



Brigham and Women's Hospital

Founding Member, Mass General Brigham

Diabetic Kidney Disease

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**CONTINUING MEDICAL EDUCATION
DEPARTMENT OF MEDICINE**



**HARVARD MEDICAL SCHOOL
TEACHING HOSPITAL**

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Clinical Focus

- Lupus Nephritis
- ICU Nephrology

Disclosures

Consultant for GlaxoSmithKline, Apellis Pharma, Optum Consulting

Research Support from Alexion Pharmaceuticals and Allena Pharmaceuticals

Objectives

- Review the epidemiology of diabetic kidney disease
- Review pathology, pathophysiology and natural history of diabetic nephropathy
- Discuss treatment strategies to delay progression of diabetic nephropathy

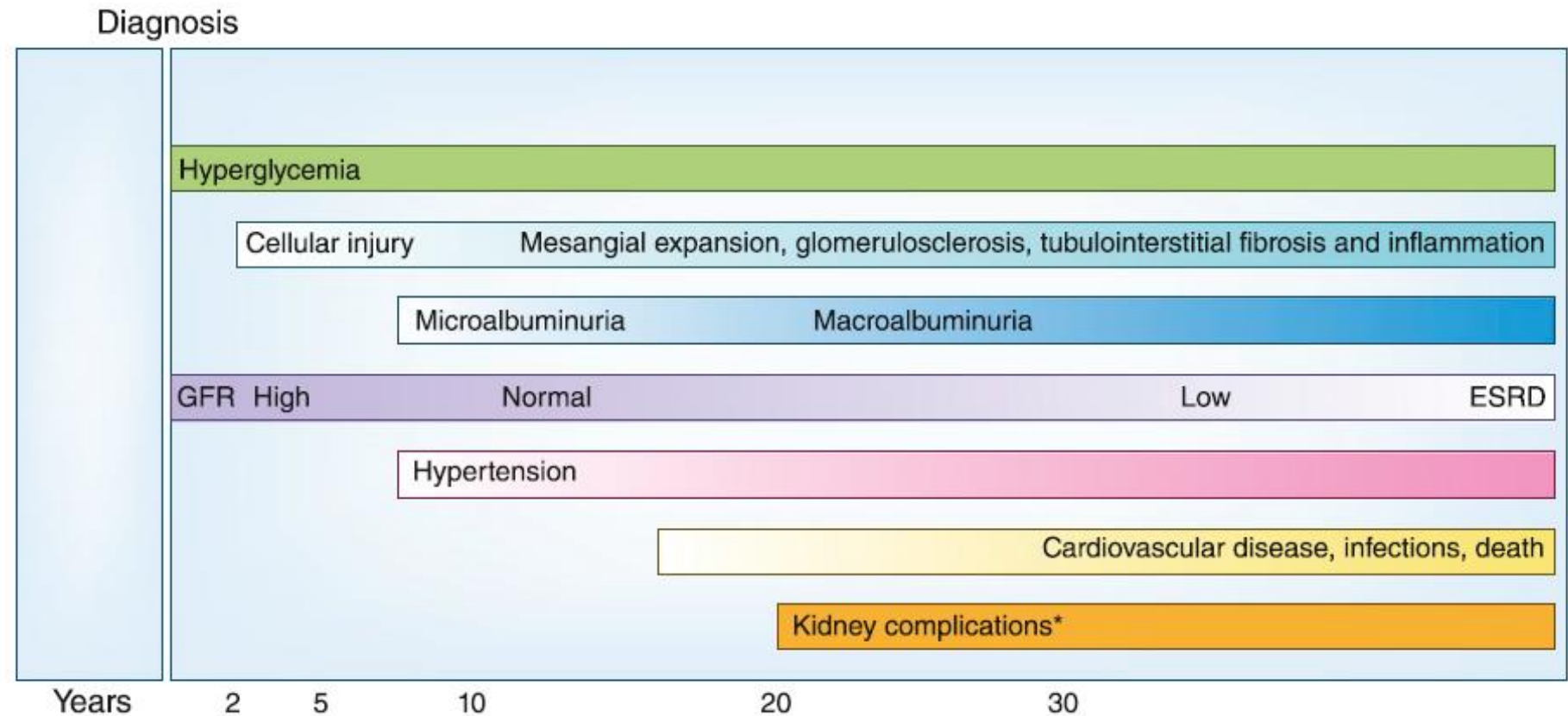
Epidemiology of Diabetic Kidney Disease

Epidemiology of Diabetic Kidney Disease

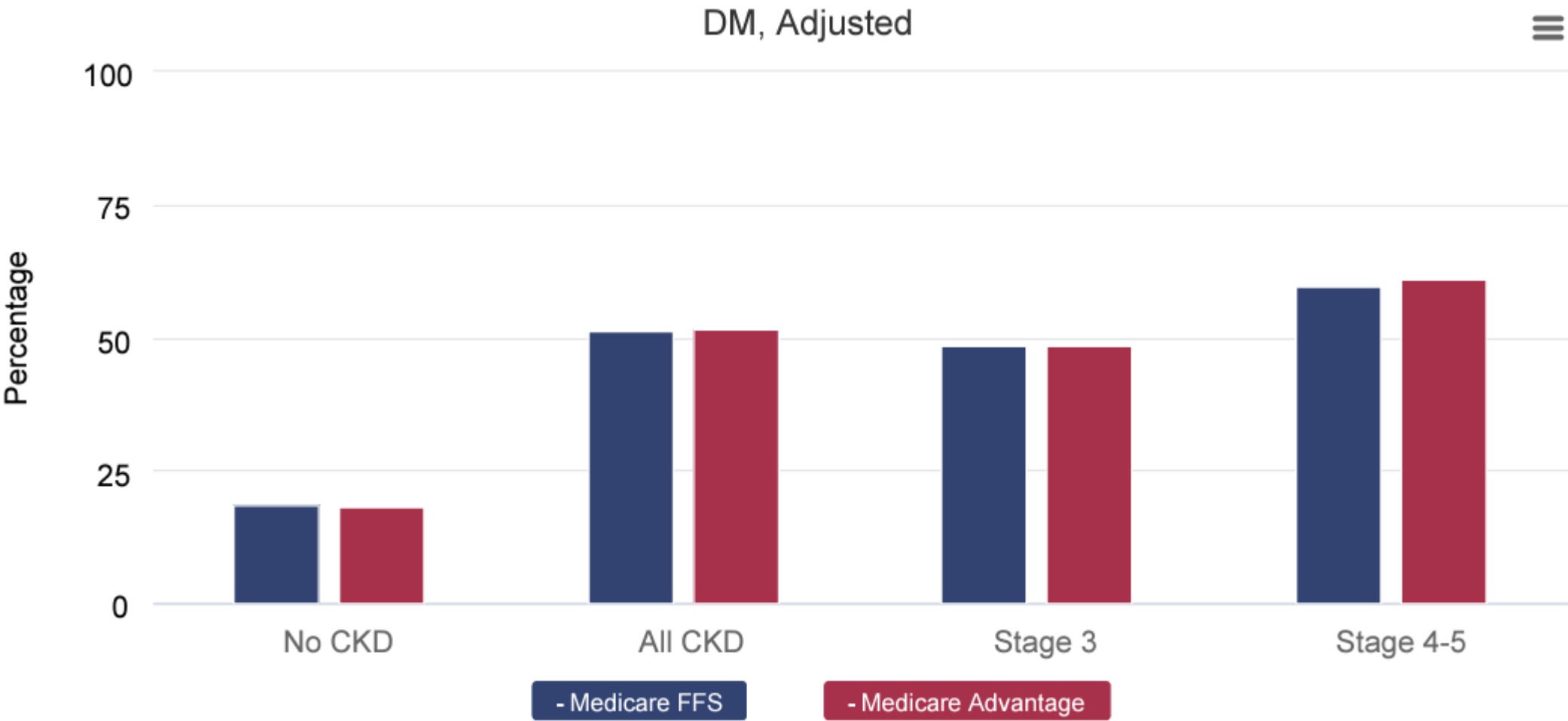
- Diabetes is the leading cause of CKD in the US and worldwide
- Overall prevalence of DM has increased from 6-10% over 20 years
- Proportion with CKD has remained stable (25-30%)
- Although it is the commonest cause of ESRD, proportion with ESRD is very low as the majority die before requiring RRT
- T2DM accounts for 90% of DM cases so most DN patients have T2DM
- Genetic variation accounts for much of the heterogeneity in presentation
- Outcomes for patients with T1 and T2DM who develop CKD are worse than for those who don't.

Natural History of DN in T2DM

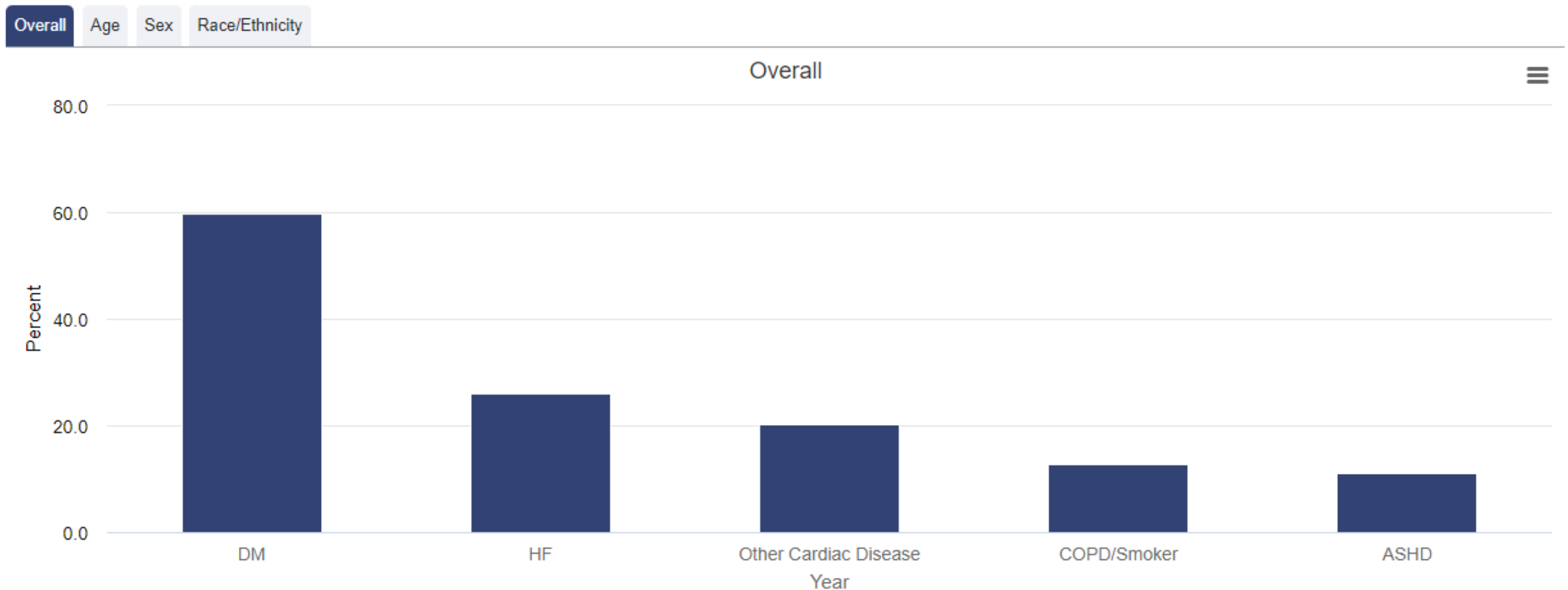
- Proteinuria developed 11-23 years after diagnosis
- GFR decline after 18-25 years
- ESRD after 18-30 years



Diabetes is common in patients with CKD



DN is common in patients starting dialysis



Natural History of Diabetic Nephropathy

Not all patients fit the micro → macro → CKD paradigm

2%/year proteinuria progression

40% never developed albuminuria

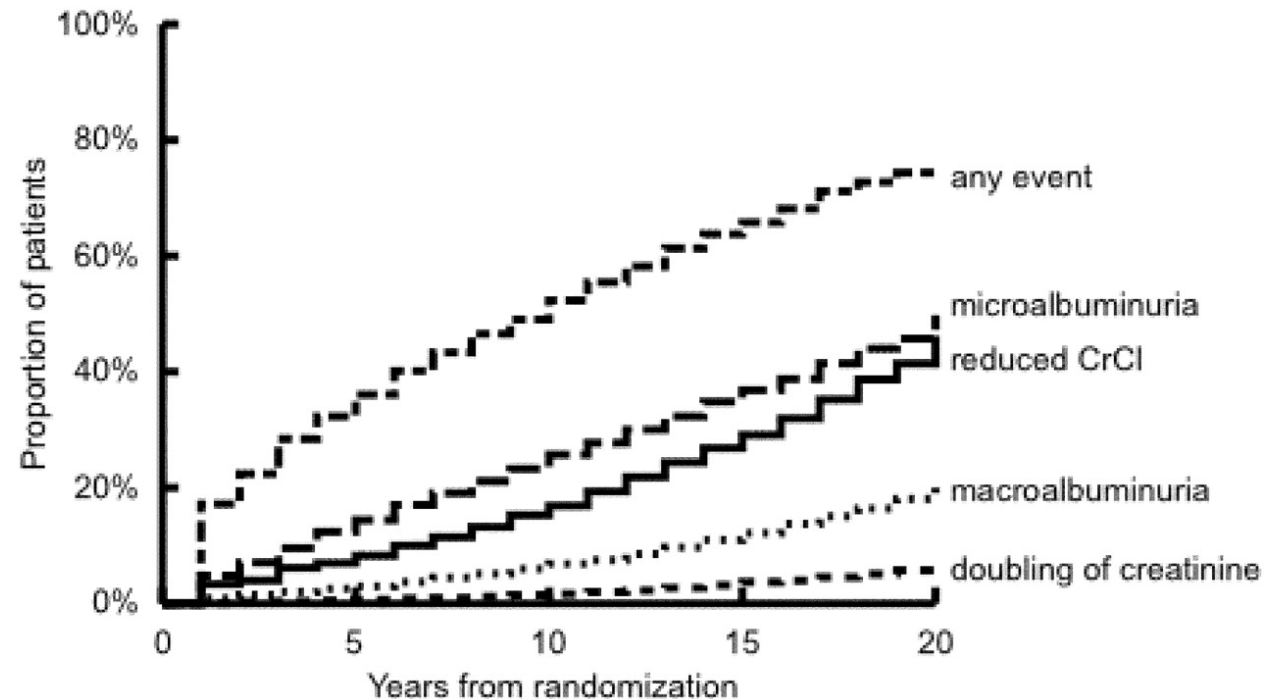
60% developed CKD without albuminuria

In patients with microalbuminuria

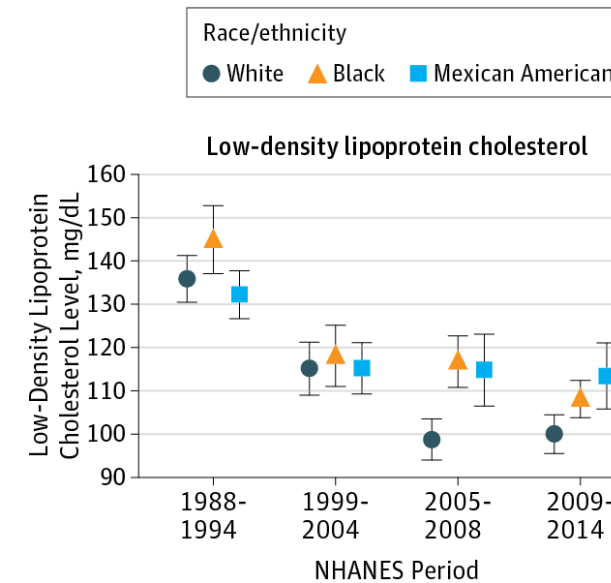
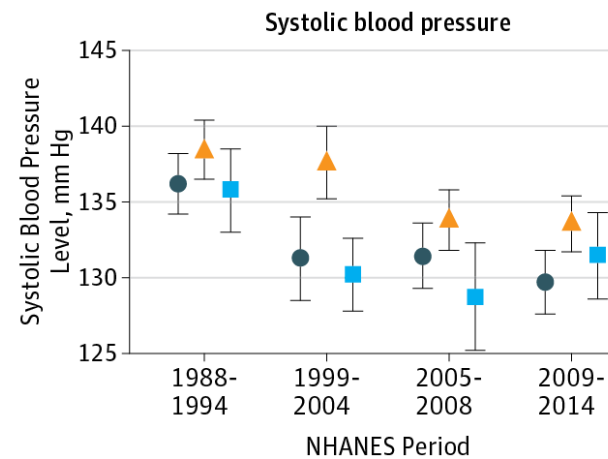
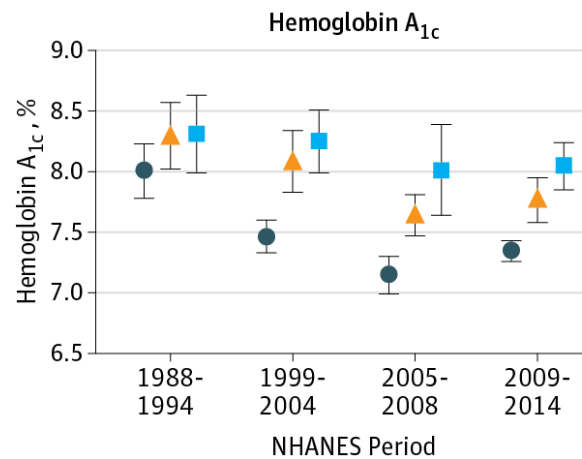
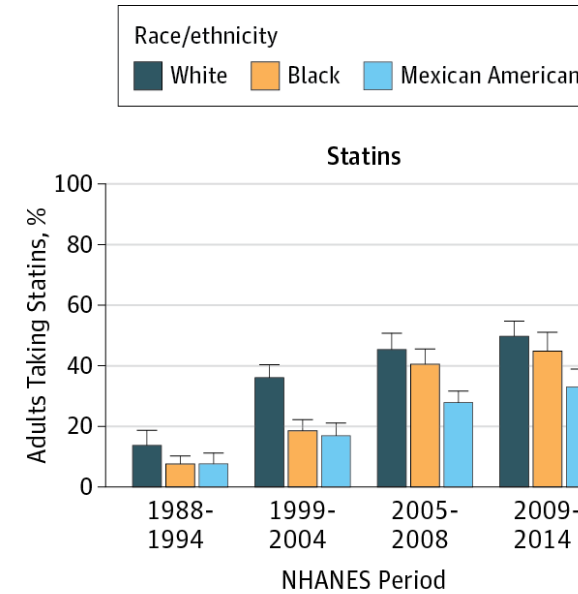
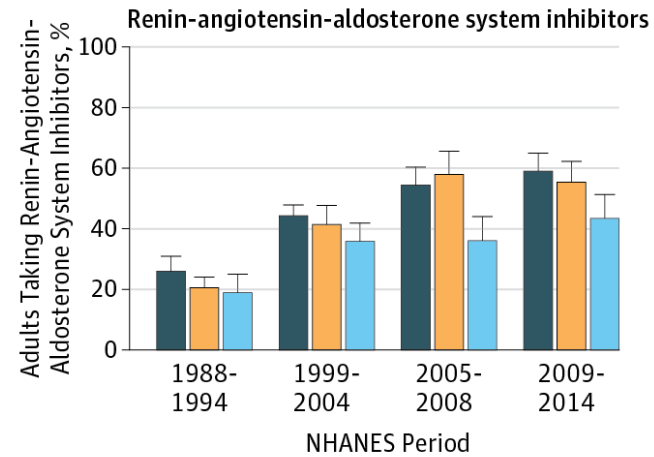
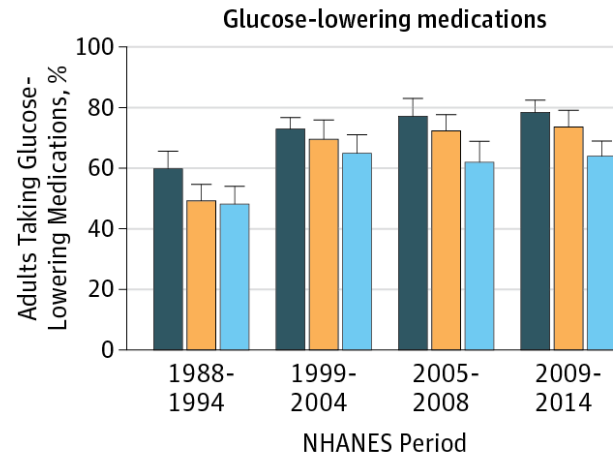
31% progressed to macroalbuminuria

