

Chronic Kidney Disease

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**CONTINUING MEDICAL EDUCATION
DEPARTMENT OF MEDICINE**



**HARVARD MEDICAL SCHOOL
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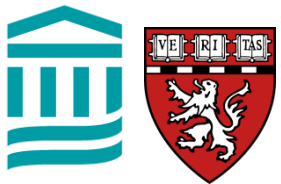
Fellowship: BWH/MGH

Clinical Interests: ICU Nephrology, Lupus Nephritis

Academic Interests:

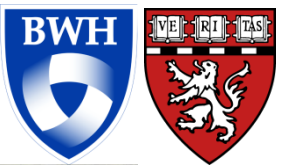
Lupus Nephritis

Post-graduate Education



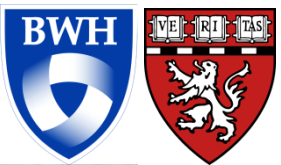
Disclosures

- Consultant for Apellis Pharma, Optum Consulting, Advanced instruments
- Research Support from Alexion Pharmaceuticals



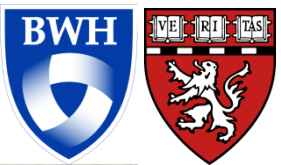
Learning Objectives

- Discuss the definition, diagnosis and prevalence of CKD
- Discuss strategies to reduce progression of CKD



Case

- 75yo man with a history of hypertension, T2DM for 8 years presents for evaluation.
- Scr 1.5 mg/dl. eGFR 53 ml/min
- BP 140-150 mmHg range.
- Medications: lisinopril, ASA, hydrochlorothiazide, metformin
- HbA1c 7.4%



Case

- Lab values:
 - UA – trace protein
 - UACR 60 mg/g
- Does he have kidney disease?
- Do we need to worry about it?
- What are the next steps we should take?

CKD Definition

Criteria for CKD (present for at least 3 months)	
Decreased GFR	GFR <60 ml/min/1.73m ²
Kidney Damage	<p>Albuminuria (ACR ≥ 30mg/g)</p> <p>Structural Abnormalities found on imaging</p> <p>Electrolyte disorder attributable to abnormal tubular function</p> <p>Glomerular hematuria and other urine sediment abnormalities</p> <p>History of Kidney Transplantation</p> <p>Abnormalities detected by histology</p>

