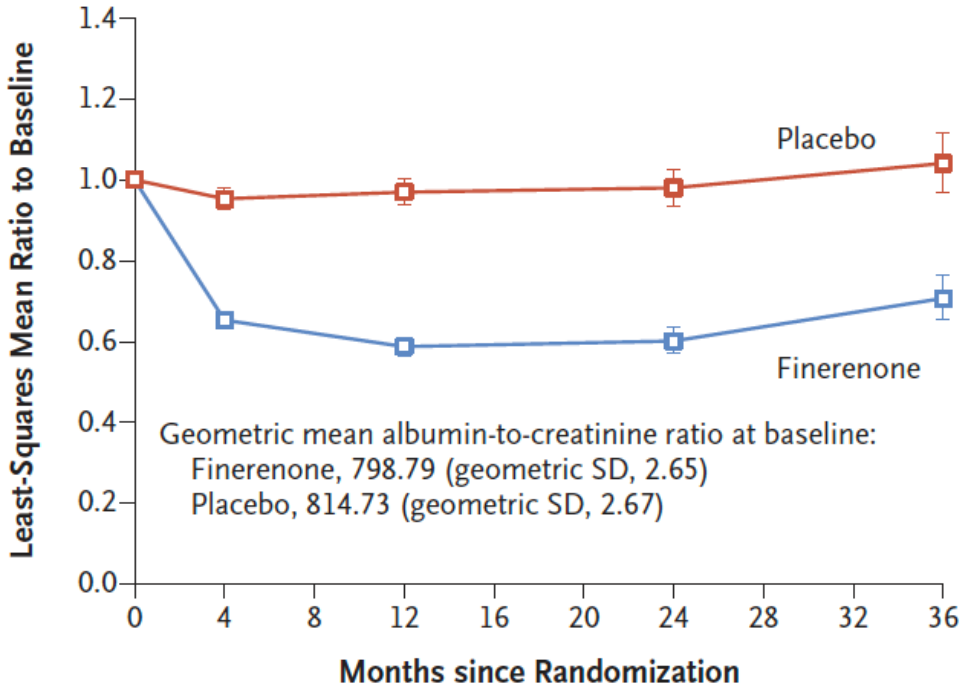
88% with urine ACR ≥ 30 mg/mmol

Outcome	Finerenone (N=2833)	Placebo (N=2841)	Finerenone (N=2833)	Placebo (N=2841)	Hazard Ratio (95% CI)	P Value
	no. of patients with event (%)		*no. of patients with event per 100 patient-yr*			
Primary composite outcome	504 (17.8)	600 (21.1)	7.59	9.08	0.82 (0.73–0.93)	0.001
Kidney failure	208 (7.3)	235 (8.3)	2.99	3.39	0.87 (0.72–1.05)	—
End-stage kidney disease	119 (4.2)	139 (4.9)	1.60	1.87	0.86 (0.67–1.10)	—
Sustained decrease in eGFR to <15 ml/min/1.73 m^2	167 (5.9)	199 (7.0)	2.40	2.87	0.82 (0.67–1.01)	—
Sustained decrease of ≥40% in eGFR from baseline	479 (16.9)	577 (20.3)	7.21	8.73	0.81 (0.72–0.92)	—
Death from renal causes	2 (<0.1)	2 (<0.1)	—	—	—	—
Key secondary composite outcome	367 (13.0)	420 (14.8)	5.11	5.92	0.86 (0.75–0.99)	0.03
Death from cardiovascular causes	128 (4.5)	150 (5.3)	1.69	1.99	0.86 (0.68–1.08)	—
Nonfatal myocardial infarction	70 (2.5)	87 (3.1)	0.94	1.17	0.80 (0.58–1.09)	—
Nonfatal stroke	90 (3.2)	87 (3.1)	1.21	1.18	1.03 (0.76–1.38)	—
Hospitalization for heart failure	139 (4.9)	162 (5.7)	1.89	2.21	0.86 (0.68–1.08)	—
Death from any cause	219 (7.7)	244 (8.6)	2.90	3.23	0.90 (0.75–1.07)	—
Hospitalization for any cause	1263 (44.6)	1321 (46.5)	22.56	23.87	0.95 (0.88–1.02)	—
Secondary composite kidney outcome	252 (8.9)	326 (11.5)	3.64	4.74	0.76 (0.65–0.90)	—
Sustained decrease of ≥57% in eGFR from baseline	167 (5.9)	245 (8.6)	2.41	3.54	0.68 (0.55–0.82)	—



N Engl J Med 2020; 383: 2219-29.