31% regressed

38% remained with microalbuminuria



Change in diabetes care over time



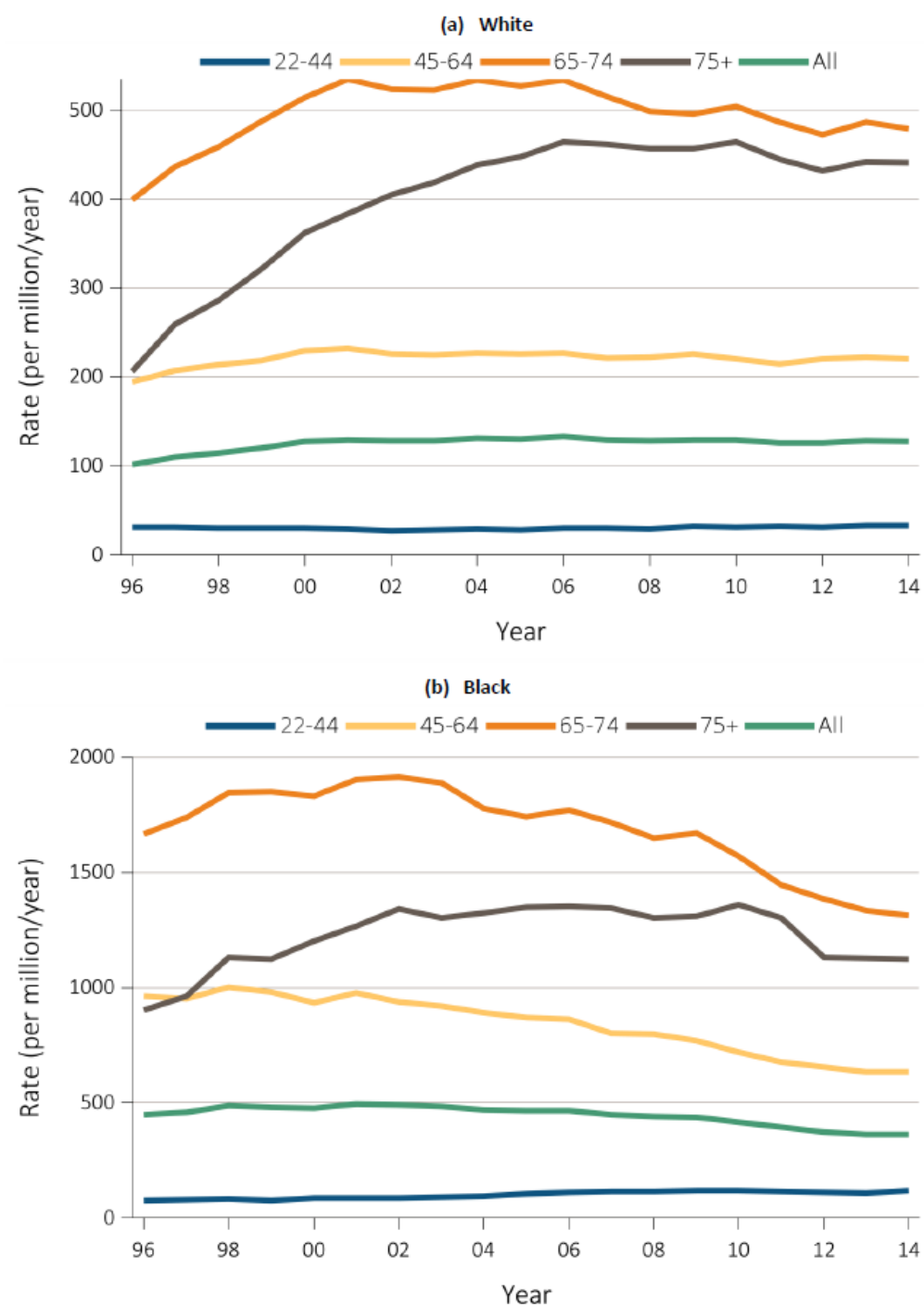
Decreasing prevalence of albuminuria but more reduced eGFR in individuals with diabetes

Table 3. Prevalence of Albuminuria and Reduced Estimated Glomerular Filtration Rate Among US Adults With Diabetes by Age, 1988 Through 2014

NHANES Period	No. With Diabetes	Unadjusted Prevalence, % (95% CI)		Adjusted Prevalence Ratio (95% CI) ^b	P Value for Trend
		Based on a Single Laboratory Value	Accounting for Persistence ^a		
Albuminuria (ACR ≥30 mg/g) ^c					
Adults aged <65 y					
1988-1994	256	33.5 (28.3-39.1)	19.5 (13.5-25.4)	1 [Reference]	.001
1999-2004	244	30.0 (25.9-34.4)	17.6 (12.9-22.3)	0.89 (0.72-1.11)	
2005-2008	224	26.6 (22.9-30.7)	15.7 (10.5-20.8)	0.80 (0.64-0.99)	
2009-2014	327	23.9 (20.6-27.6)	14.0 (10.1-18.0)	0.70 (0.57-0.87)	
Adults aged ≥65 y					
1988-1994	278	37.7 (31.7-44.2)	22.1 (15.9-28.4)	1 [Reference]	.15
1999-2004	287	35.7 (31.6-39.9)	20.7 (15.9-25.5)	0.94 (0.77-1.15)	
2005-2008	223	36.8 (33.6-40.2)	21.9 (17.0-26.8)	0.96 (0.80-1.16)	
2009-2014	318	32.3 (28.2-36.7)	19.2 (14.9-23.4)	0.84 (0.68-1.03)	
Reduced Estimated Glomerular Filtration Rate (eGFR <60 mL/min/1.73 m ²) ^d					
Adults aged <65 y					
1988-1994	40	4.0 (2.4-6.5)	2.9 (0-5.9)	1 [Reference]	.15
1999-2004	43	5.3 (3.8-7.4)	3.9 (1.3-6.5)	1.45 (0.80-2.61)	
2005-2008	53	6.0 (4.3-8.3)	4.3 (1.8-6.9)	1.62 (0.89-2.94)	
2009-2014	95	7.6 (5.9-9.9)	5.5 (2.9-8.2)	1.95 (1.12-3.39)	
Adults aged ≥65 y					
1988-1994	174	27.3 (23.3-31.8)	19.3 (13.4-25.3)	1 [Reference]	<.001
1999-2004	230	34.3 (30.1-38.8)	24.6 (18.4-30.9)	1.26 (1.04-1.54)	
2005-2008	189	34.6 (28.6-41.3)	24.4 (18.0-30.9)	1.28 (0.99-1.64)	
2009-2014	355	40.6 (36.5-44.8)	28.9 (22.9-34.9)	1.53 (1.27-1.85)	

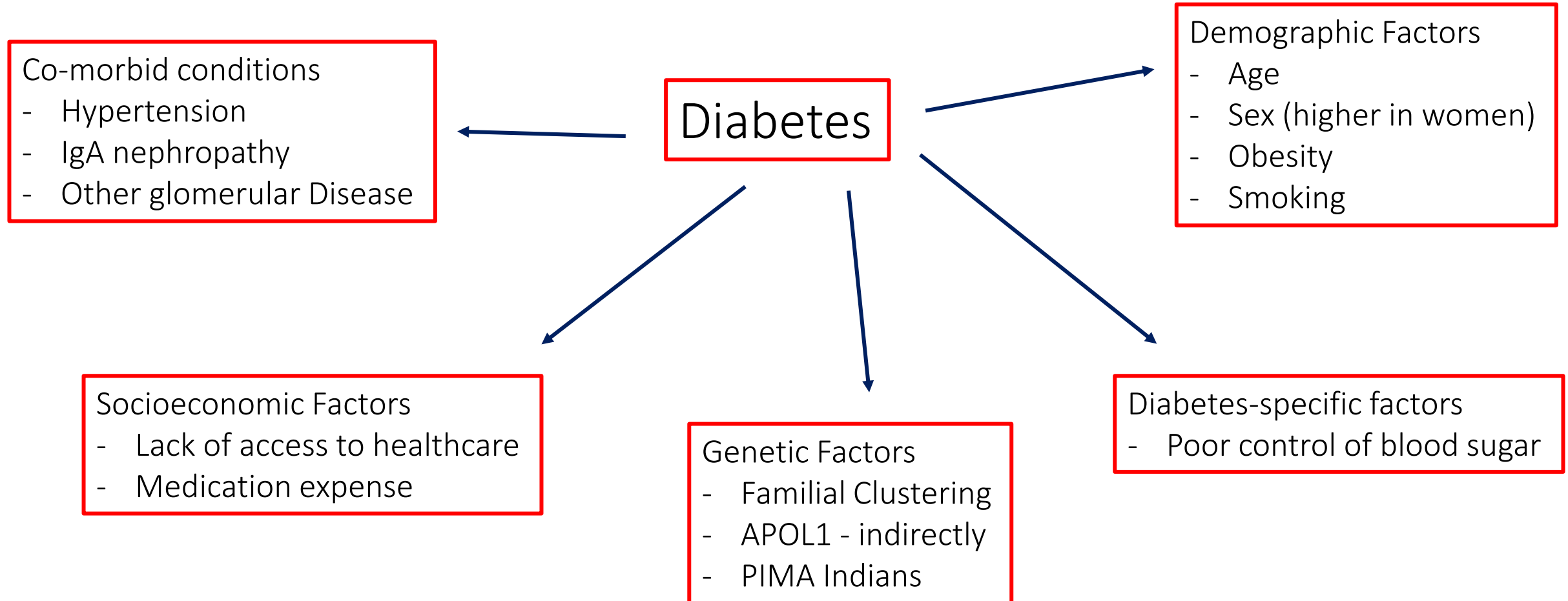
Marked reduction in ESRD cases due to diabetes, particularly in African Americans

Annual Report, USRDS 2016



Pathophysiology of DN

Risk factors for CKD in patients with Diabetes



Pathophysiology of DKD

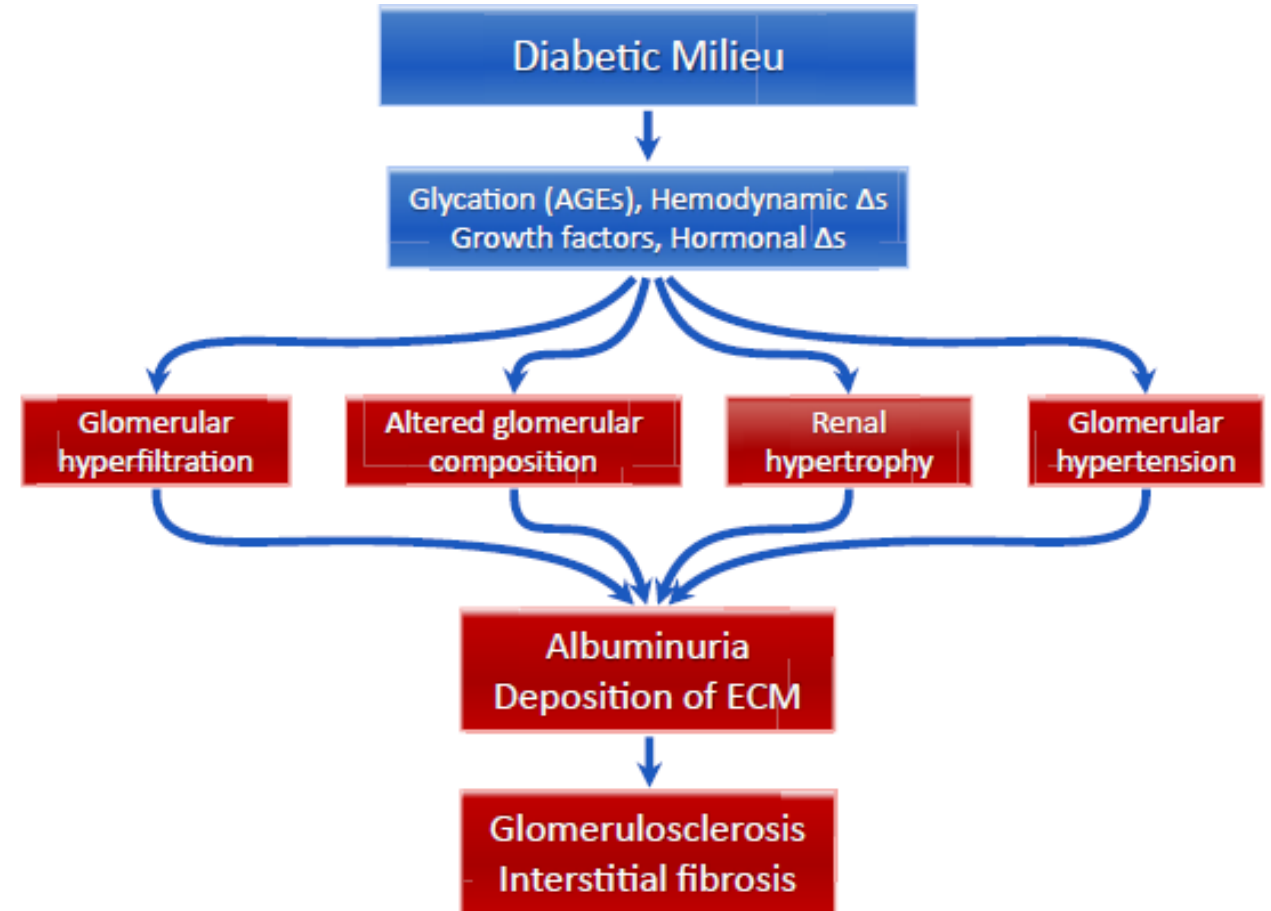
Diabetic milieu promotes the formation of AGE, pro-inflammatory and pro-fibrotic growth factors

Increased production of ROS, epigenetic alterations (metabolic memory)

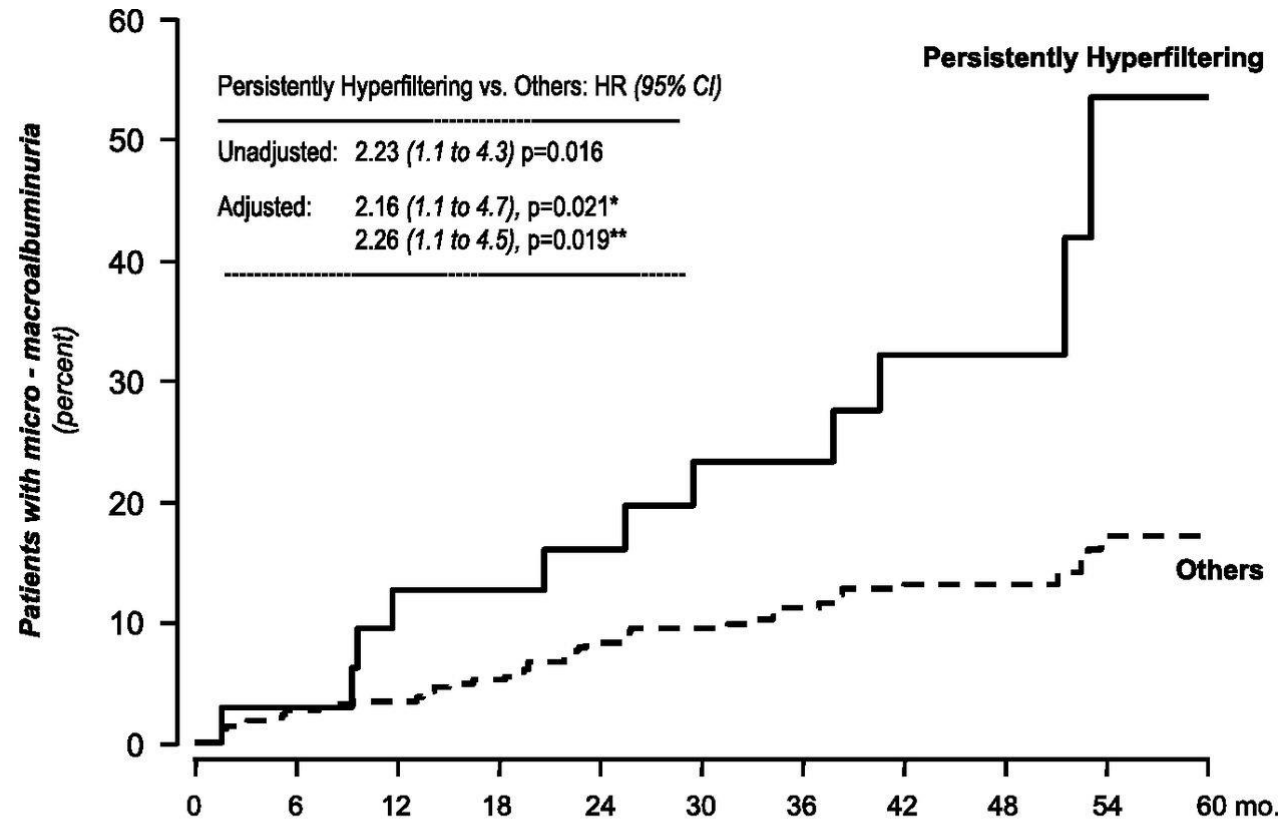
Increased renal plasma flow and filtration with initial increase in GFR (hyperfiltration)

Likely important role of TGF

Glomerular structural changes ultimately lead to albuminuria and CKD



Role of Hyperfiltration in DN



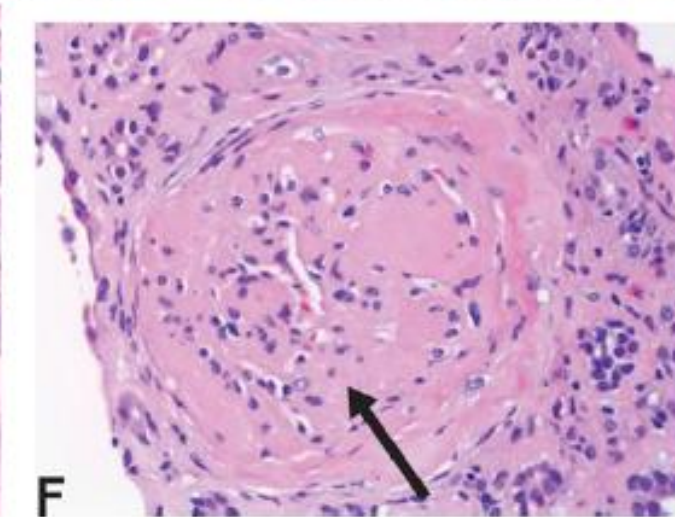
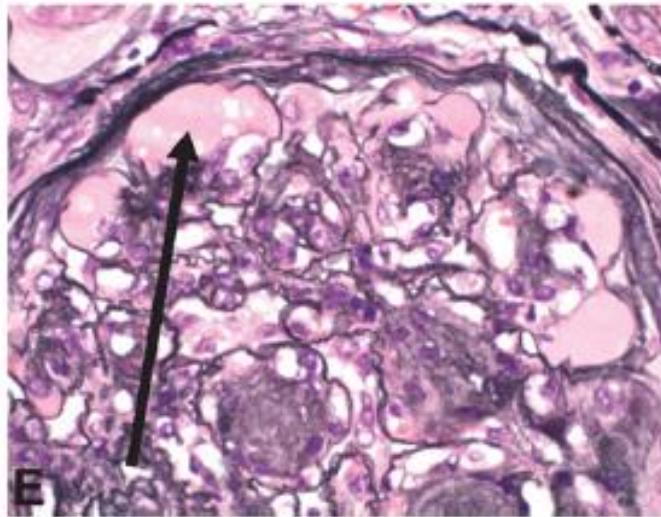
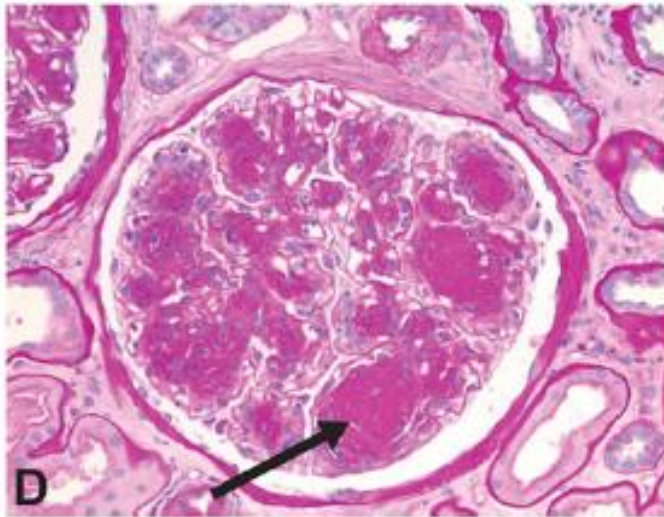
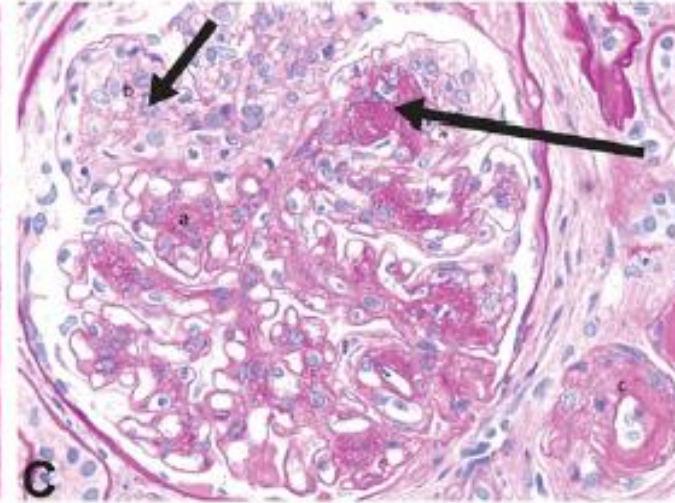
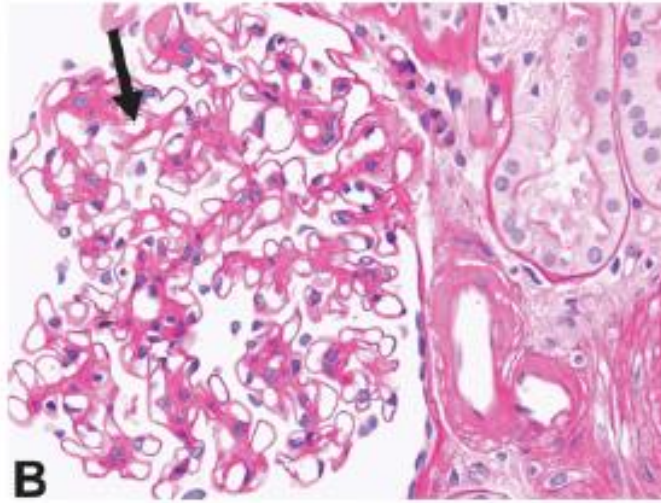
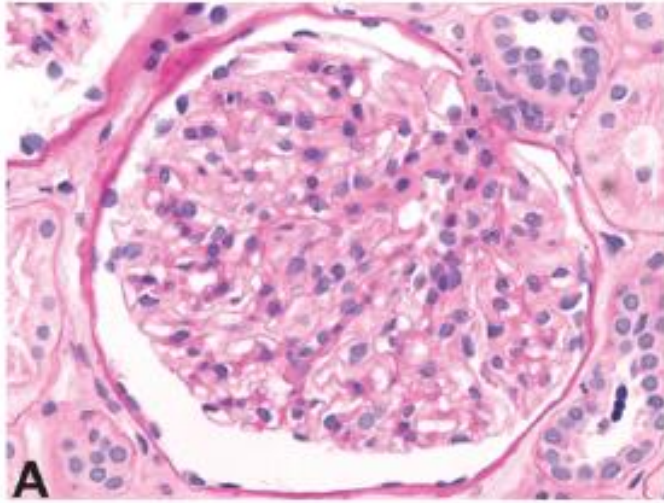
Patients at risk