Risk Factors for CKD Initiation

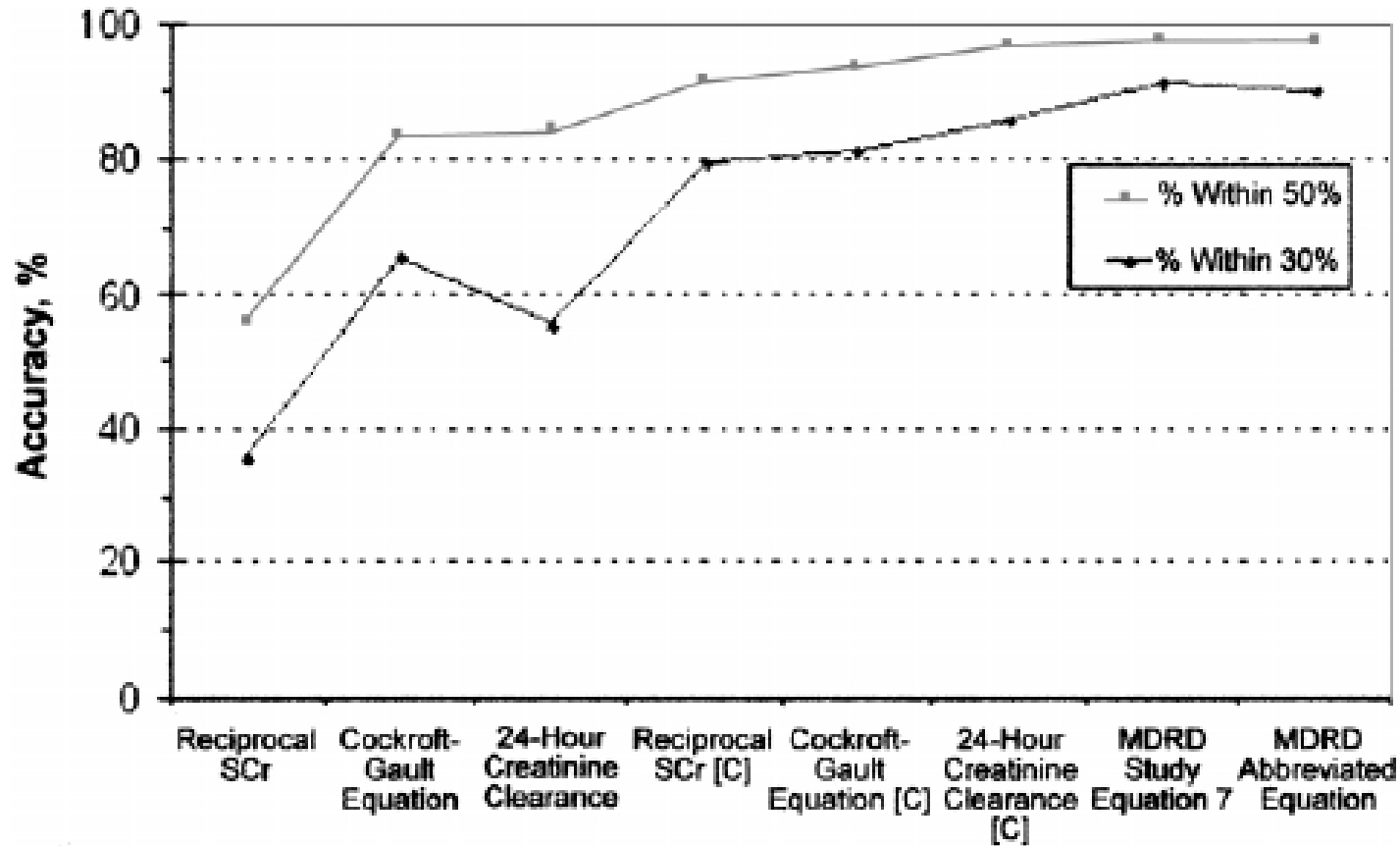
Clinical Factors	Diabetes	Autoimmune Disease
	Hypertension	Systemic Infections
	Urinary Tract Infections	Urinary Stones
	Urinary Tract Obstruction	Neoplasia
	Family History of CKD	Recovery from AKI
	Low birth Weight	Exposure to nephrotoxins
Sociodemographic Factors	Older Age	Low income/education
	Chemical and Environmental Exposures	Ethnic Minority Status (African American, American Indian, Hispanic or Pacific Islander)



