

Treatment of Diabetic Nephropathy: what does the future hold?

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Disclosures

- RDT is a consultant for Akebia, Amgen, Amgen, Bayer, Boehringer Ingelheim, Chinook, Medscape, Novo Nordisk, Otsuka, Reata and Vifor

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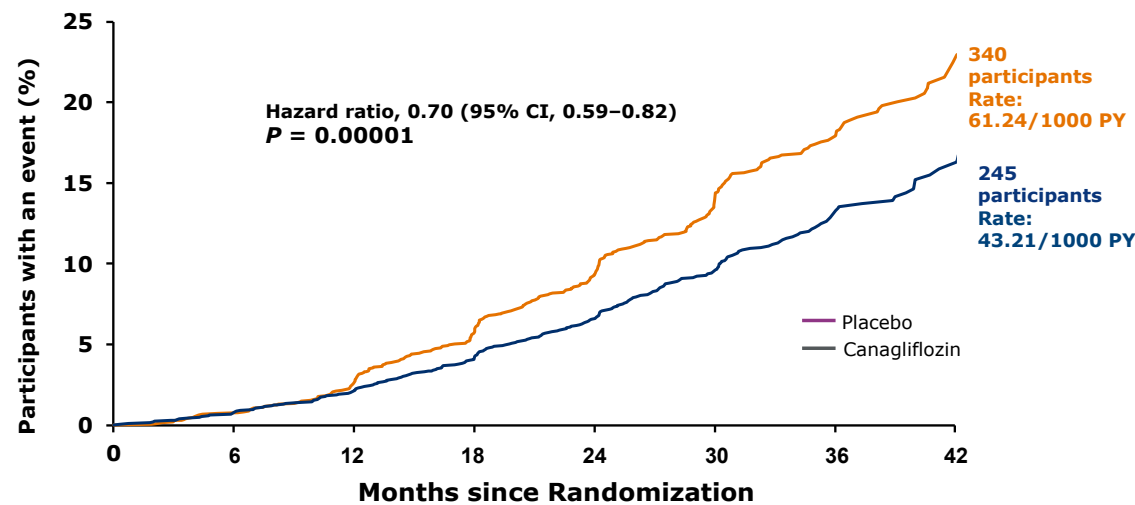
Take Home Message

- Translate trials into practice
 - Sodium glucose co-transporter-2 inhibitors (SGLT2i)
 - Non-steroidal mineralocorticoid receptor antagonist (MRA)-Finerenone
- Combination therapy (SGLT2, MRA, GLP-1 Ra) trials
- Anti-Inflammatory agents (e.g., anti-IL6)
- Other (than Finerenone) non-steroidal MRA studies
- Discovery of new molecular targets upstream

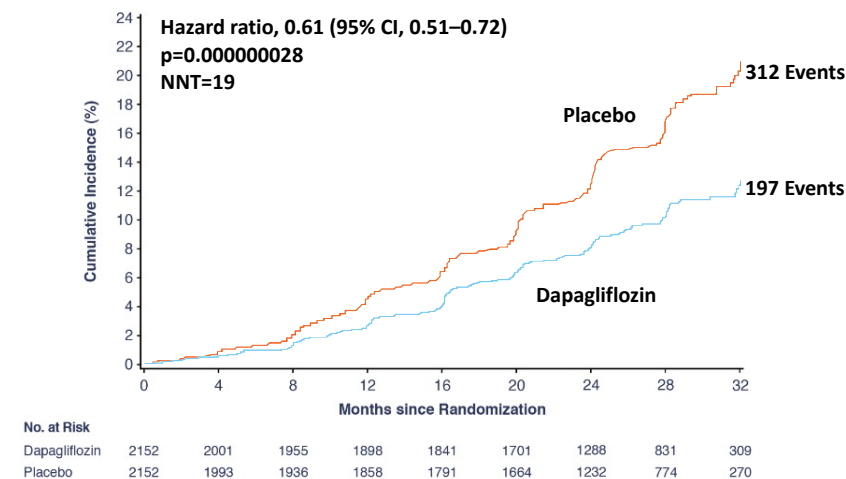


CREDENCE and DAPA CKD: Kidney and CV Outcomes (Primary Composite Outcome)