Persistently-Hyperfiltering	47	45	40	39	38	34	33	28	21	17	15
Others	502	389	373	361	327	302	299	235	183	132	65

Persistent hyperfiltration after ACE initiation predicts future albuminuria

Helps explain why ACE/SGLT2 are helpful in delaying progression

Glomerular Changes in DKD



Microvascular disease and DN

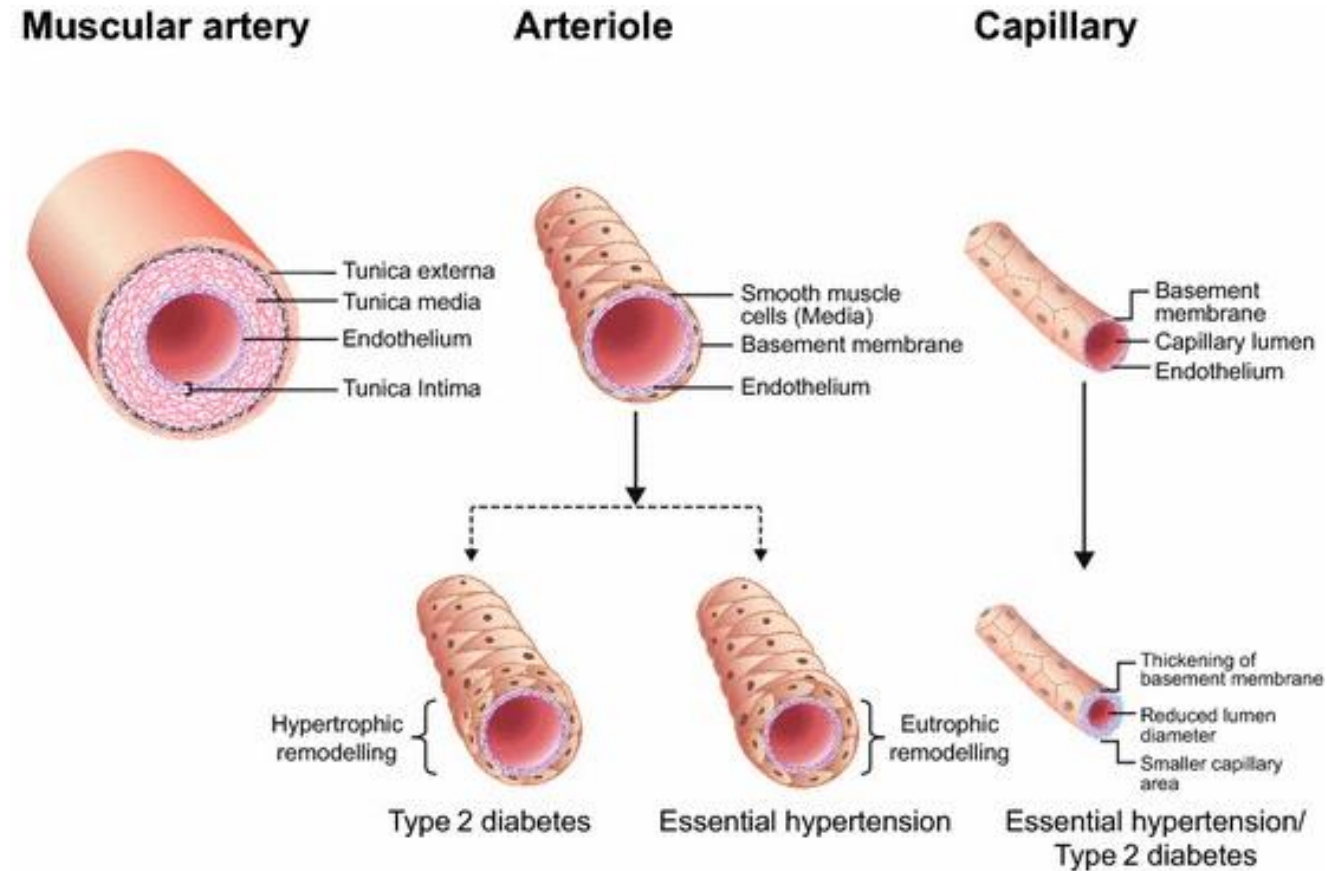
- Microcirculatory changes precede glomerular changes leading to nephropathy, retinopathy and neuropathy.

- Hypertrophic remodeling of vascular wall

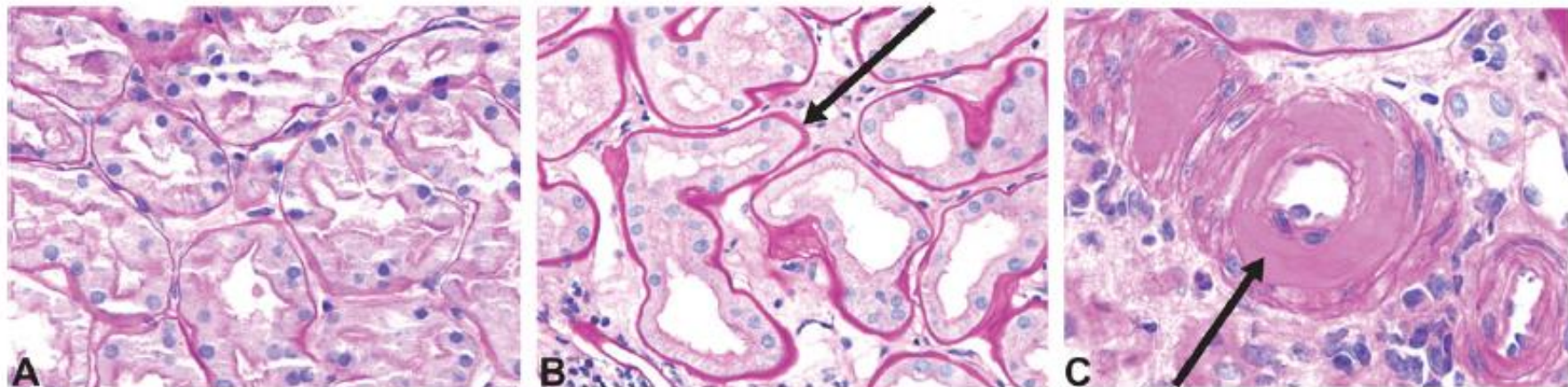
- ↓ Decreased luminal diameter
- ↑ Medial and BM thickness
- ↑ Microvascular permeability

- Potential Mechanisms

- Accumulation of AGEs
- Oxidative Stress



Tubulointerstitial and vascular changes in DKD



Bias in Biopsy Studies

- Most patients getting biopsies for CKD with Diabetes will be atypical – more proteinuria/hematuria/rapid progression
- The “typical” diabetic nephropathy patient almost never gets a biopsy
- We don’t know what the majority of diabetic kidney disease looks like.
- Study of 52 patients with classic clinical DN
 - 36% “classic” diabetic nephropathy
 - 31% primarily ischemic/vascular changes
 - 33% another superimposed glomerular disease

Gambara, JASN 1993

DKD Progression

Definition of Progression

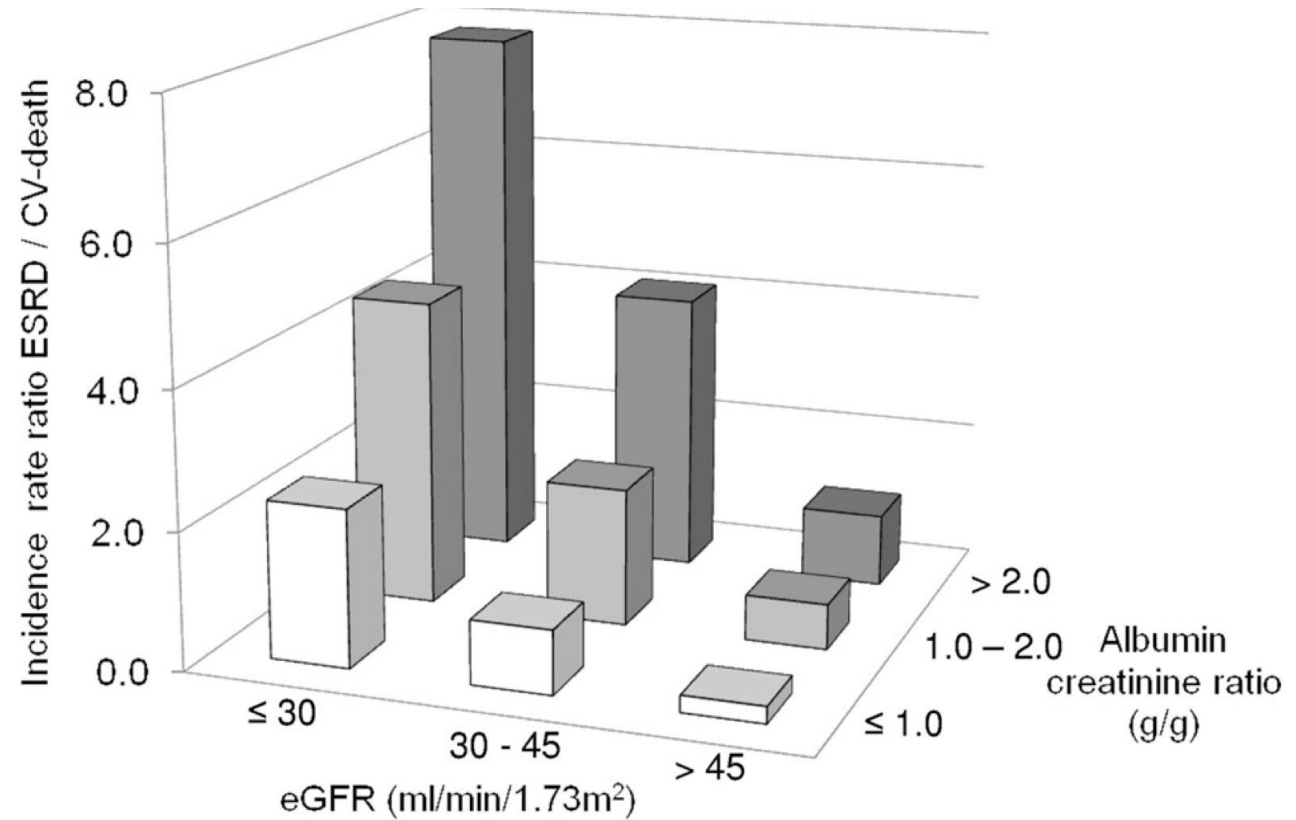
In population-based cohorts with healthy volunteers, “normal” GFR decline is 0.2-1ml/min/1.73m²/year

No clear definition of progression and rapid progression

Suggested definitions (KDIGO 2012):

Category	Definition
Progression	Decline in eGFR Category
Certain progression	Decline in eGFR category + 25% reduction in GFR
Rapid Progression	>5 ml/min/1.73m ² /year fall in eGFR

Risk for ESRD
increases as
proteinuria
increases and GFR
decreases



		eGFR (ml/min/1.73m ²)		
		≤30	30 - 45	>45
ACR (g/g)	> 2.0	12.87 (5.97-27.74)	7.46 (3.63-15.33)	7.40 (3.32-16.47)
	1.0 – 2.0	7.12 (3.16-16.04)	3.47 (1.63-7.40)	2.80 (1.18-6.64)
	≤1.0	3.61 (1.49-8.73)	1.49 (0.64-3.48)	1.00 (reference)

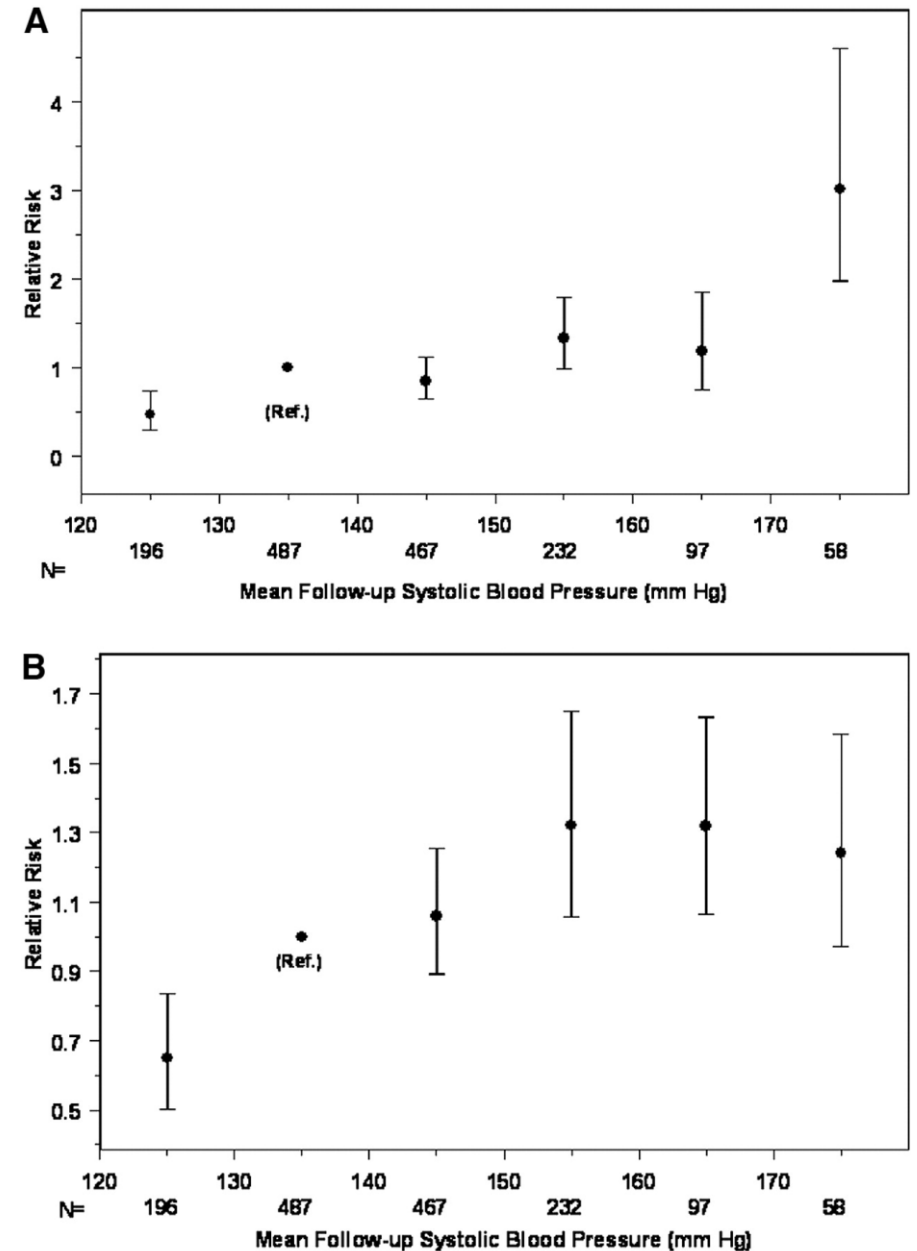
So how can we delay progression?