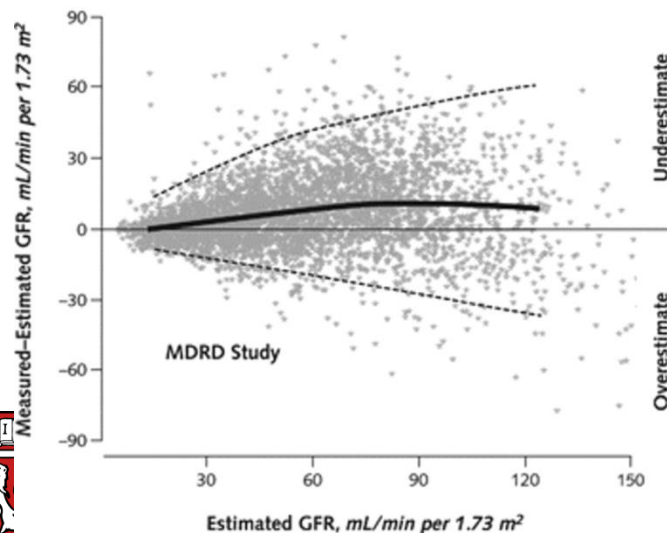
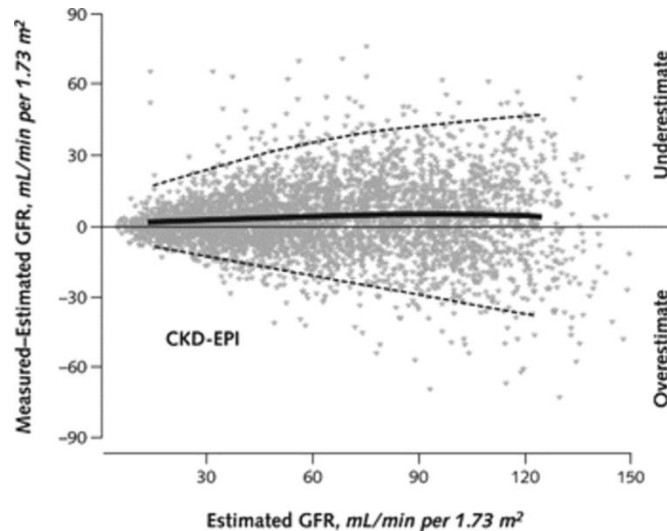
GFR Measurement and Estimation

Method	Description	Advantages	Potential Limitations
Measured GFR	<ul style="list-style-type: none">•Urinary clearance of an exogenous or endogenous filtration marker.•Plasma clearance of an exogenous filtration marker.	<ul style="list-style-type: none">•Accurate (gold standard methods)	<ul style="list-style-type: none">•Inconvenient to patients•Expensive•Not suitable for population-based screening
Estimated GFR	<ul style="list-style-type: none">•Equations based on serum levels of filtration markers (creatinine/cystatin C)	<ul style="list-style-type: none">•Suitable for population screening•Rapid result (single measurement)•Inexpensive	<ul style="list-style-type: none">•Non-GFR determinants of marker concentrations•Assay variation•Inaccurate particularly in non-steady state situations (AKI)