CREDENCE: ESKD, DScr renal or CV death



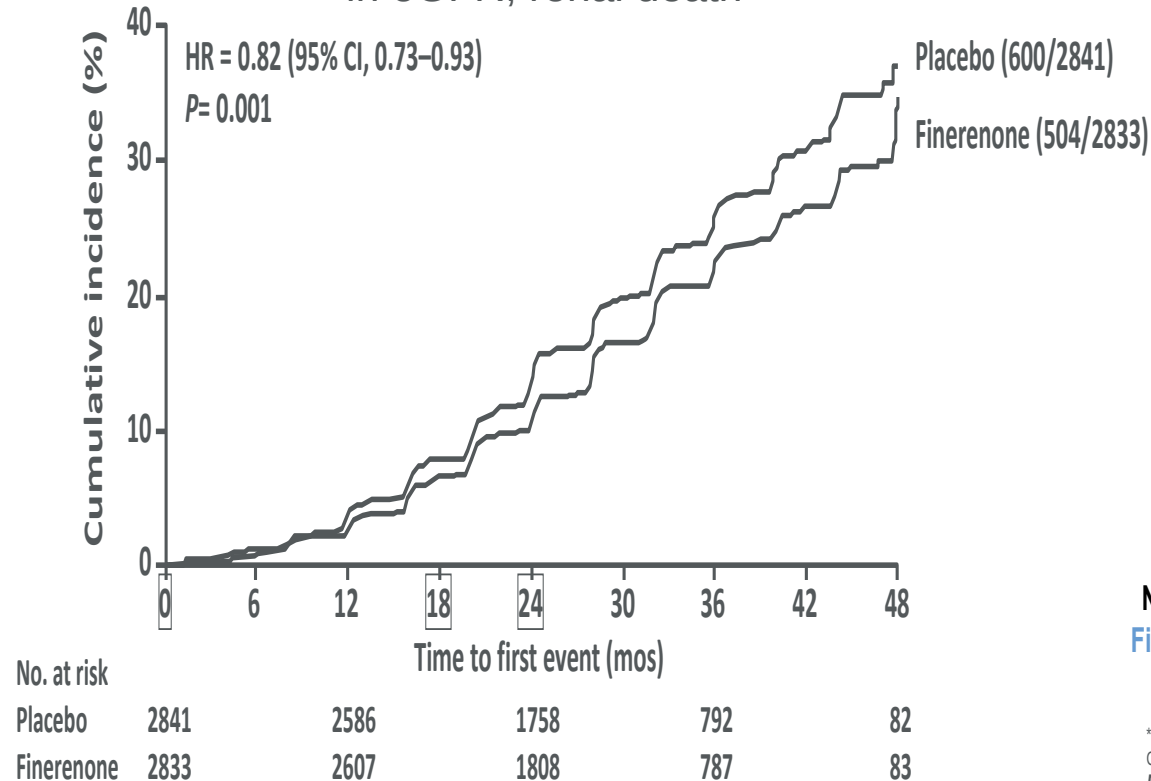
DAPA CKD: ESKD, 50% dec in eGFR, renal or CV death



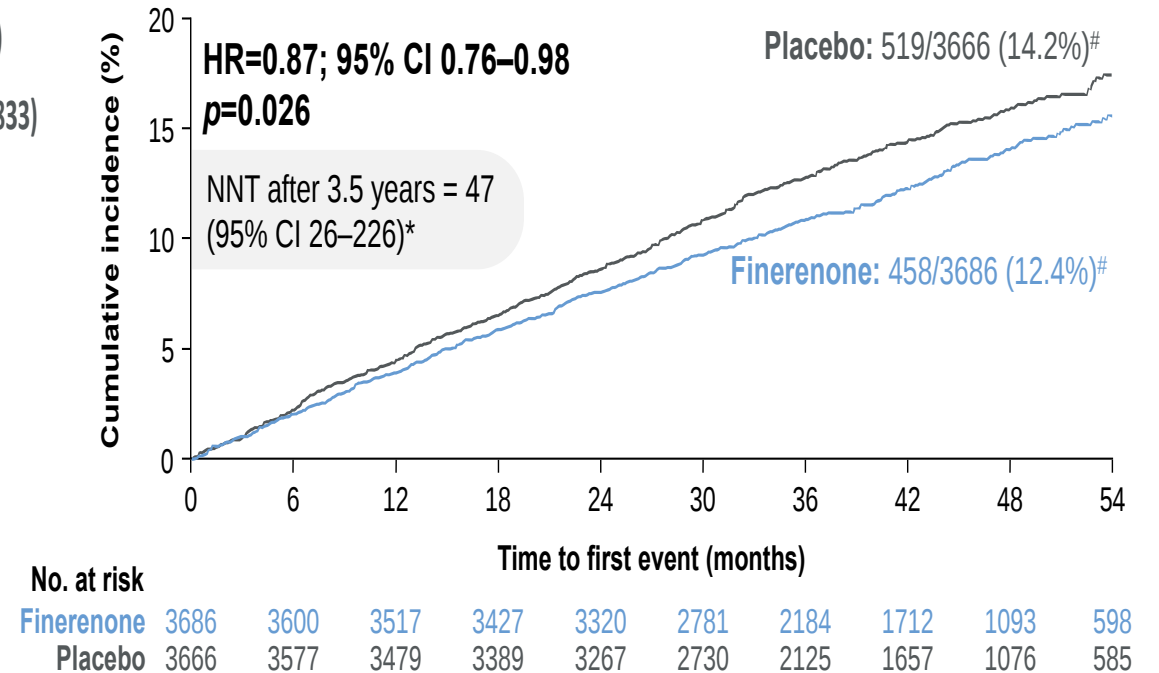
No. at Risk									
Placebo	2199	2178	2132	2047	1725	1129	621	170	
Canagliflozin	2202	2181	2145	2081	1786	1211	646	196	