A Urinary Albumin-to-Creatinine Ratio



No. of Patients					
Finerenone	2831	2725	2582	1841	856
Placebo	2840	2726	2598	1825	834
Mean Change from Baseline (percent)					
Finerenone	Ref.	–34.7	–41.3	–39.9	–29.3
Placebo	Ref.	–4.7	–3.0	–2.0	4.1

31% reduction in albuminuria at 4 months

Slows CKD progression

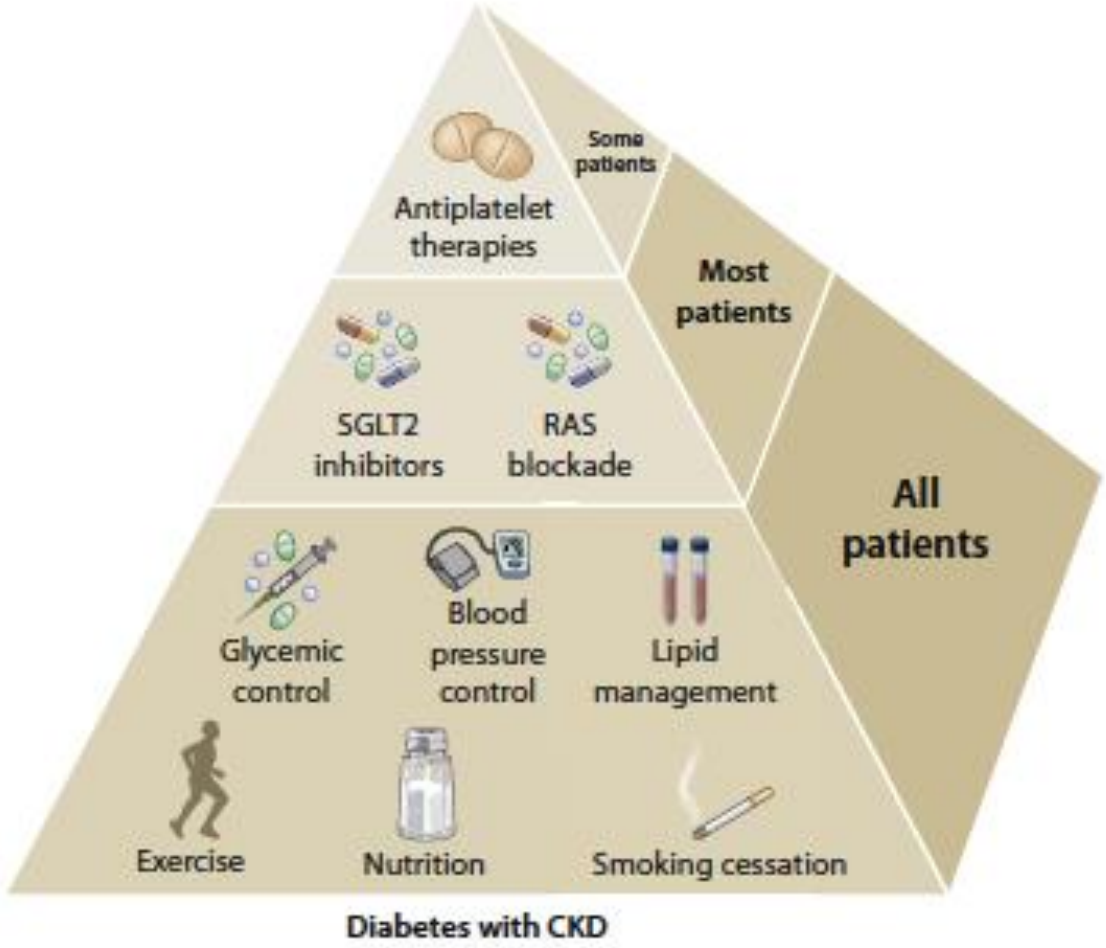
Similar adverse events profile

N Engl J Med 2020; 383: 2219-29.

Summary

- Diabetes management = hyperglycaemia + diabetic complications
- New therapies have pleotropic actions
- Treatment with GLP1 R agonists and SGLT 2 inhibitors (in addition to standard therapy) is associated with lower risk of adverse renal outcomes
  - No hypoglycaemia risk
  - Outcome-driven management to guide choice in therapies

Current standard of care in DKD



Kidney Int. 2020; 98: 4S

SGLT2 inhibitors

- Class effect
  - Cardiorenal benefit is independent of glycaemia and BP control
  - In addition to AT II inhibition (Risk reduction 42% with concomitant use cf. 30% in non-users, p = 0.065)
  - Concomitant metformin use
- Generalizable?
  - ✓ T2D and no diabetes (DAPA-CKD) with robust results
  - X Insufficient studies in T1D
  - ✓ Across all stages of CKD and degree of proteinuria
- Special authority prescription in NZ in those with eGFR ≥30ml/min/1.73m^2
- Safety
  - Hypovolemic AKI – reduce diuretics
  - Euglycaemic ketoacidosis
  - Increased risk for urinary infections, genital mycotic infections

Nephrol Dial Transplant (2020) 35: i48–i55

Who should not receive SGLT 2 inhibitors?

- T1D; history of DKA
- Recurrent genital tract infection; catheterized patients
- On immunosuppression
- Dynamic volume status
- Limited mobility
- Cognitive impairment

Thanks

- Questions or comments?

Greenlane
Medical Specialists