Accuracy of Commonly Used Methods for Estimating GFR



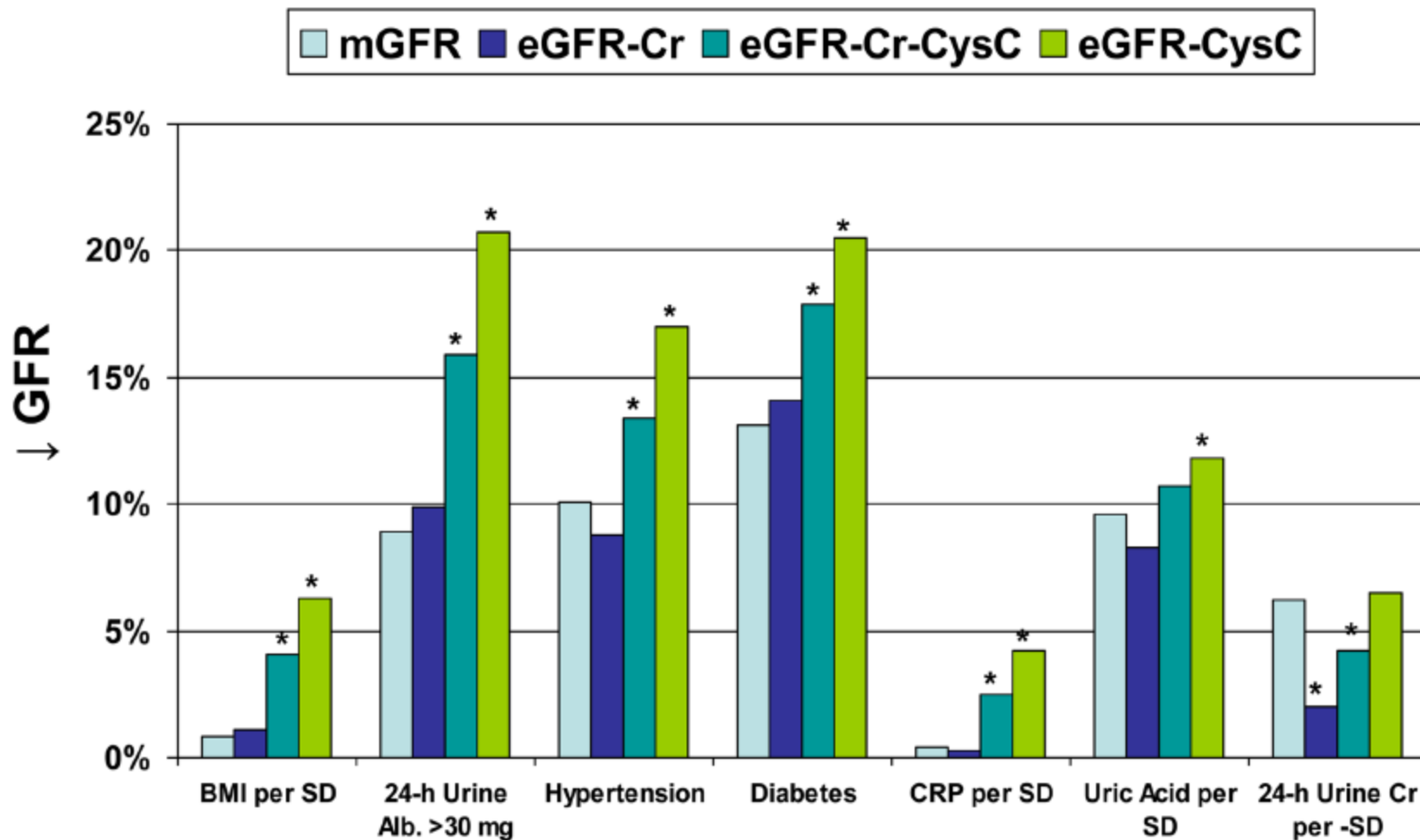
CKD-Epi Equation



- KDIGO recommends using the CKD-Epi equation in clinical practice and for research.
- Compared to MDRD
 - Less Bias
 - More accurate
 - Improved risk reclassification
- Approximately 84% of measurements within 30% of the true (measured GFR)

Levey et al, *Annals Int Med* 2009

Cystatin C



Accuracy of eGFR in Individuals

- eGFR was never designed for individual-level decision-making.
- Mean difference between mGFR and eGFR_{cr} was 0.6ml/min
- Wide range of values for individuals at a given eGFR
- No improvement with eGFR_{cys}
- Likely should be reported as a range rather than a single number