FIDELIO-DKD and FIGARO-DKD Primary Composite Outcomes

Fidelio DKD: kidney failure, 40% de
in eGFR, renal death



FIGARO-DKD: CV death, non-fatal MI, CVA, HHF



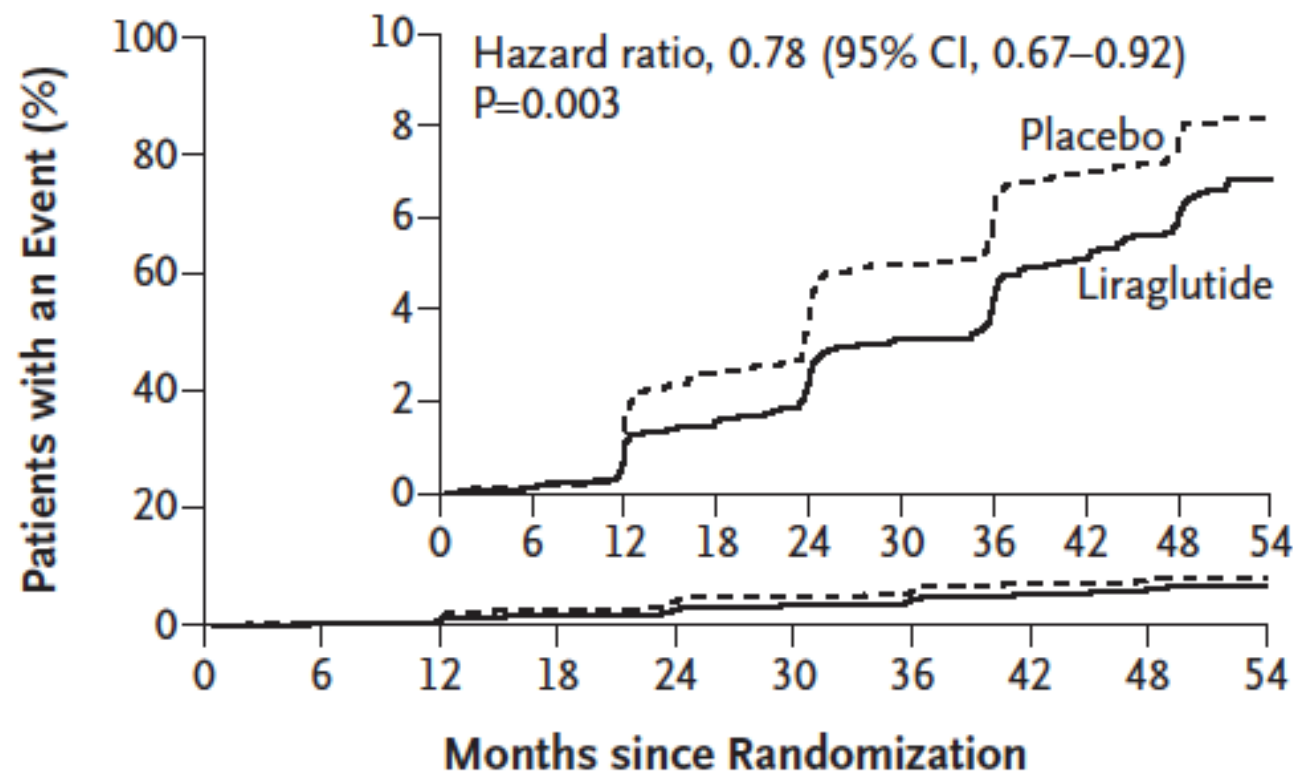
*NNT calculations based on an absolute risk reduction after 3.5 years of 2.1% (95% CI 0.4-3.8); #number of patients with an event over a median of 3.4 years of follow-up
CI, confidence interval; CV, cardiovascular; hHF, hospitalization for heart failure; HR, hazard ratio; MI, myocardial infarction; NNT, number needed to treat
Ruilope L, et al. *Am J Nephrol* 2019;50:345-356; Pitt B, Filippatos G, et al...Bakris GL 2021 *N Engl J Med* in press

Some GLP1-Receptor Agonists and Kidney (Secondary) Outcomes in Type 2 Diabetes*

Trial (N)	Agent	Subjects	Outcome	Result
LEADER (9,340)	Liraglutide	T2D, high CV risk	New onset albuminuria, DScr, ESKD, renal death	HR 0.78 (95% CI: 0.67-0.92)
SUSTAIN-6 (3297)	Semaglutide	T2 DM Age > 50 +CVD or stage 3-5 CKD, Age > 60 + high CV risk	New or worsening albuminuria, DScr and Ccr < 45 , RRT	HR 0.64 (95% CI: 0.46-0.88)
REWIND (9,901)	Dulaglutide	T2D + CV event or CV risk factors	New onset macroalbuminuria,> 30% decline in eGFR or RRT	HR 0.85 (95%CI: 0.77-0.93)
AWARD-7 (576)	Dulaglutide	T2D + Stage 3-4 CKD	Change in eGFR and UACR	eGFR decline: =1.2 to -1.5 vs 2.0, UACR no difference
ELIXA (6068)	Lixisenatide	T2D with ACS	% change in UACR and eGFR	eGFR no sig change, 21 to 39% lower UACR

Liraglutide and Renal Outcomes in Type 2 Diabetes

A Composite Renal Outcome



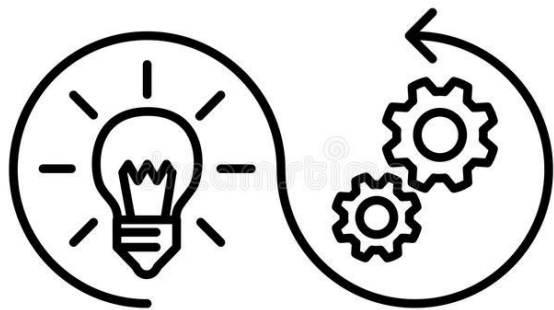
No. at Risk

Placebo	4672	4643	4540	4428	4316	4196	4094	3990	1613	433
Liraglutide	4668	4635	4561	4492	4400	4304	4210	4114	1632	454