BP control to prevent progression of DN

Most trials of intensive BP reduction traditionally excluded patients with CKD

IDNT found J-shaped relationship between achieved systolic BP and outcomes (best at SBP 120-130mmHg)

UKPDS – lower risk microvascular complications with SBP 144 vs 154



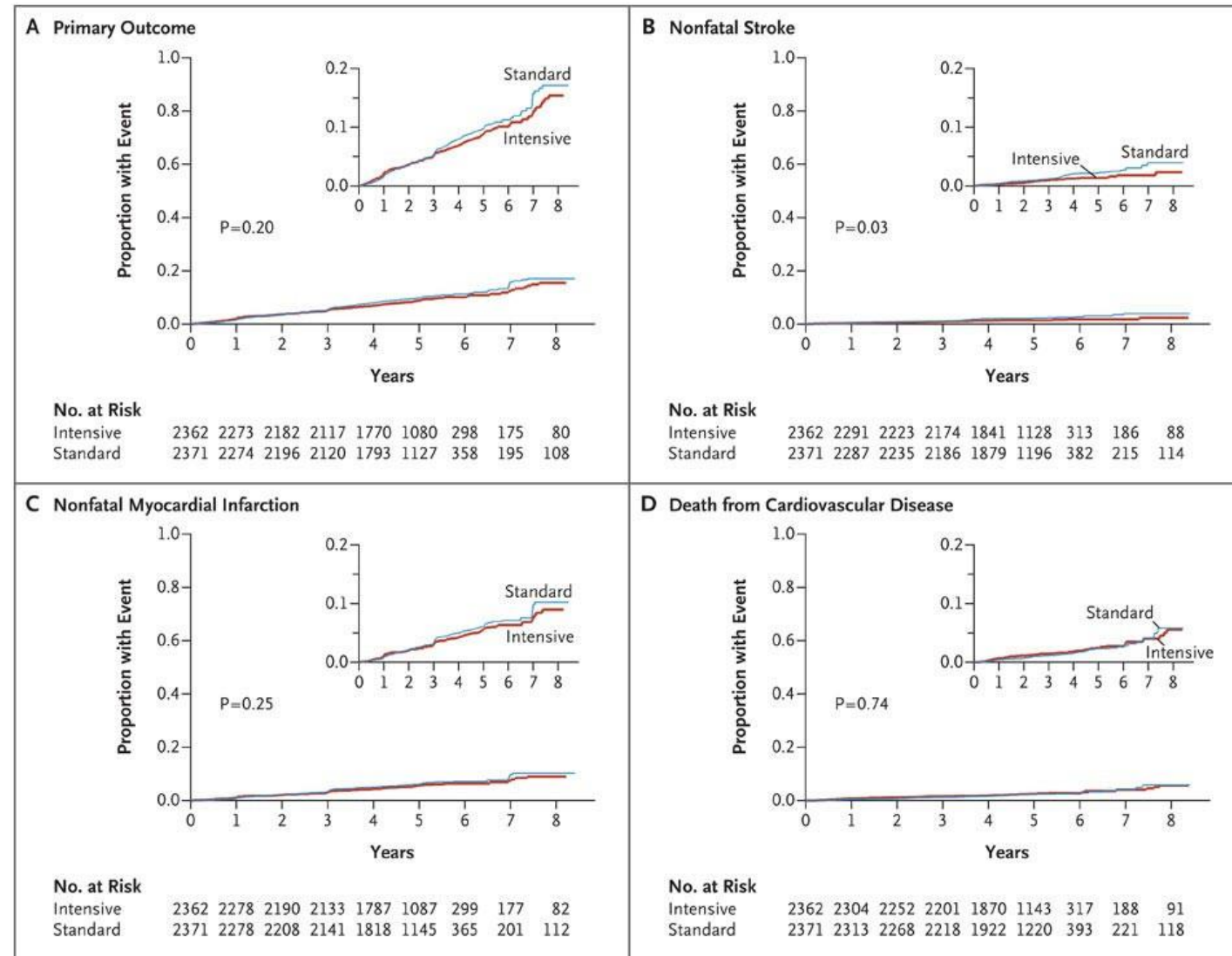
BP control to prevent progression of DN

ACCORD – no CV benefit for intense BP control (<120 vs <140) in T2DM

Reduction in albuminuria but no reduction in ESRD (underpowered)

SPRINT Trial showed 25% reduction in CV outcomes but **patients with diabetes were excluded**

More rapid decline in GFR in patients with CKD



Risk of AKI with intensive BP control

Post-hoc analysis of SPRINT

Increased risk of AKI with intensive BP control

Most cases were mild and returned to baseline

Subsequent analysis suggests higher CV risk in this group

Unclear if proteinuria modifies this effect (proteinuria >1g excluded from study)

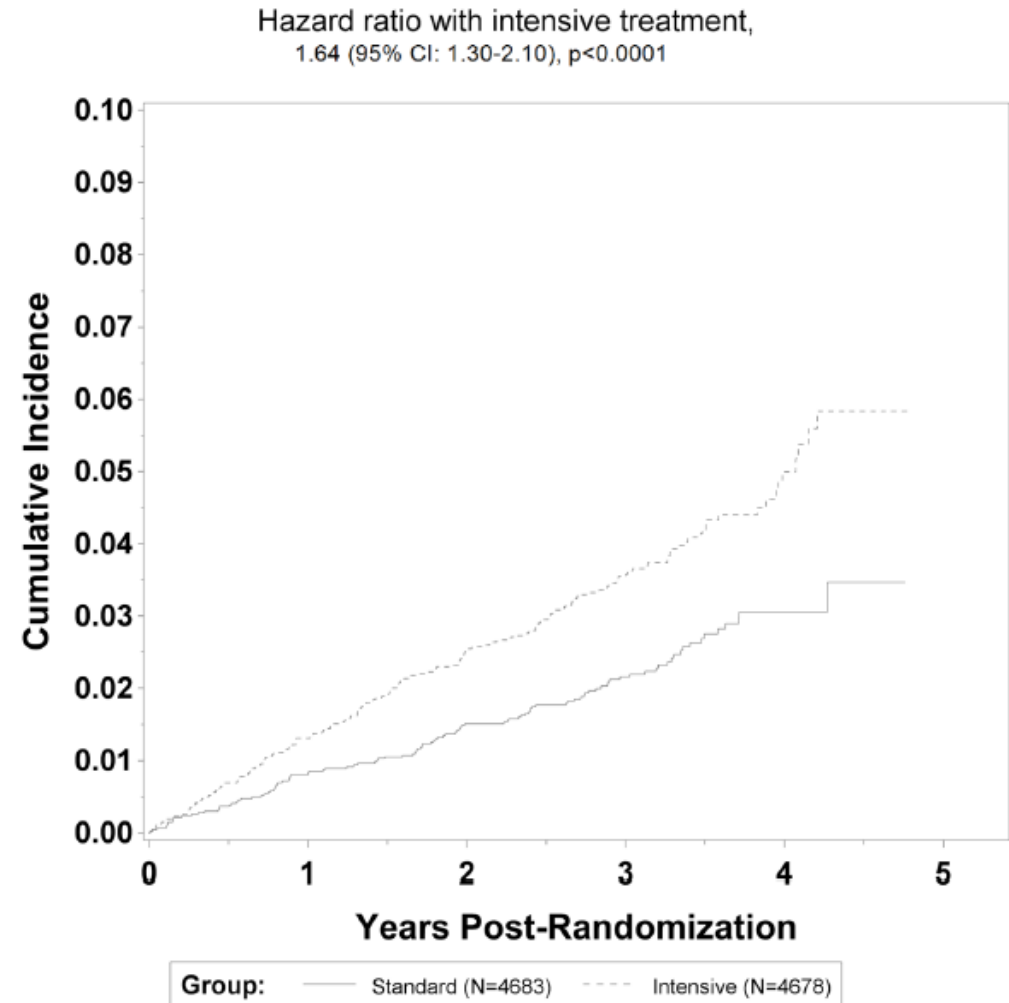


Figure 2.
Cumulative Hazard Plot for Acute Kidney Injury (CI denotes confidence interval).

Current Society Guidelines - UPDATE

BP target (mmHg)

Systolic			
<140			
<130	●	●	
<120		●	
Diastolic			
<90		●	●
<80	●		
Guideline	ACC/ AHA (2017, Ref 47)	ESC/ ESH (2018, Ref 48)	KDIGO (2021 Ref 5)
		Non-diabetics	
		Diabetics and /or ACR ≥ 70 mg/mmol	
		NICE (2019, 2021 Ref 49, 50)	

KDIGO 2021

Goal systolic BP <120 (using standardized measures only)

No evidence for CKD benefit but primarily for CV benefit

ESC 2018

Goal systolic BP 130-139

2017 ACC/AHA Guideline

Goal BP <130/90

2017 American Diabetes Association

Goal BP <140/90 but lower in individuals at higher risk of CV events

Intensive Glucose Control

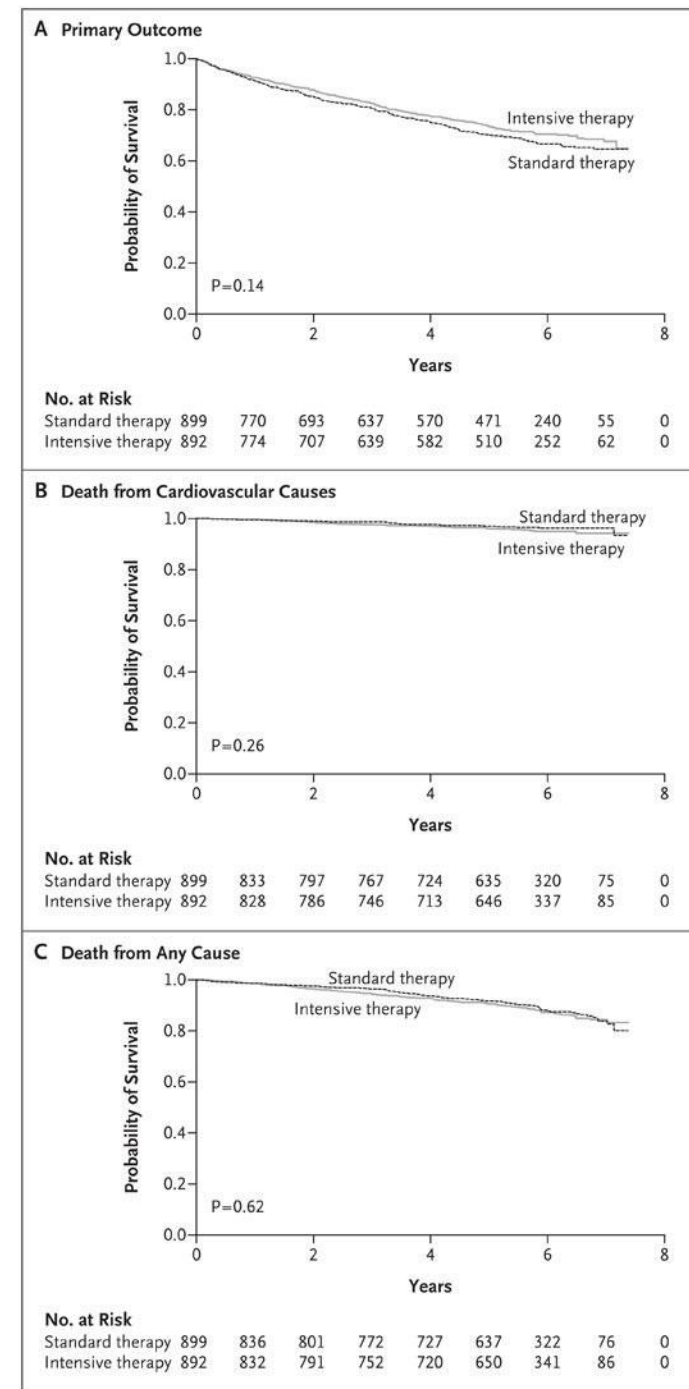
Intensive glucose control early in T1DM reduces the risk for microvascular complications

Less clear for T2DM likely reflecting delay in diagnosis in many cases

Strict glucose control in patients with established complications is not beneficial

Increased risk of hypoglycemia

No change in mortality in non-CKD population



Intensive Glucose Control increases CV and All-cause mortality in patients with established CKD

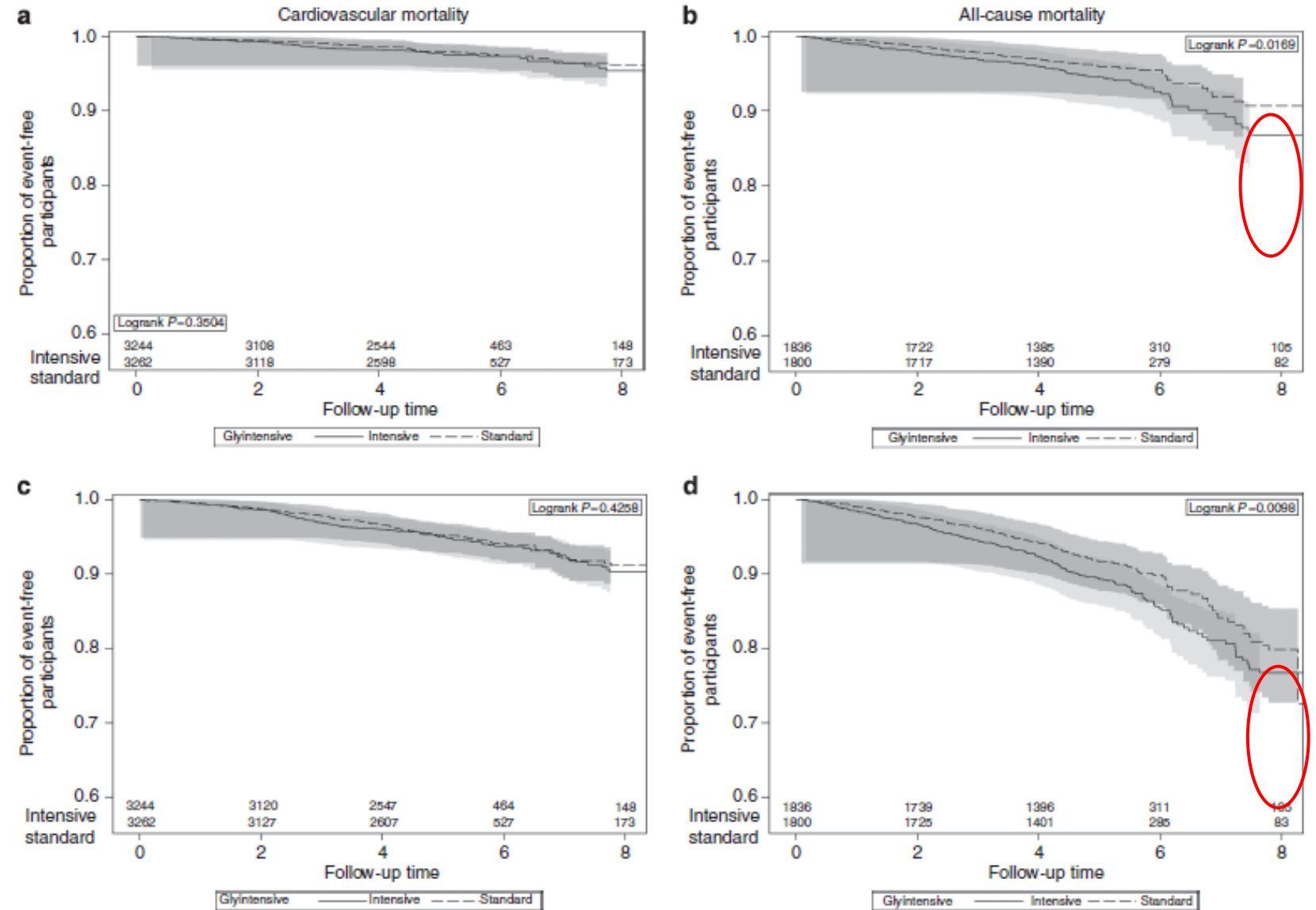


Figure 5 | Cardiovascular and all-cause mortality stratified by intensive or standard treatment group and by chronic kidney disease (CKD) status. Cardiovascular and all-cause mortality with intensive versus standard glycaemic control in patients without CKD (a, c) and with CKD (b, d).

Glucose Control Targets

ADA recommends

- Strict HbA1c target ($<6.5\%$) in younger patients without complications

- Target $<8\%$ in those with known microvascular complications or CKD

KDIGO recommends

- Target HbA1c $<7\%$ to delay onset of microvascular complications of diabetes

- Target not appropriate for those with established CKD and patients with a risk of hypoglycemia

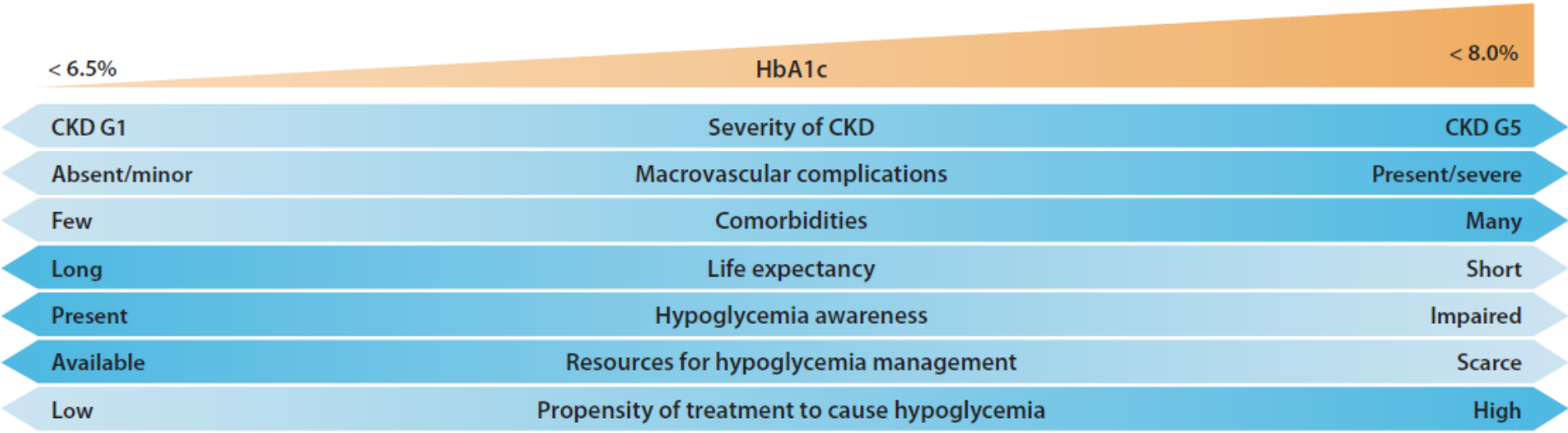
Glucose Control Targets

ADA recommends

- Strict HbA1c target (<6.5%) in younger patients without complications
- Target <8% in those with known microvascular complications or CKD

KDIGO recommends

- Target HbA1c <7% to delay onset of microvascular complications of diabetes
- Now recommend an individualized approach to HbA1c targets (DKD Clinical Practice Guideline 2022)



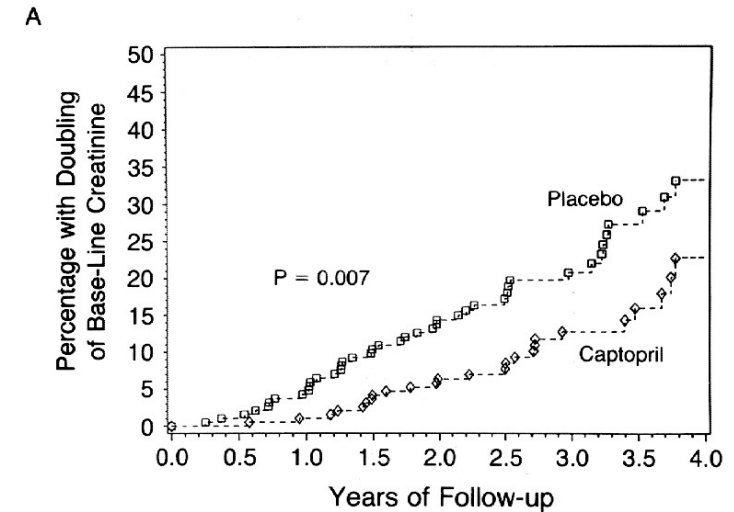
RAS Blockade

ACEi, ARB, Direct Renin Inhibitors and mineralocorticoid antagonists.

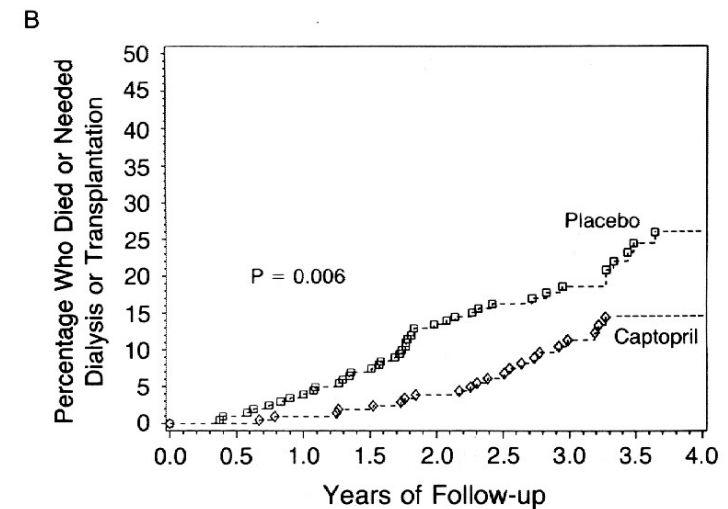
Single most effective therapy for slowing down the progression of diabetic nephropathy.