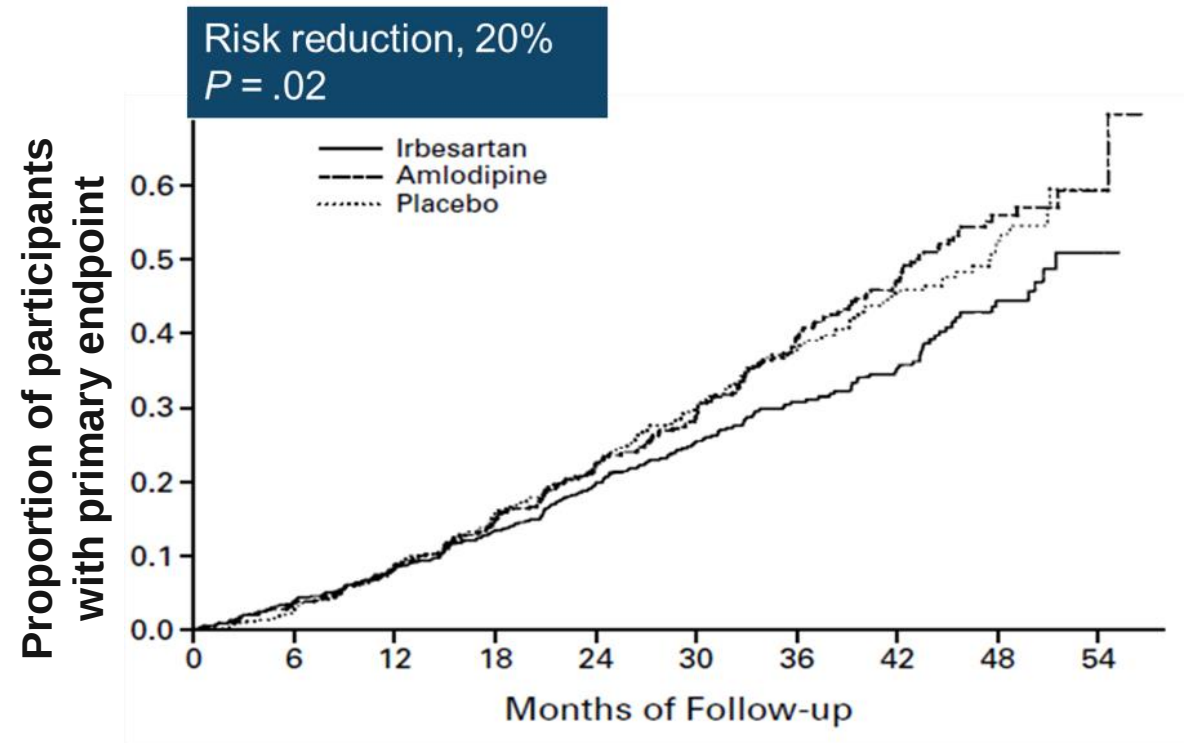
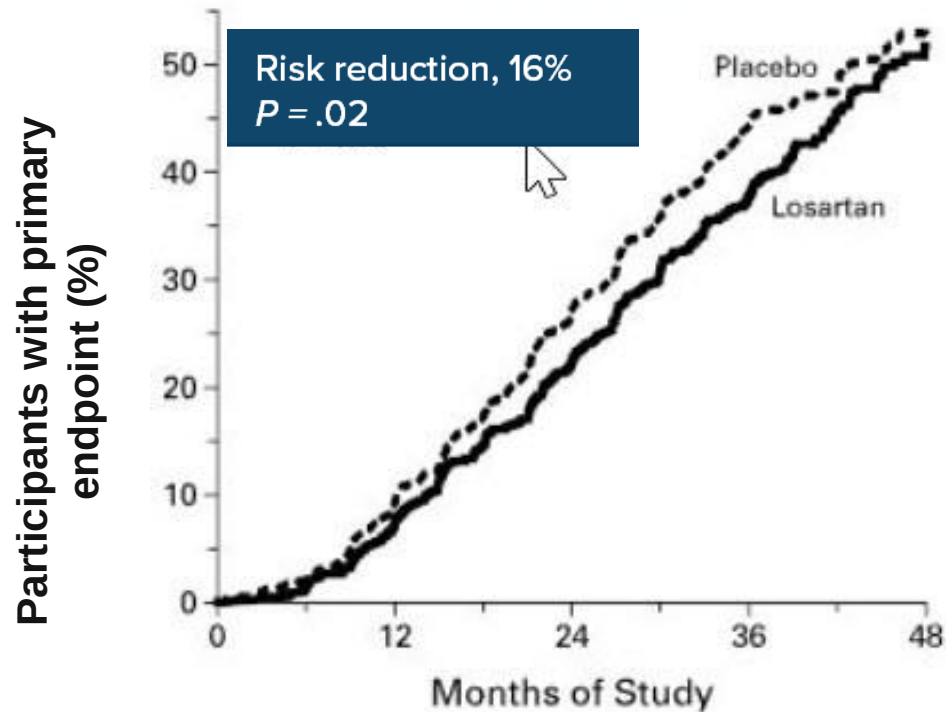
Now What?