Seminal Captopril Trial

Reduction in doubling of creatinine
50% reduction in death/ESRD



Placebo	202	184	173	161	142	99	75	45	22
Captopril	207	199	190	180	167	120	82	50	24



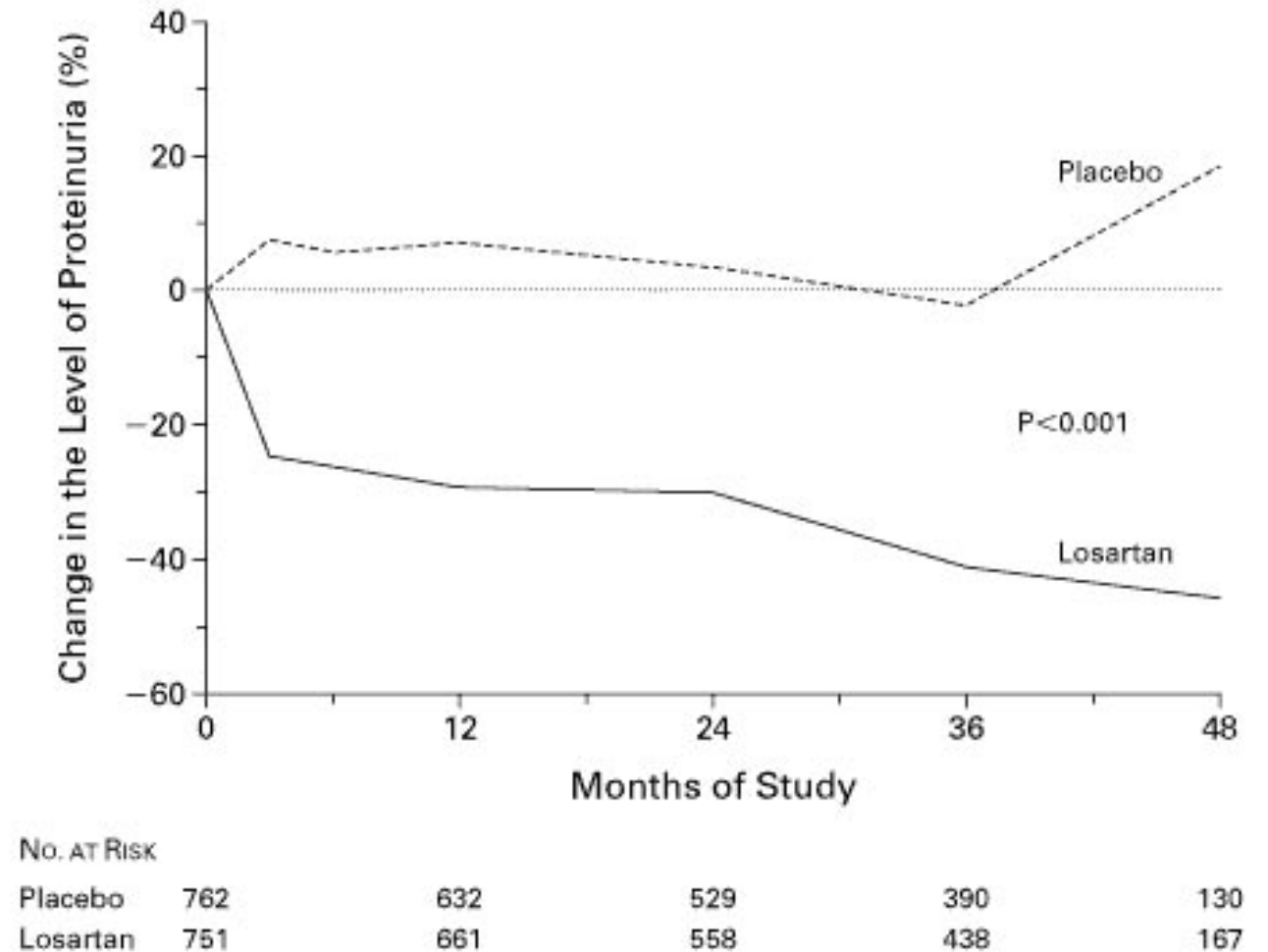
Placebo	202	198	192	186	171	121	100	59	26
Captopril	207	207	204	201	195	140	103	64	37

ARBs are as effective as ACEi

IDNT and RENAAL trial studied the effect of irbesartan and losartan on DN progression in patients with T2DM

Both reduced the risk for doubling sCR, death and ESRD

Effect driven in part by a reduction in proteinuria



Can RAS blockade prevent development of microalbuminuria?

No benefit in T1DM (DIRECT Prevent-1 and DIRECT Protect-1 studies)

Mixed results in T2DM trials

HOPE (ramipril)

no effect on DN progressions

BENEDICT (trandolopril)

Reduction in new albuminuria independent of BP

ROADMAP (Olmesartan)

1.6% absolute risk reduction for the development of new albuminuria over 3 years (8.2 vs 9.8%)

Significant difference in BP between the two arms.

IRMA (irbesartan)

Reduced the risk of progression from micro to macro albuminuria

Is more RAS-blockade better?

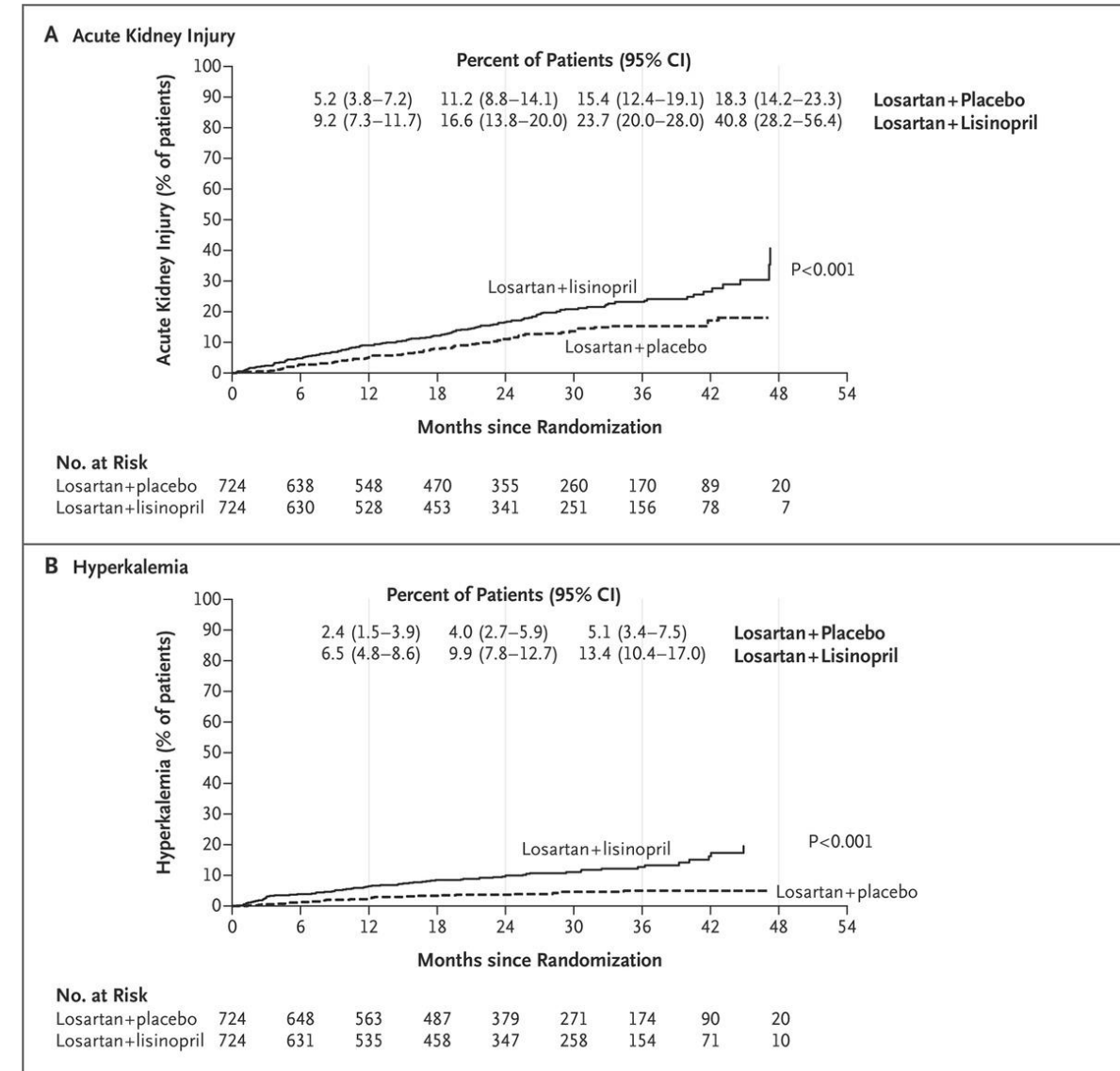
CONSENSUS study in the lancet suggested benefit for dual ACE/ARB therapy

Subsequent studies showed clear harm

VA Nephron D (losartan + lisinopril) – increased risk of AKI and hyperkalemia. No benefit

ONTARGET (Telmisartan + Ramipril) – no CV benefit. Some reduction in proteinuria. Increased risk of AKI and ESRD

ALTITUDE (aliskiren +ACE/ARB) – study terminated early due to adverse events and no positive signal



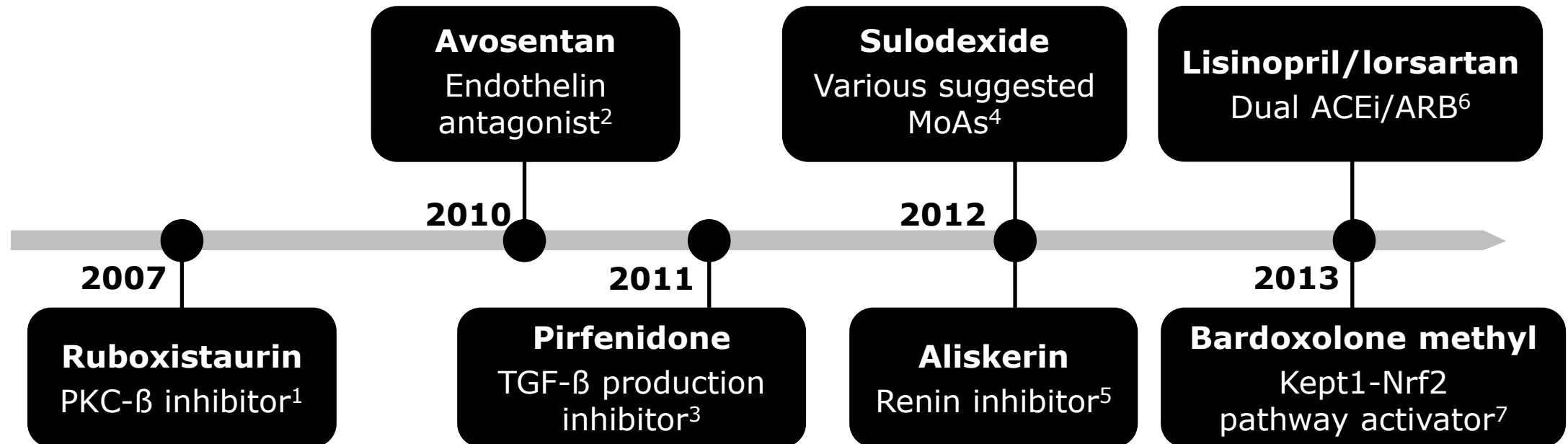
Key RAS Inhibition Trials

Trial	Population	N	Intervention	Results
Captopril Trial	T1DM with proteinuria	509	Captopril vs placebo	Captopril reduced risk of renal outcomes
RENAAL	T2DM with proteinuria and reduced GFR	1513	Losartan vs placebo	Losartan reduced risk of renal outcomes
ROADMAP	T2DM without albuminuria	4449	Olmesartan vs placebo	Olmesartan delayed onset of macroalbuminuria
IDNT	T2DM with proteinuria and reduced GFR	1715	Irbesartan vs amlodipine vs placebo	Irbesartan reduced risk of renal outcomes
IRMA-2	T2DM and microalbuminuria	590	Irbesartan vs placebo	Irbesartan reduced the development of overt proteinuria
VA NEPHRON-D	T2DM and proteinuria	1448	Losartan and lisinopril vs losartan and placebo	Terminated early due to hyperkalemia and AKI in combination therapy arm
ALTITUDE	T2DM, proteinuria, and CV risk	8561	ACE-I or ARB and aliskiren vs ACE-I or ARB and placebo	Trial terminated early due to increase adverse events and no benefit from dual therapy

RAAS Guidelines

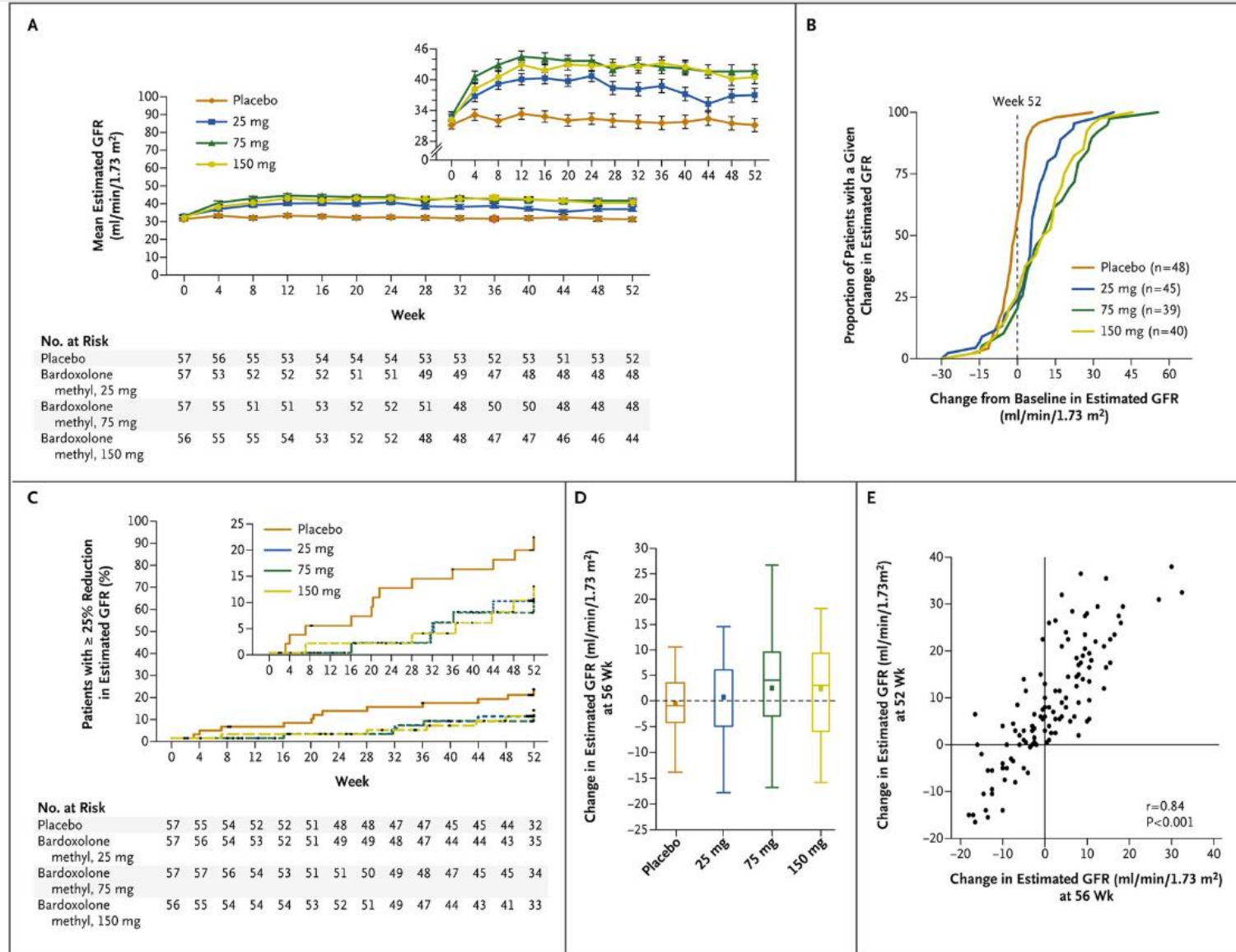
- ACE/ARB should be given to patients with diabetes and microalbuminuria to delay progression to overt proteinuria and reduce the rate of decline in GFR
- No role for ACE/ARB for prevention of albuminuria in patients with T1DM
- May be a role in primary prevention in T2DM but this is less clear
- Dual ACE/ARB blockade is not indicated due to the risk of hyperkalemia, AKI and ESRD.
- May be a role for dual blockade in severely nephrotic patients but this remains unclear
- Continue ACEi where possible until the patient starts RRT

Many failed therapeutic strategies since RENAAL



Bardoxolone and CKD Progression

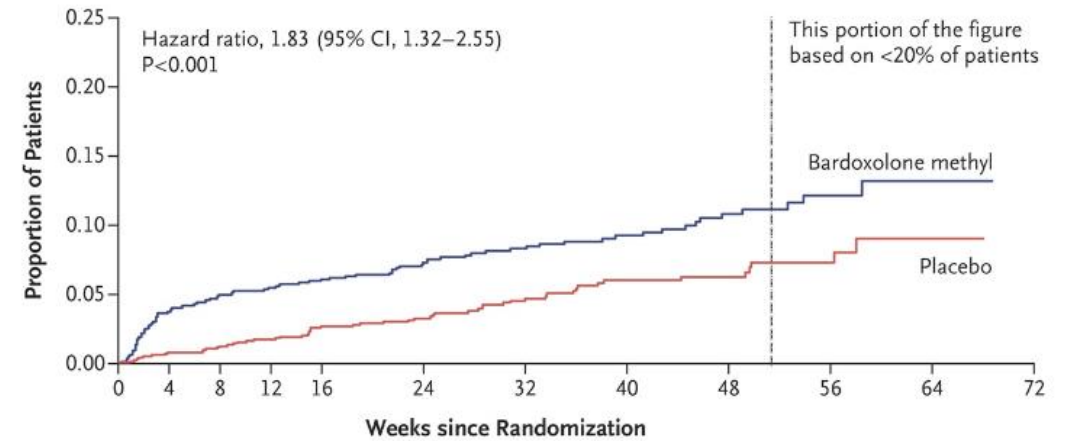
- Phase 2 Trial of novel prostaglandin agonist
- Noted in preclinical cancer studies to affect renal function
- Dose dependent increase in GFR maintained through one year
- Increase in proteinuria also



Bardoxolone and CKD Progression

- Subsequent Phase 3 Trial of 2400 patients with diabetes and CKD
- Higher GFR and proteinuria in the bardoxolone group
- Terminated early due to an excess of heart failure and cardiovascular death in the treatment group.
- CKD studies are hard!

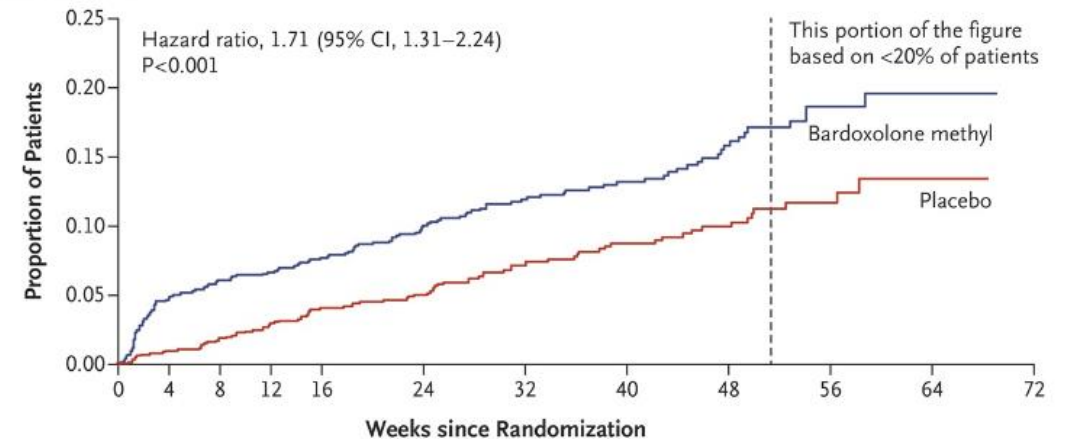
A Heart Failure



No. at Risk

Bardoxolone methyl	1088	1045	1006	942	864	723	548	417	288	133	15	0
Placebo	1097	1089	1070	994	907	762	591	436	315	135	20	0

B Secondary Composite Outcome

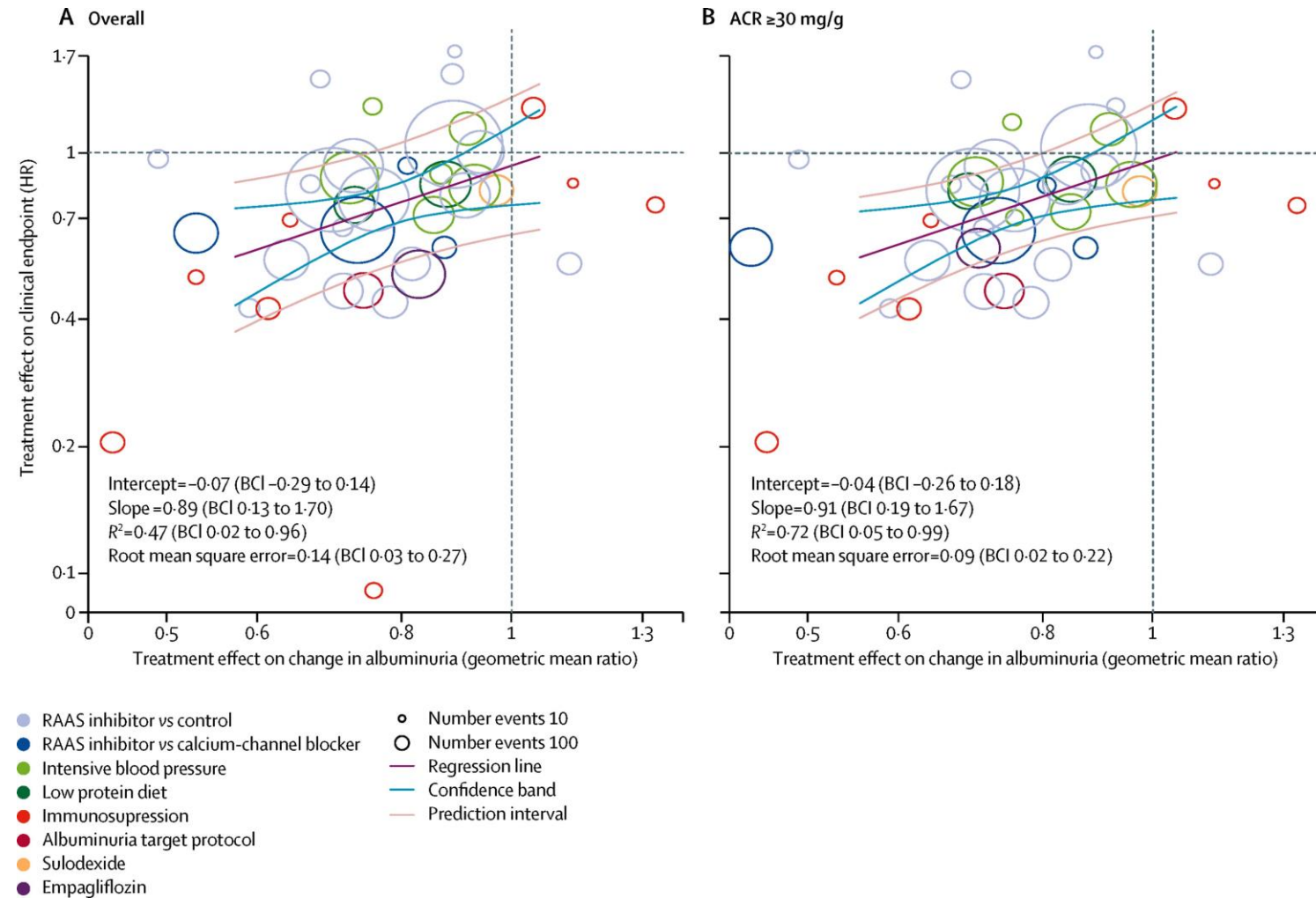


No. at Risk

Bardoxolone methyl	1088	1038	999	935	855	712	537	409	278	126	15	0
Placebo	1097	1088	1068	990	902	754	582	430	310	132	20	0

The use of surrogate outcomes in DN trials

- Hard outcomes preferred for intervention trials but for ESRD/death this requires studying advanced disease
- Δ albuminuria has been proposed as a surrogate marker for DN progression
- Meta-analysis of albuminuria trials
 - 20% change in geometric mean ACR = 20% change in likelihood of ESRD
 - Strongly associated with outcome in individuals with $ACR > 30 \text{ mg/g}$
 - Lack of change in ACR associated with no clinical benefit.



Newer Therapies

Glucagon-like peptide-1 Receptor Agonists

Critical metabolic regulatory program

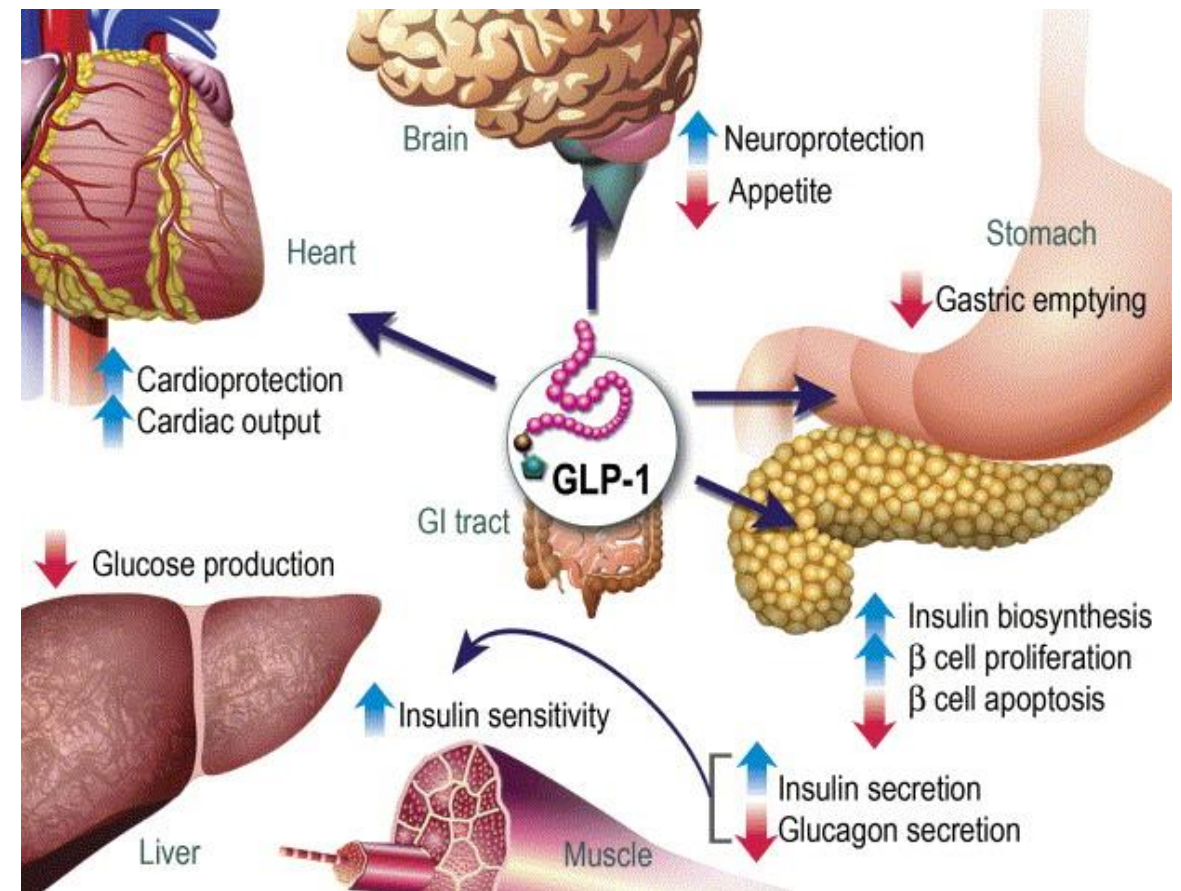
Incretin hormone secreted by the intestine after glucose ingestion

Enhances insulin secretion, slows gastric emptying, decreases appetite stimulation in the brain

Improve glucose control with no risk of hypoglycemia

Significant weight loss

Lower risk of CV events in high risk populations



SUSTAIN-6 Trial

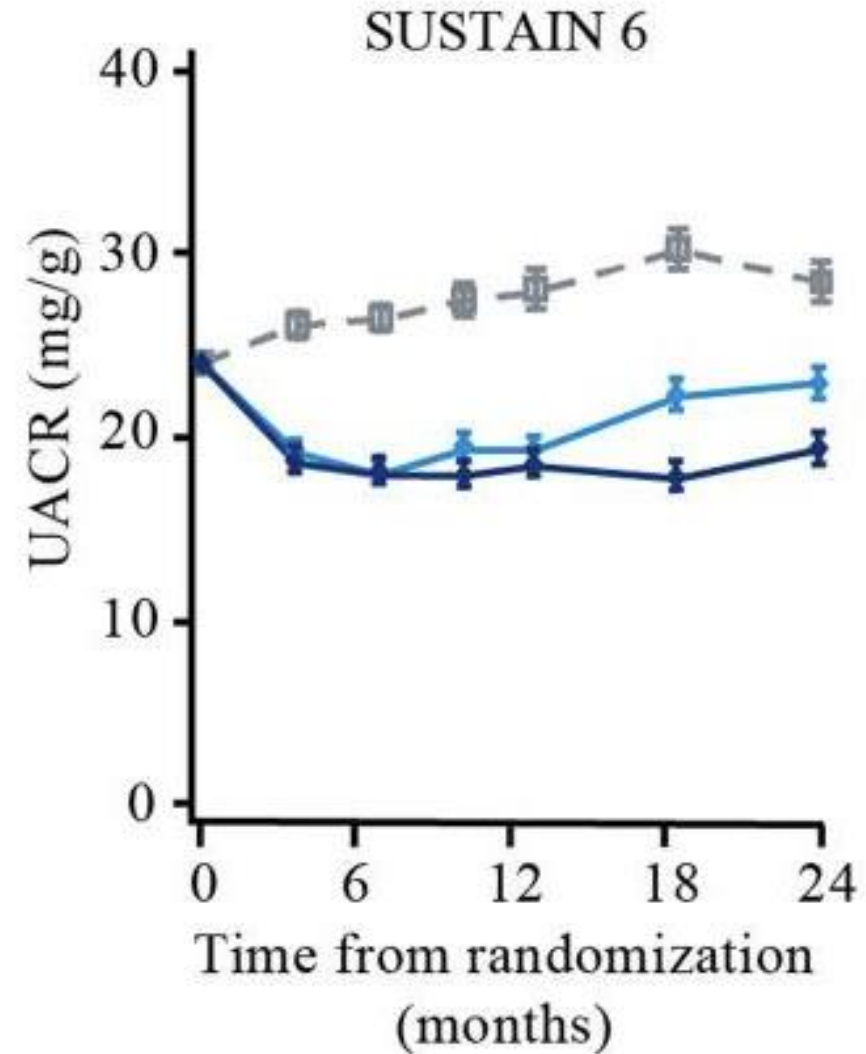
3297 patient randomized to Semaglutide or placebo

Primary outcome CV

26% reduction in MACE (no heterogeneity by CKD status)

No change in GFR

46% reduction in primary renal outcome (increased albuminuria, doubling of creatinine or need for RRT)



LEADER Trial

9340 patient randomized to liraglutide or placebo

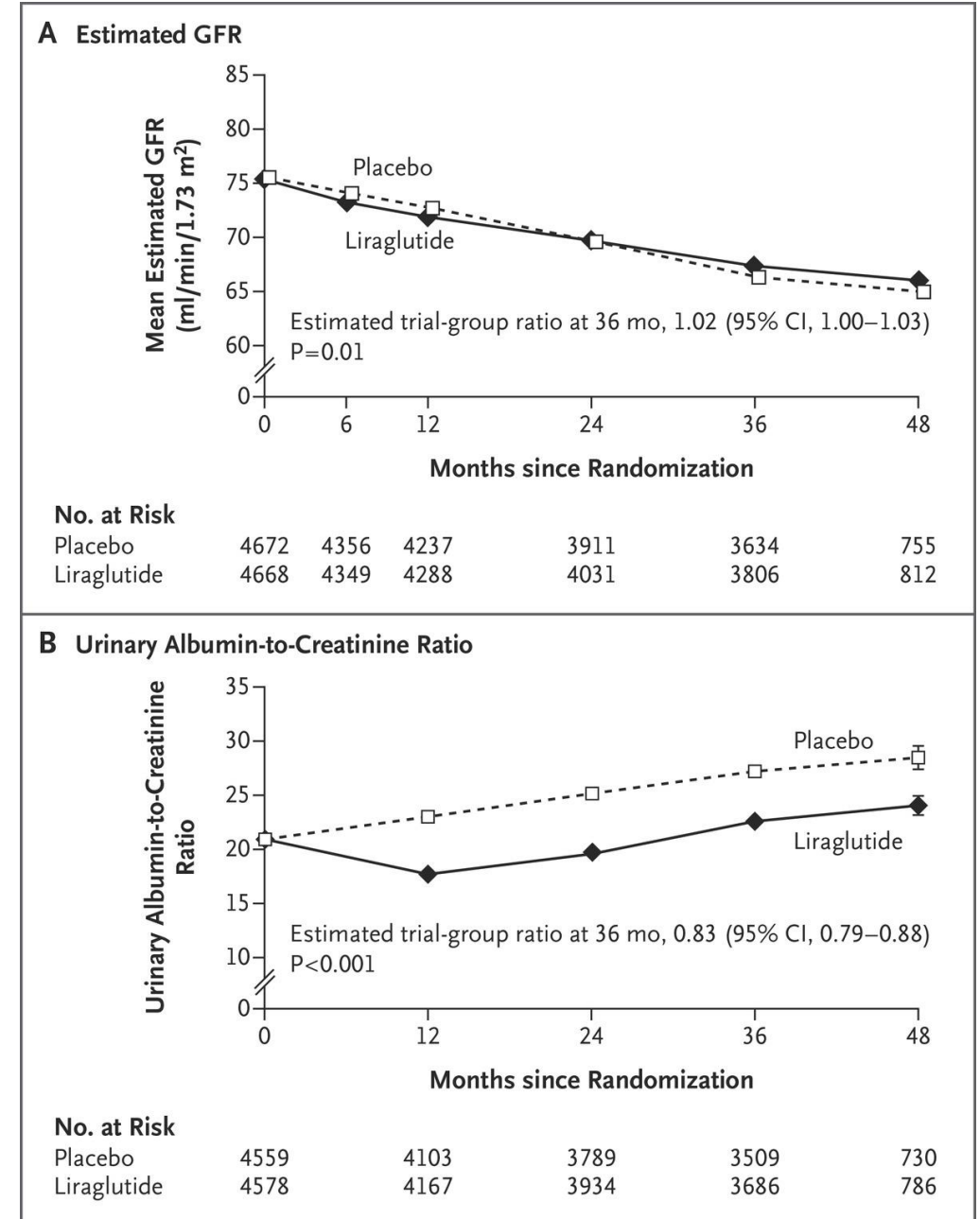
Primary outcome CV

22% reduction in renal outcomes - driven by lower rate of onset of persistent macroalbuminuria

Low absolute difference (5.7 vs 7.2%)

Clear CV benefit which was higher for those with CKD

No clear benefit for GFR progression



DPP4 inhibitors

Dipeptidyl peptidase-4 cleaves GLP-1 – DPP4 inhibitors lead to higher levels of GLP-1

No consistent effect on renal outcomes across clinical trials

Linagliptin – short and medium term studies showed no effect on GFR or ACR

Saxagliptin – lowering of ACR in patients with established CKD and albuminuria

May be an added benefit to DPP4 inhibitors added to SGLT2i.

All patients in these studies were on stable doses of ACE/ARB

Endothelin receptor antagonists

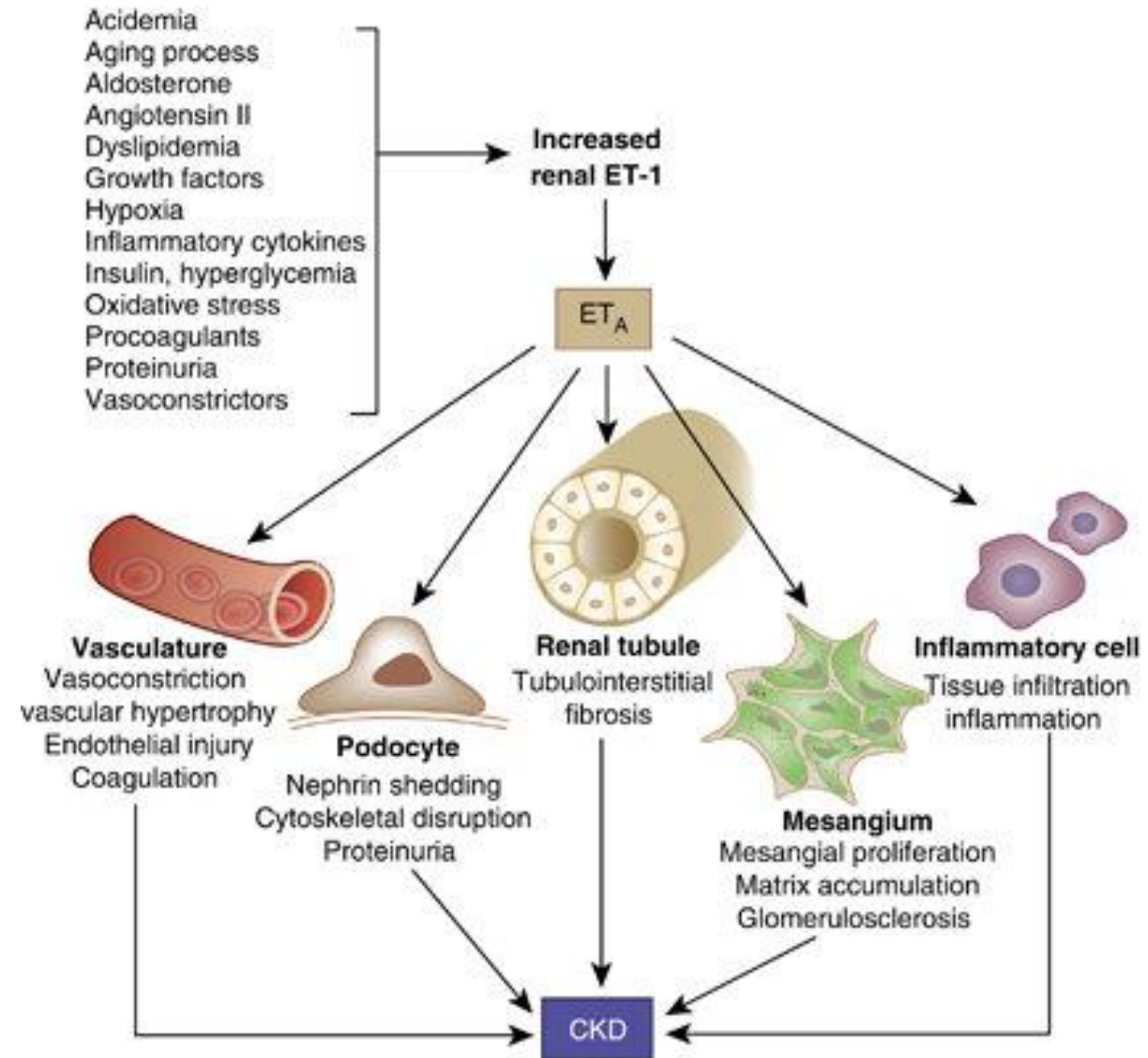
Endothelin-1 increases in CKD leading to multiple adverse consequences:

- Mesangial cell proliferation
- Interstitial fibrosis
- Podocyte injury.