Translation into Practice

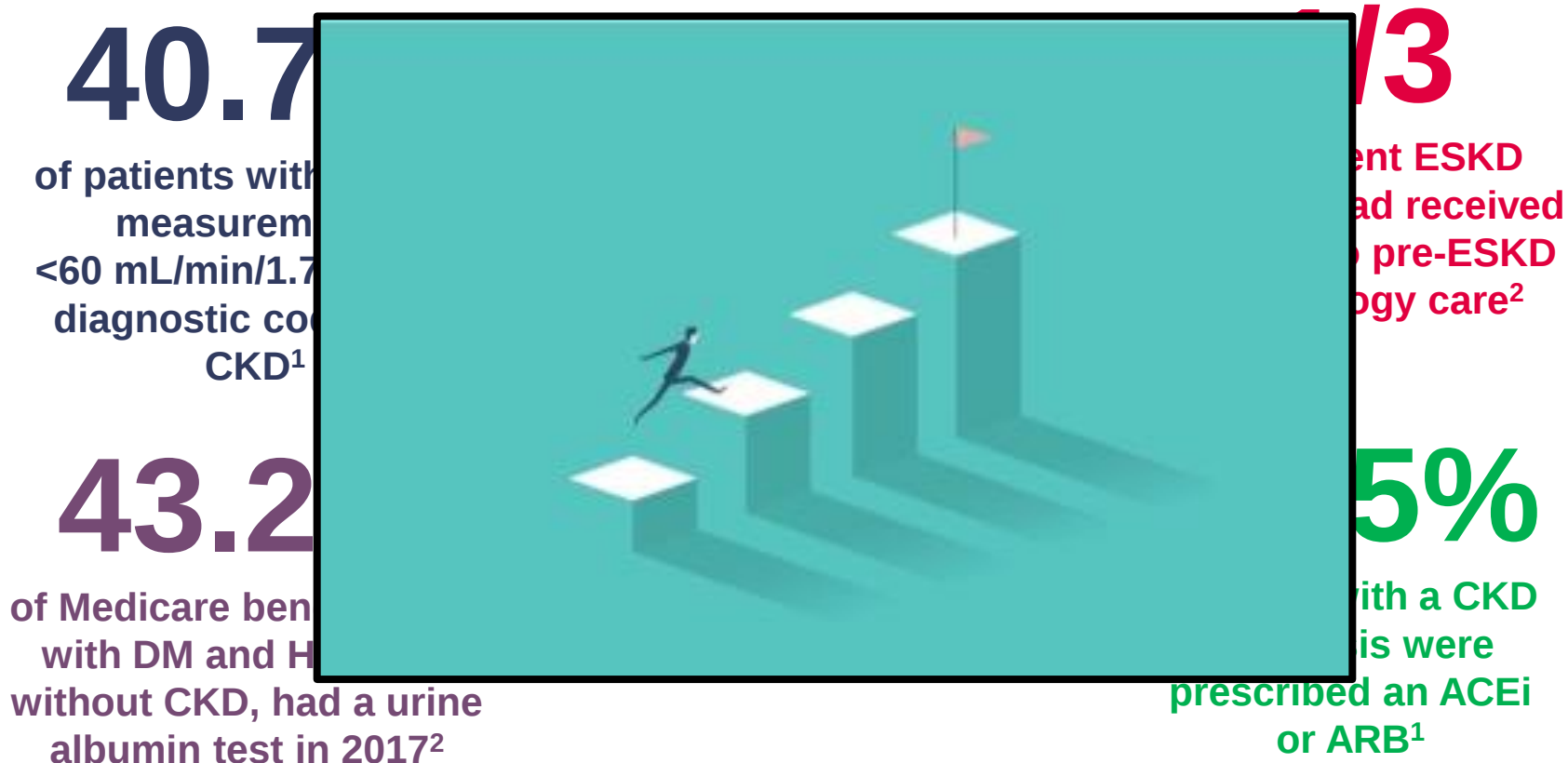


Translation: ARBs FDA approved to reduce risk for Kidney Failure in DKD 20 years ago



- *Composite of doubling of serum creatinine, ESKD, or death.
- a. Brenner BM, et al. *N Engl J Med*. 2001;345:861; b. Lewis EJ, et al. *N Engl J Med*. 2001;345(12):851-860.

Translation into Practice is a Major Problem



ESKD = end-stage kidney disease; ACEi = angiotensin-converting enzyme inhibitor; ARB = angiotensin-receptor blocker.

1. Tuttle KR, et al. *JAMA Netw Open*. 2019;2:e1918169. 2. Saran R, et al. *Am J Kidney Dis*. 2020;75(suppl 1):A6-A7. 3. Chu CD, et al. *Am J Kidney Dis*. 2020;76:174-183.

Translation to Clinical Practice: Barriers

- Inertia
- Unfamiliarity
- Adverse Effects
- Dissemination
- Cost



Combinations

- What will guidelines recommend
 - Sequential add on?
 - Start with combinations?
- What will Health Care Providers do?



Use of GLP-1 and MRA in CREDENCE and DAPA CKD and GLP-1 Ra and SGLT-2 in FIGARO

CREDENCE: GLP-1 Ra and MRA use at Baseline

With GLP-1 use		Without GLP-1 use	
Canagliflozin	Placebo	Canagliflozin	Placebo
4	4	2198	2195
With MRA use		Without MRA use	
0		2202	2199

DAPA CKD: GLP-1 Ra and MRA use at Baseline

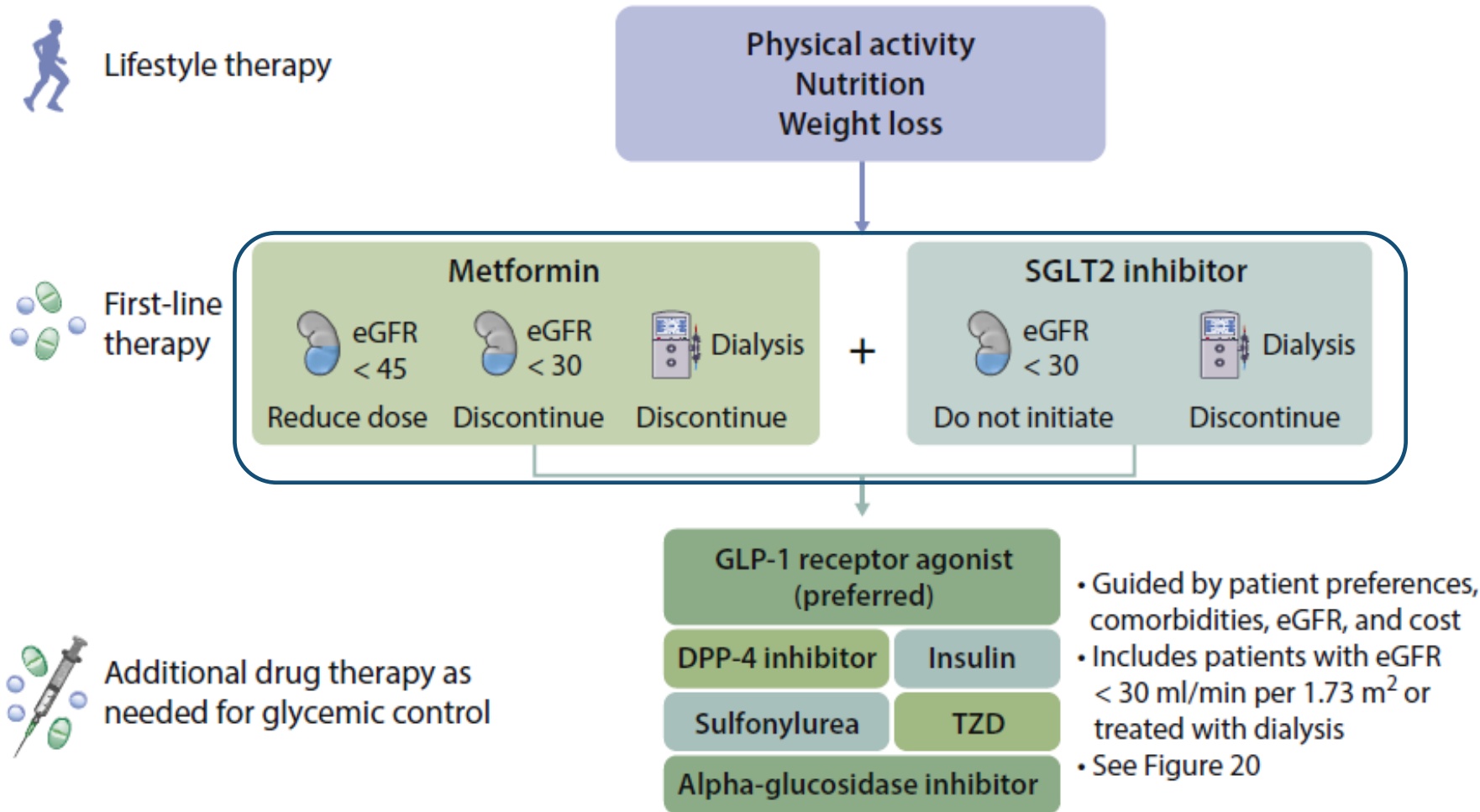
With MRA use		Without MRA use	
Dapagliflozin	Placebo	Dapagliflozin	Placebo
109	120	2040	2029
With GLP-1Ra Use		Without GLP-1Ra Use	
63	59	2089	2093

FIGARO: SGLT-2 and GLP-1 Ra use at baseline

With GLP-1 use		Without GLP-1 use	
Finerenone	Placebo	Finerenone	Placebo
308	242	3378	3424
With SGLT-2 use		Without SGLT-2 use	
314	304	2202	2199