Avosentan Trial

- decreased ACR

- increased CHF due to Na retention and increased cardiovascular mortality

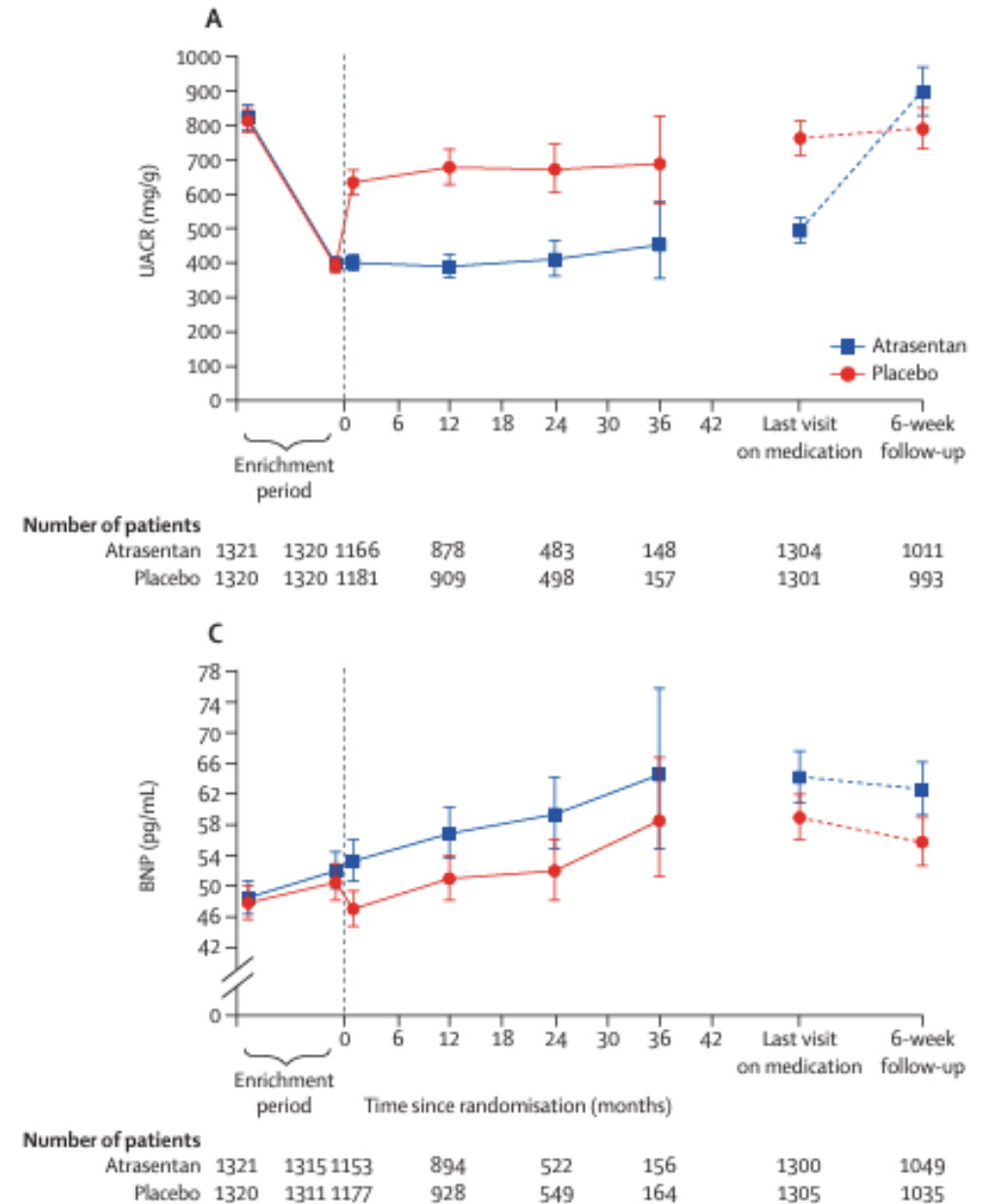


SONAR Trial

Atrasentan (more selective endothelin 1-receptor antagonist)

Study enriched – only included those who did not have edema in the run-in period AND at least a 30% reduction in ACR

- Reduction in renal endpoint (doubling creatinine or ESRD) from 7.9% to 6% after 2 years
- Higher rates of heart failure (NS) and CV mortality (NS) in the atrasentan group
- May be a role in combination with SGLT2i



Non-Steroidal MRA

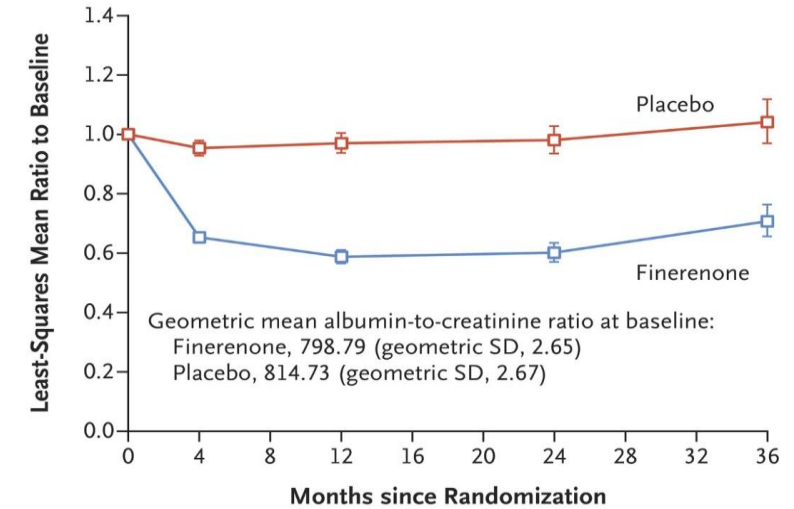
Steroidal MRAs have been used to treat DKD but the use is limited by hyperkalemia

Non-steroidal MRAs are an alternative – no estrogen effects and less hyperkalemia

Finerenone:

- Patients with DKD and 300-5000 mg albuminuria
- Reduction in renal outcome 21.1% to 17.8%
- Marked reduction in albuminuria
- Prevalence hyperkalemia 2.3% (compared with 9.2% in ACE/ARB studies)

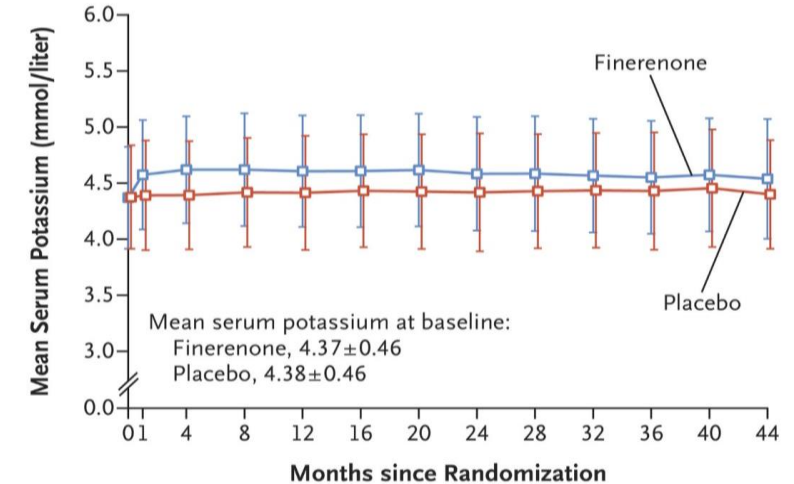
A Urinary Albumin-to-Creatinine Ratio



No. of Patients

Finerenone	2831	2725	2582	1841	856
Placebo	2840	2726	2598	1825	834

B Mean Serum Potassium



No. of Patients

Finerenone	2827	2708	2600	1872	882	344
Placebo	2831	2709	2596	1865	862	348

SGLT2 Inhibitors

Glucose freely filtered in the kidney

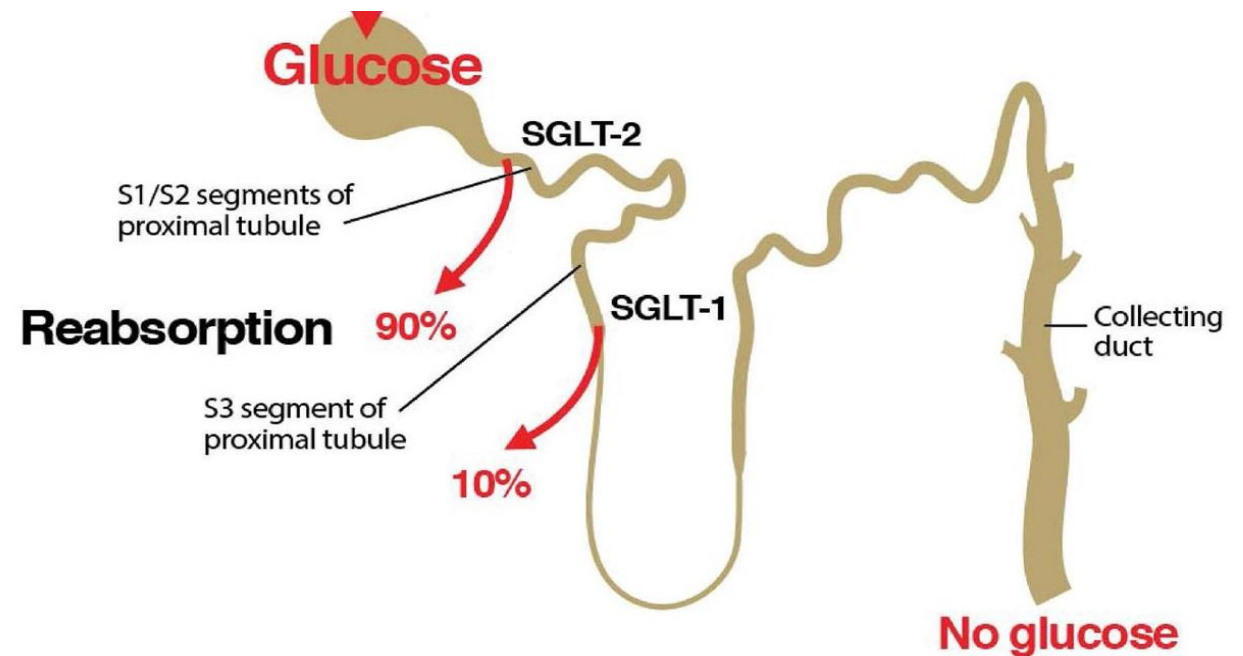
Reabsorbed in the proximal tubule by

SGLT2 (90%)

SGLT1 (10%)

In the absence of hyperglycemia, all glucose is reabsorbed in the tubules

SGLT2 inhibitors block glucose reabsorption leading to glycosuria with low serum glucose levels

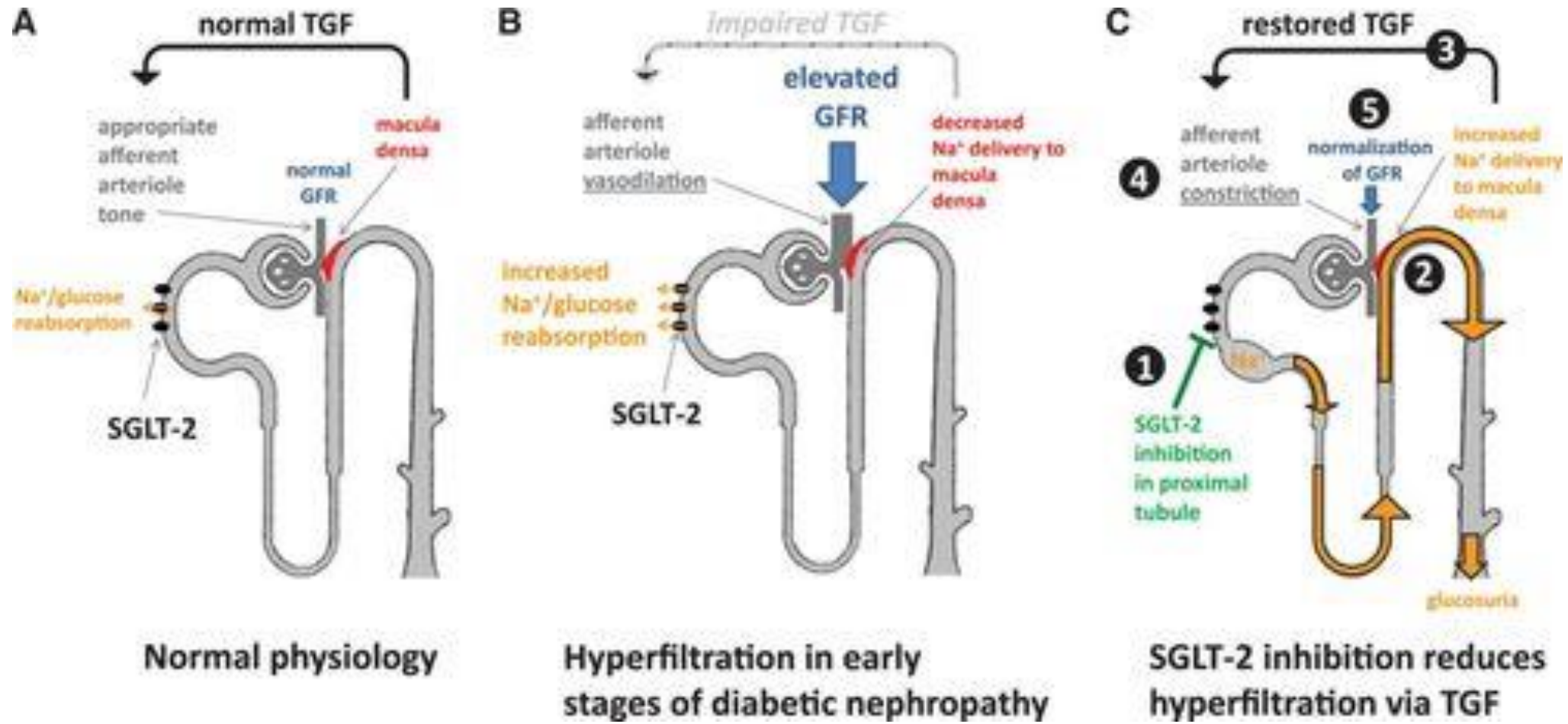


Mechanisms for protective effects of SGLT2i

True mechanism for the benefit is unclear but a number of mechanisms have been proposed:

- Abolition of hyperfiltration through restoration of TGF
- Altering metabolic fuel energetics
- Stimulating fasting-like condition
- Inhibition of Na-proton exchange

Restoration of normal TGF with SGLT2i



Effects of SGLT2 inhibitors

Block sodium and glucose reabsorption at the proximal tubule

Restore TGF and abolish hyperfiltration

Effect on GFR only seen in individuals who are already hyperfiltering

Mild effect on BP

Some weight reduction

Decrease CV events in high-risk populations (studies powered to accumulate events rapidly so unclear if there is a benefit in lower risk patients).

EMPA-REG

7020 patients randomized to empagliflozin or placebo.

eGFR >30, no ACR indication

Primary outcome CV disease:

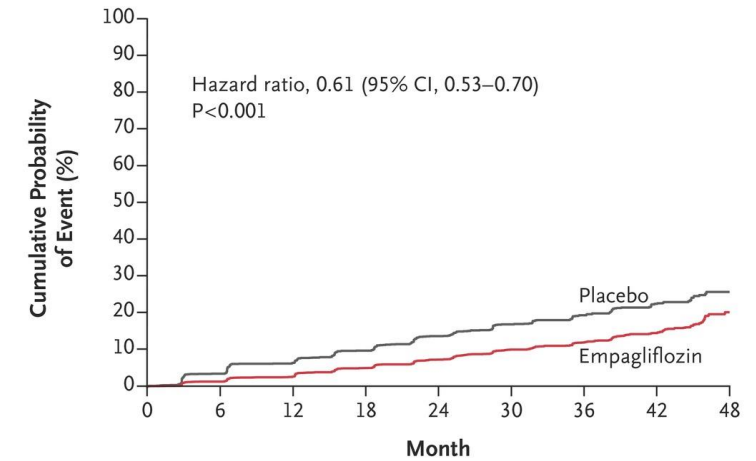
14% reduction in MACE outcome

Significant reduction in all renal outcomes apart from incident albuminuria

- Overall, 44% decrease in primary renal outcome

Care overinterpreting this study – low rate of renal outcomes and not powered for these

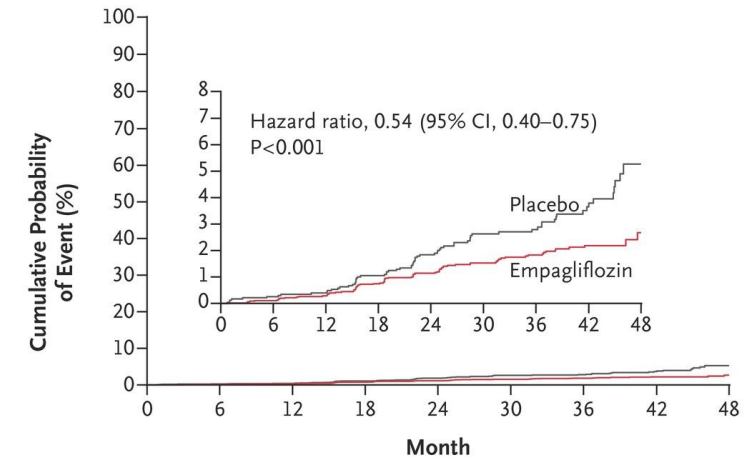
A Incident or Worsening Nephropathy



No. at Risk

Empagliflozin	4124	3994	3848	3669	3171	2279	1887	1219	290
Placebo	2061	1946	1836	1703	1433	1016	833	521	106

B Post Hoc Renal Composite Outcome



No. at Risk

Empagliflozin	4645	4500	4377	4241	3729	2715	2280	1496	360
Placebo	2323	2229	2146	2047	1771	1289	1079	680	144

CREDENCE – Study Design

Randomized trial of canagliflozin 100 mg daily versus placebo

4401 patients randomized

Inclusion criteria:

- Albumin/creatinine > 300 to 5000

- eGFR 30 to < 90

- Max treatment with RAS blockade

Primary outcomes:

- Composite of ESRD and

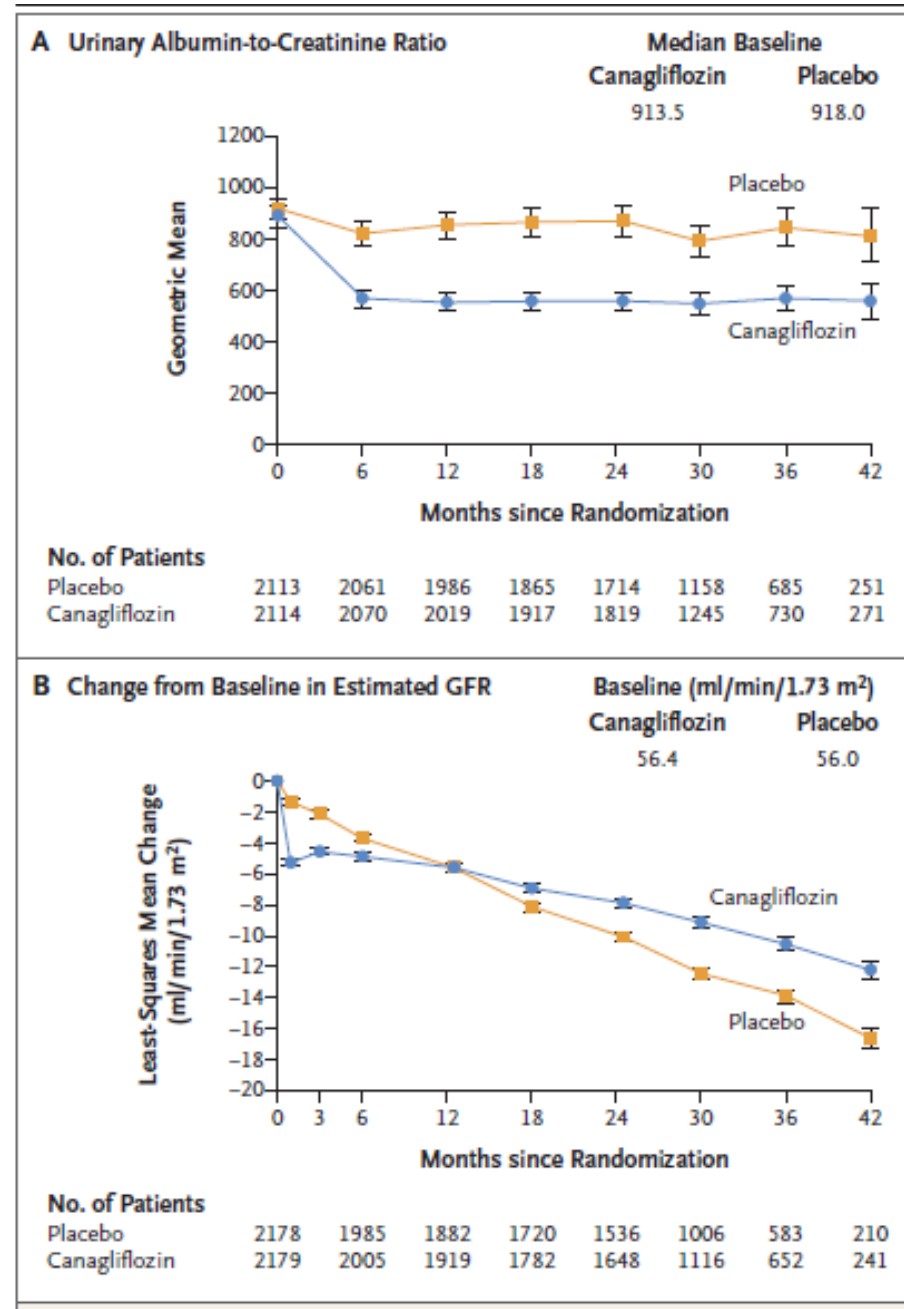
- Doubling of the serum creatinine

- Death from renal or cardiovascular causes

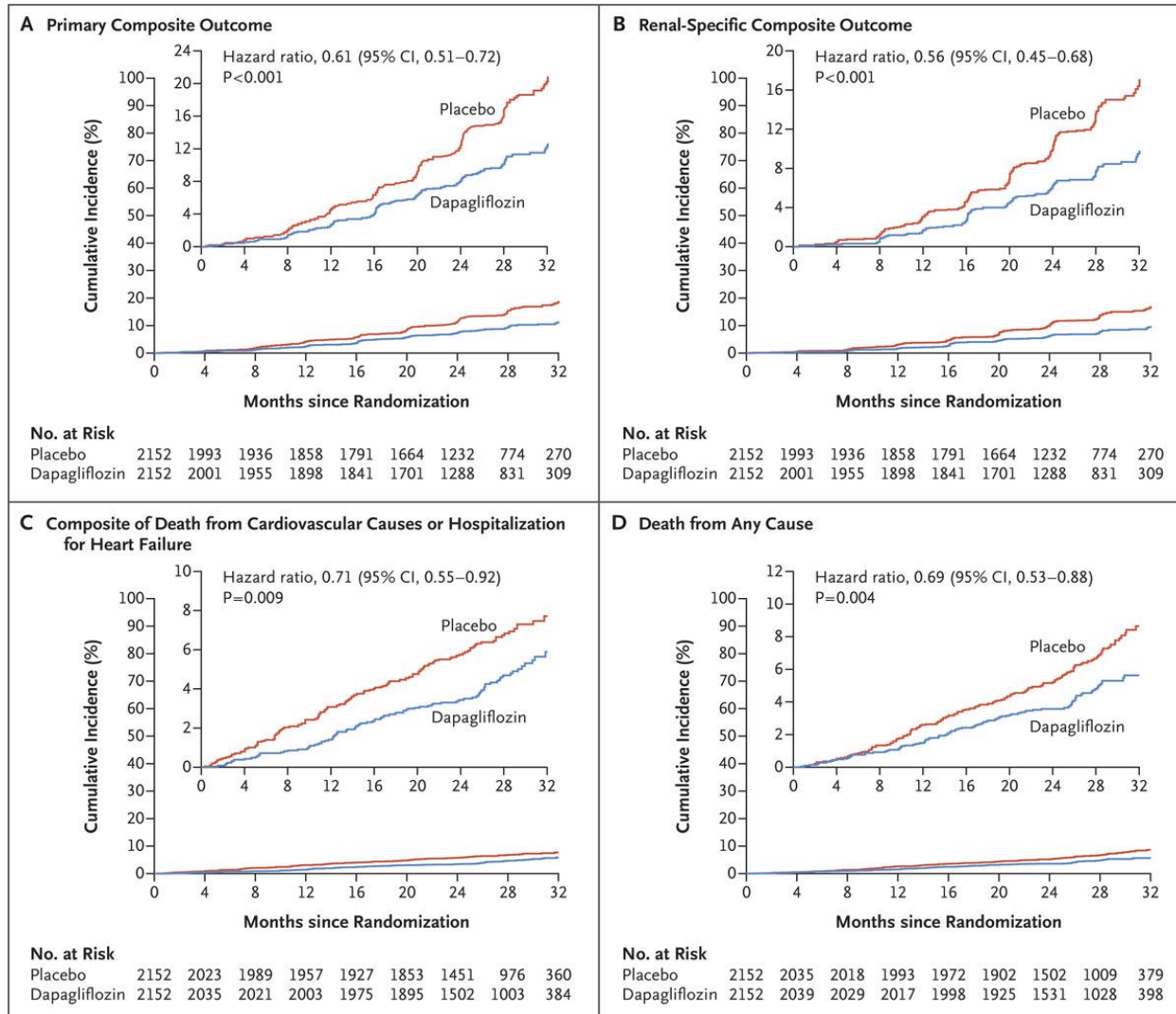
Credence

Trial stopped early due to a 30% reduction in the primary outcome (ESRD or doubling of creatinine) after only 2.5 years