KDIGO

Update for Diabetes Treatment in CKD



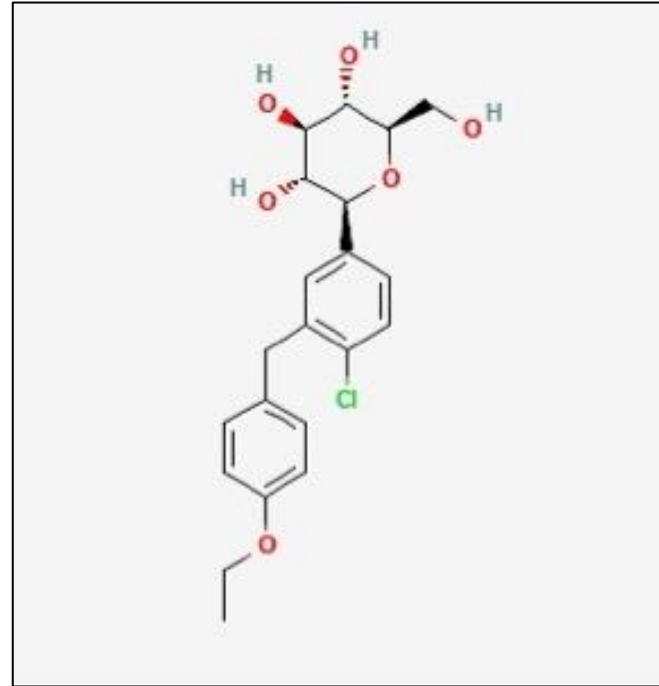
Lifestyle Changes



**First-line:
Metformin +
SGLT2
inhibitor
(if eGFR ≥
30)**

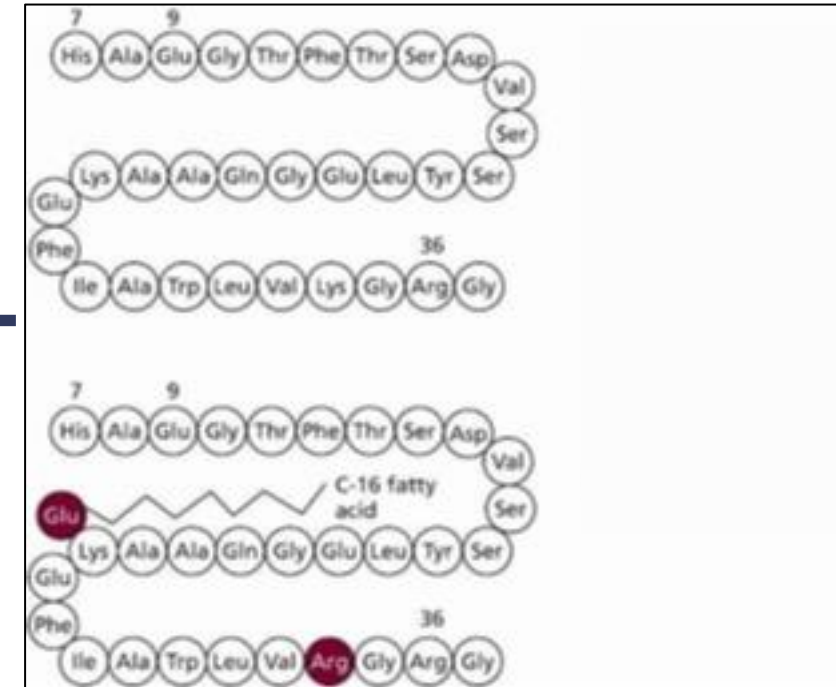
Potential Future Combination Trials: SGLT2i + GLP-1Ra

- Work together to lower blood glucose
- Different receptors and mechanisms of action
- Well tolerated in general
- Both reduce body weight
- Both reduce CV and renal (primarily surrogate) outcomes



Dapagliflozin

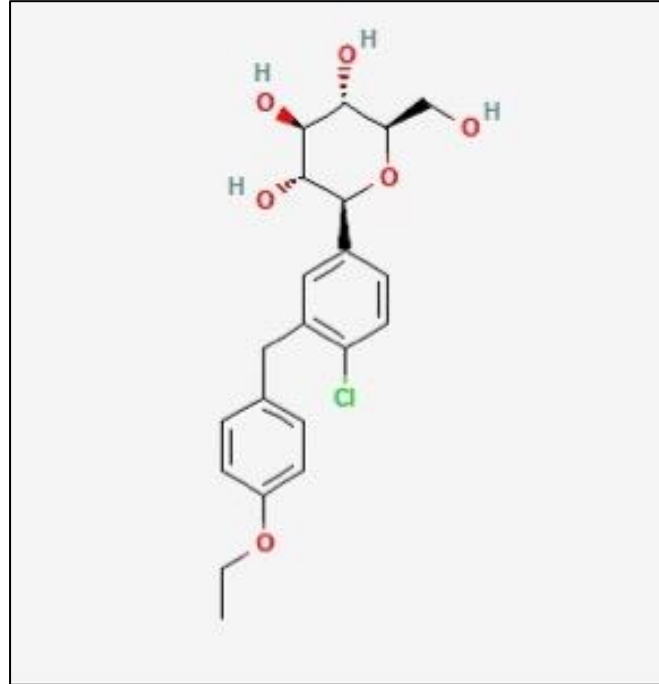
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Liraglutide

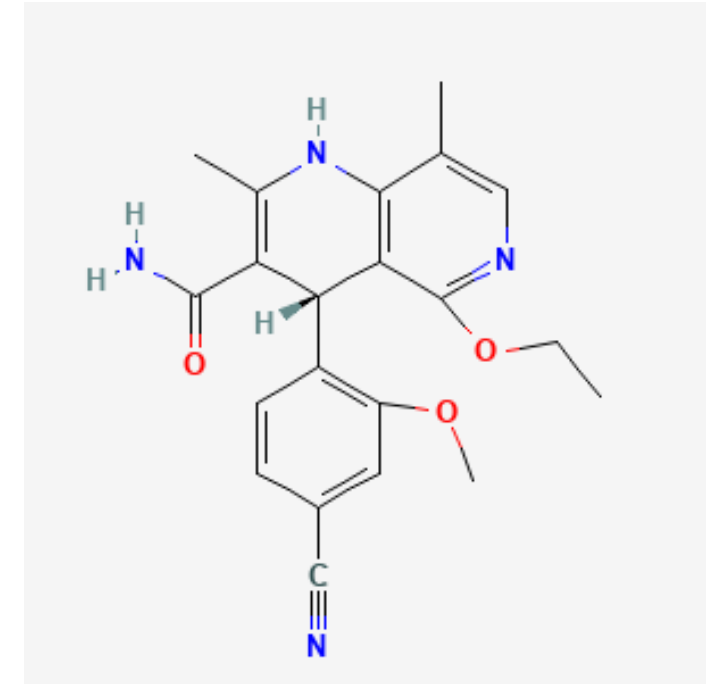
Potential Future Combination Trials: SGLT-2 + nsMRA

- Both shown to provide kidney and cardiovascular benefit
- Well tolerated
- Combination may mitigate hyperkalemia events



Dapagliflozin

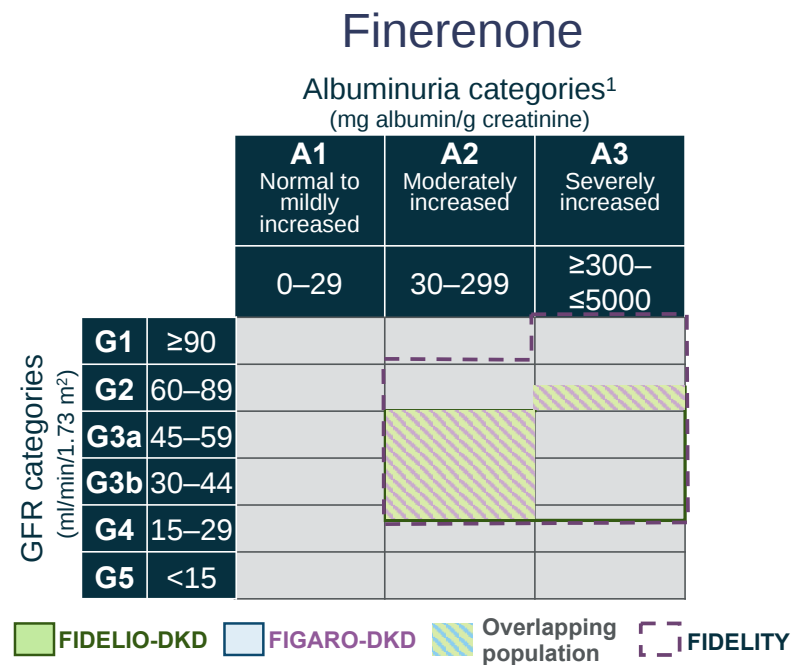
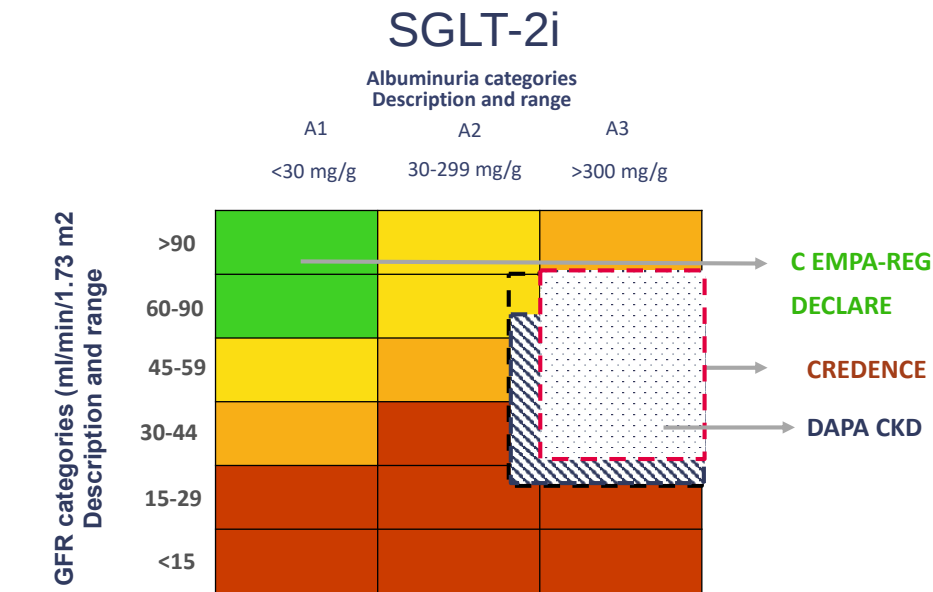
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Finerenone

Potential Outcomes Trials in DKD by Stage

Stage	Potential Combinations	Outcome
1	GLP-Ra1 and SGLT-2	CV
2	MRA and SGLT-2	CV
3	MRA + SGLT-2 + GLP-1Ra	CV and Kidney
4	MRA + SGLT-2 + GLP-1Ra	CV and Kidney
5	GLP-1Ra and SGLT-2	CV



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