Initial rapid reduction in both ACR (sustained) and eGFR (slope of decline less in SGLT2i group)



SGLT2i also reduces renal and CV outcomes in non-diabetic patients – DAPA CKD



- Rapidly becoming standard of care for the management of both diabetic and non-diabetic proteinuric kidney disease.
- Role in secondary prevention in CV disease

EMPA-Kidney

6609 patients with CKD (eGFR 20-45)

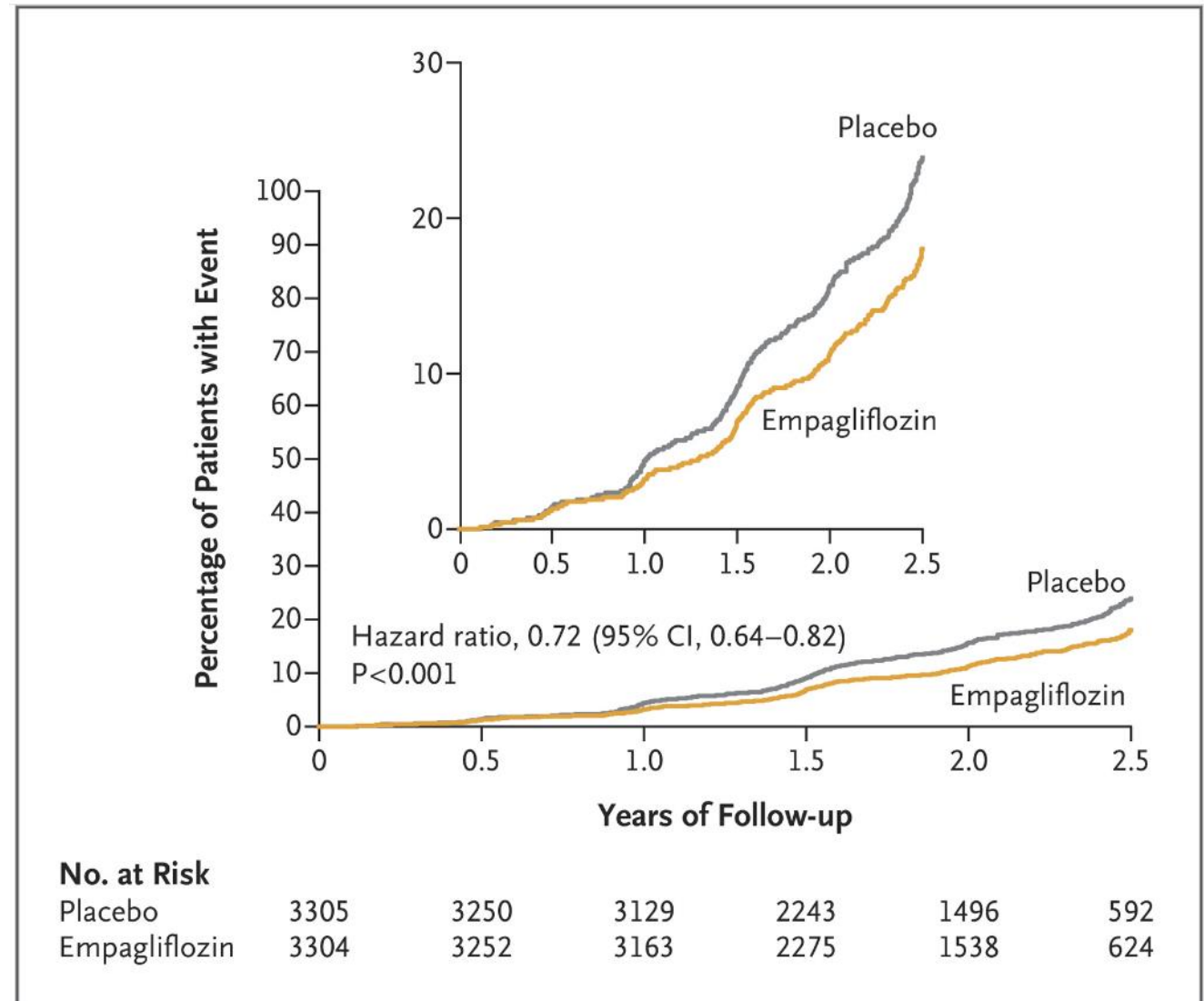
No requirement for albuminuria (50% had ACR <300)

30% had eGFR <30.

50% had diabetes

Marked reduction in primary outcome (ESRD, cardiovascular or renal death)

Study stopped early for efficacy



EMPA-Kidney

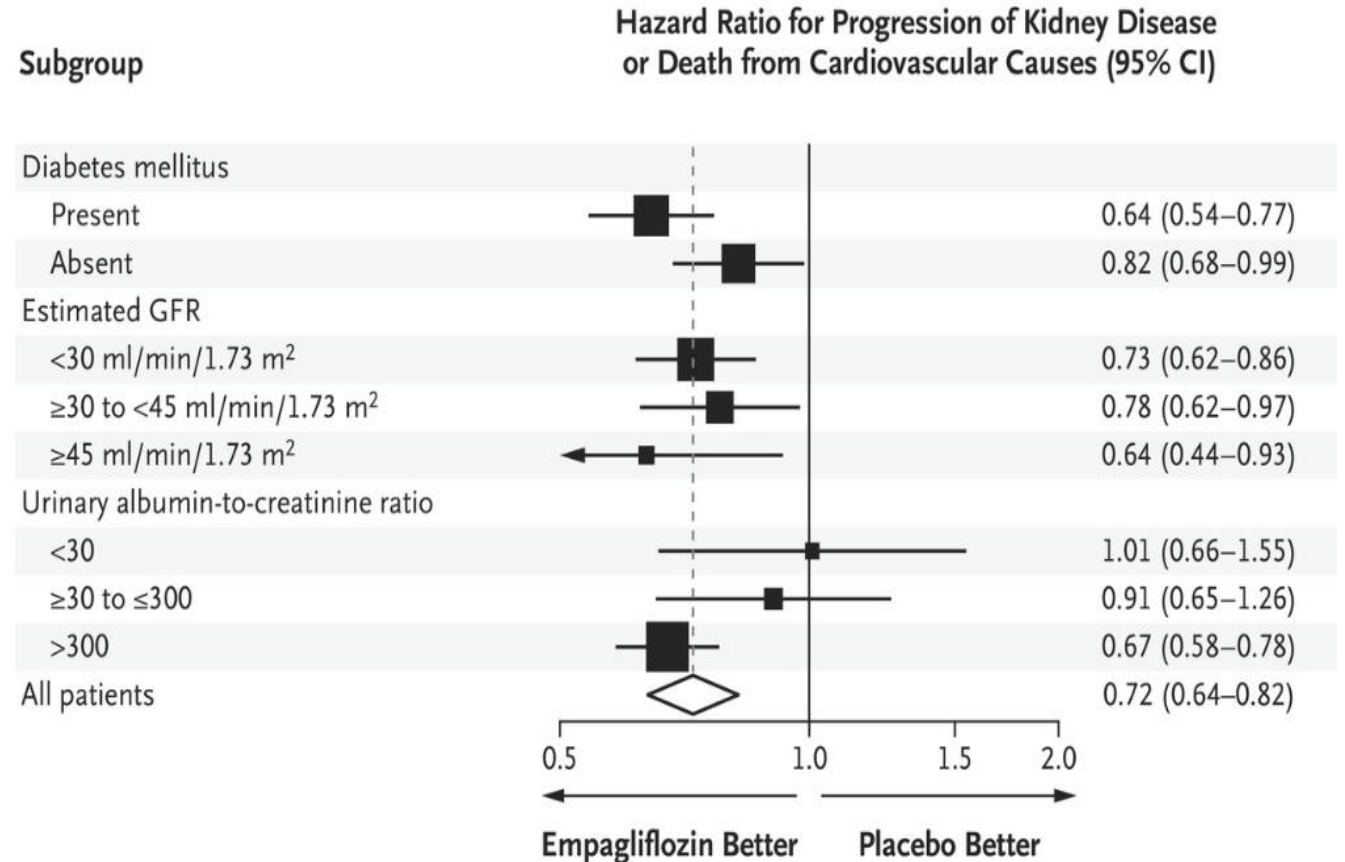
However:

No effect on primary outcome in the group with ACR <300

Largely because of the very low rate of the primary outcome in this group.

Slope of eGFR decline was lower in this group (prespecified secondary outcome)

Safe to use SGLT2 at lower GFR but effectiveness less clear with lower ACR



Note of Caution – SGLT2i

Ketoacidosis

Relatively contraindicated in patients with T1DM

Amputations

2-fold increased risk of amputation in early CV outcomes studies of canagliflozin.

Not replicated in later studies but patients at high risk of amputation were excluded

UTI

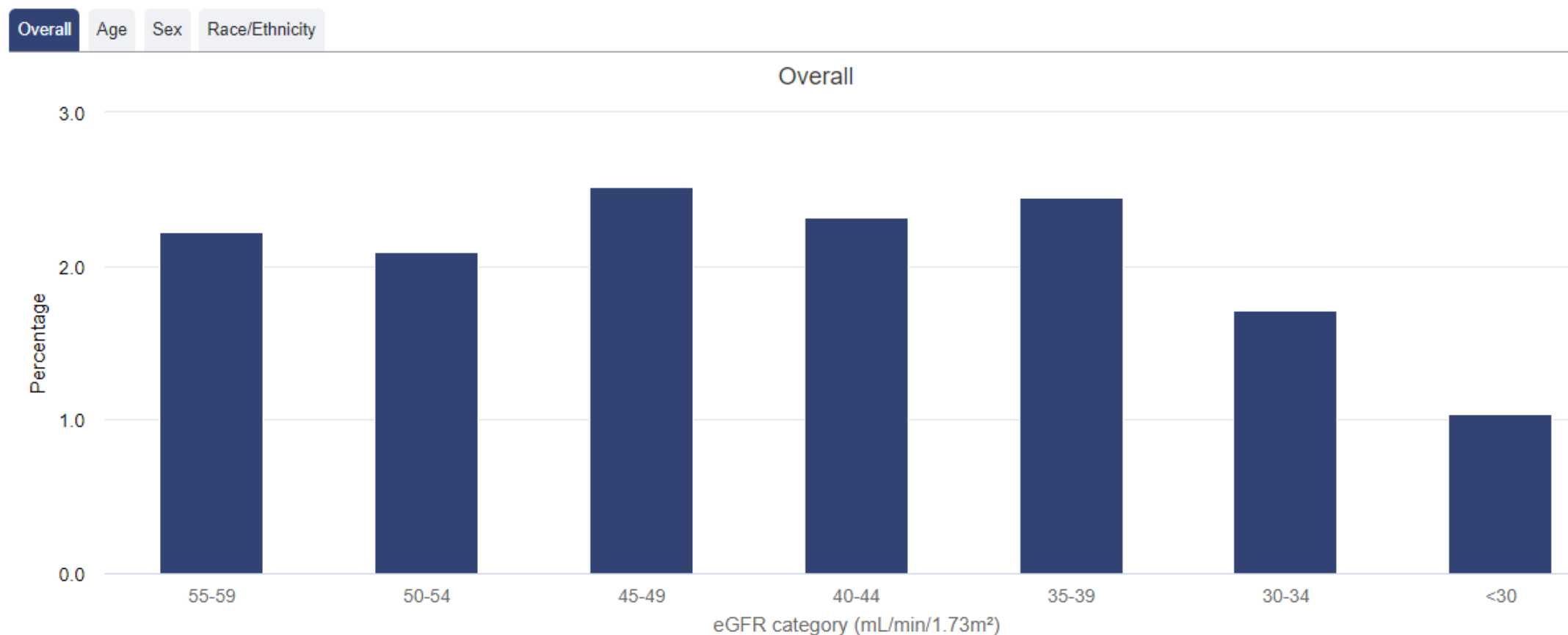
Higher risk of UTIs and mycotic infections

Increased AGE in distal nephron?

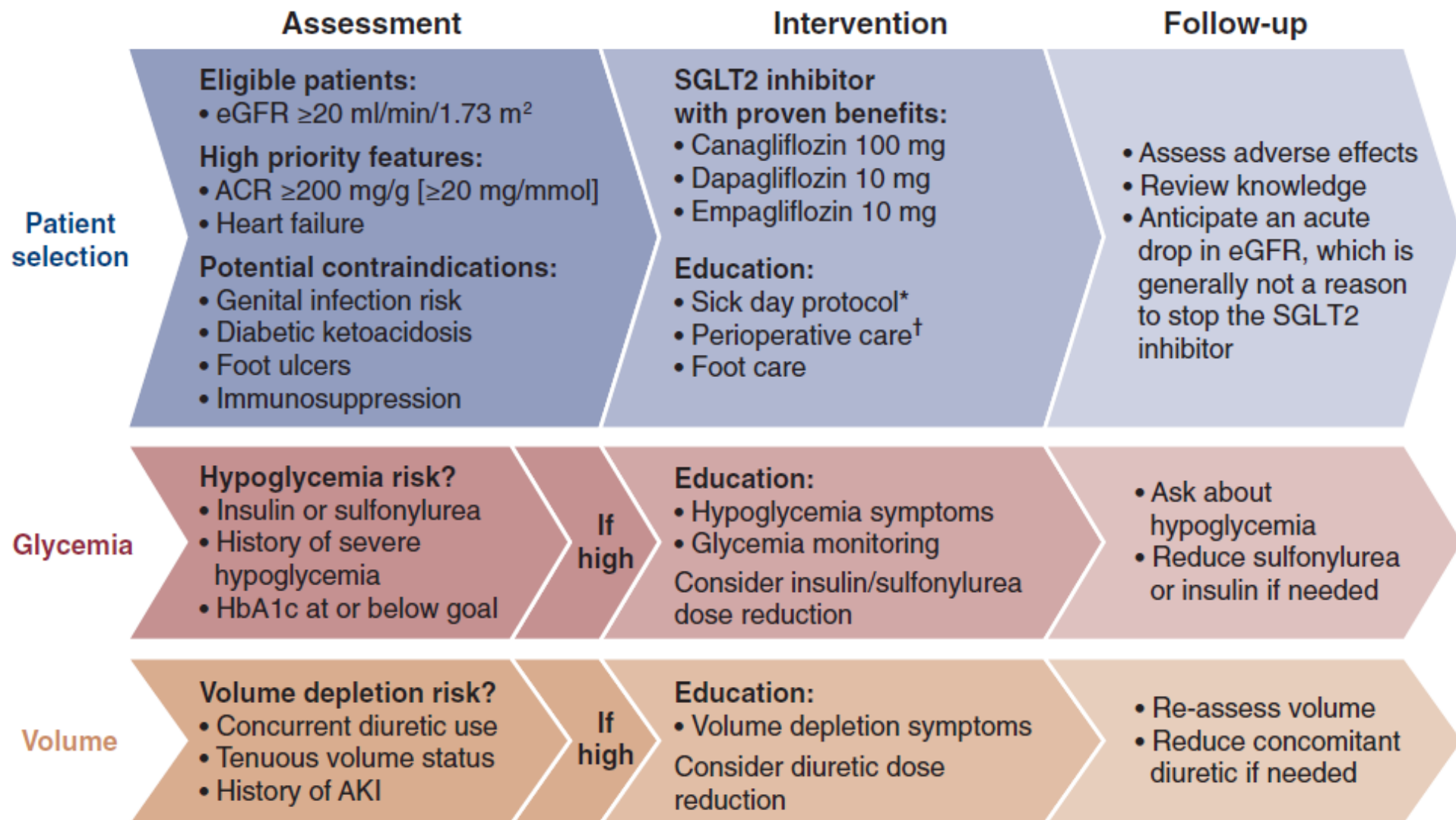
Increased expression of SGLT1 – long term effects?

Room for improvement!

Figure 8.2b Percentage of adults with stages 3-5 CKD receiving SGLT2i medications, by eGFR level, 2019-2021



Practical Guide to Initiating SGLT2i for CKD

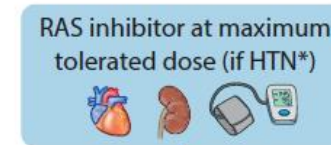
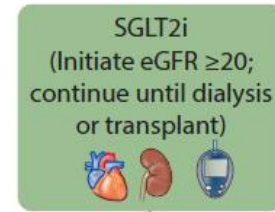


Holistic Approach to Managing Diabetic Kidney Disease in 2024

Lifestyle

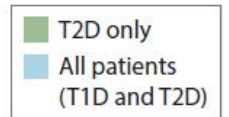
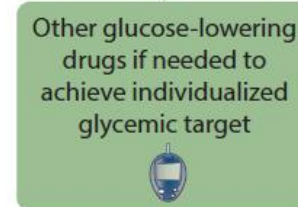
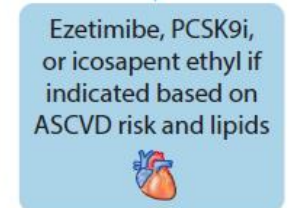
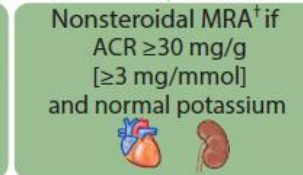
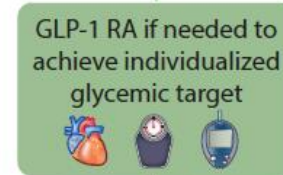


First-line drug therapy



Regular reassessment
of glycemia, albuminuria,
BP, CVD risk, and lipids

Additional
risk-based
therapy



Summary

Diabetes remains the number one cause of end-stage renal disease across the world.

Diabetic kidney disease takes years to develop.

Microalbuminuria with a preserved GFR is usually the first sign of diabetic kidney disease.

RAS blockade is beneficial in patients with diabetic nephropathy in both type 1 and type 2 diabetes.

SGLT2-inhibitors are the biggest advance in the treatment of DN since ACE inhibitors were introduced and should be standard of care in patients with established diabetic nephropathy from T2DM

GLP1a are a second line treatment for diabetic nephropathy.

MRAs may have a role in patients on maximal doses of ACE/SGLT2 with persistent proteinuria.