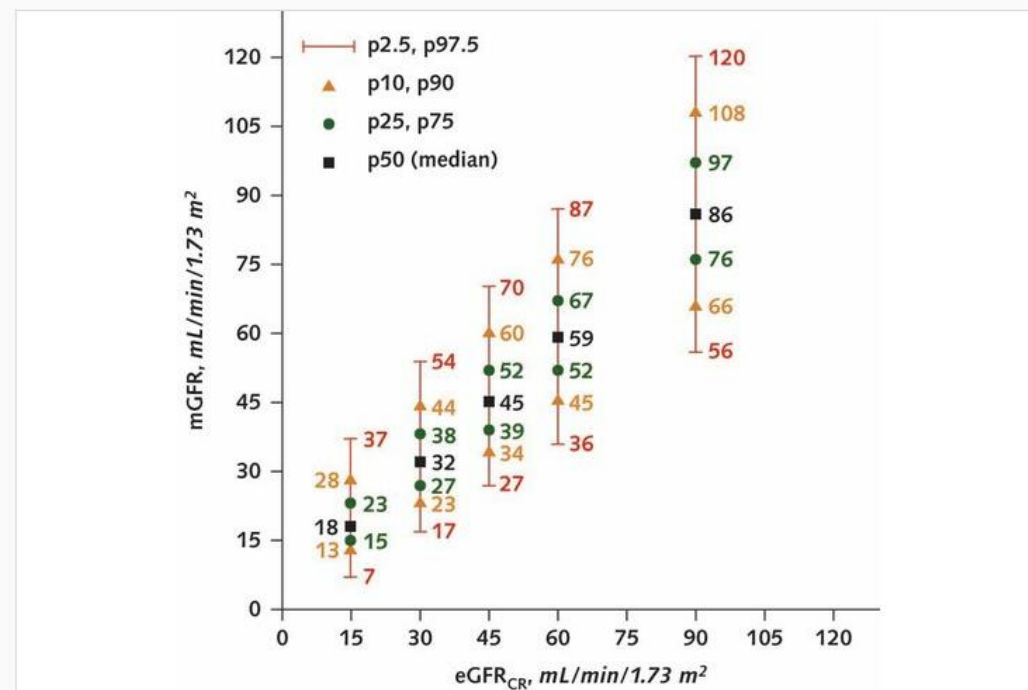
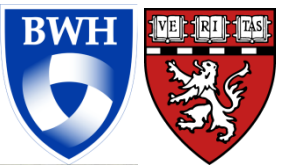
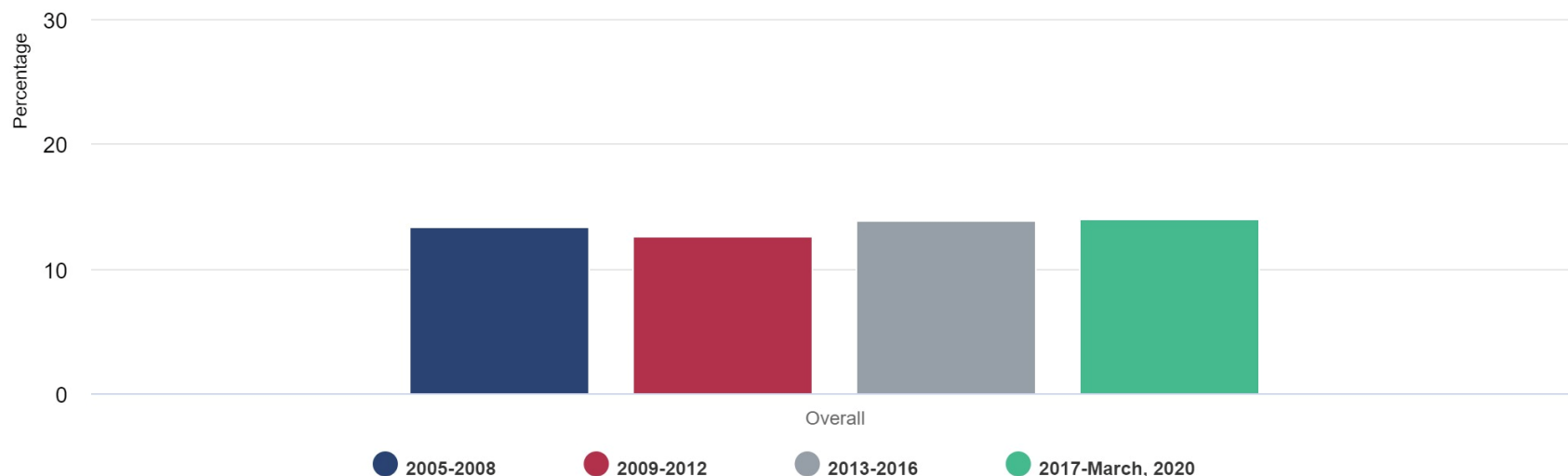


Figure 1. Distribution of mGFR at selected eGFR_{CR} thresholds in 3223 participants of 4 cohort studies.

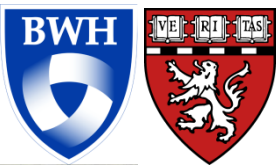
How common is CKD?



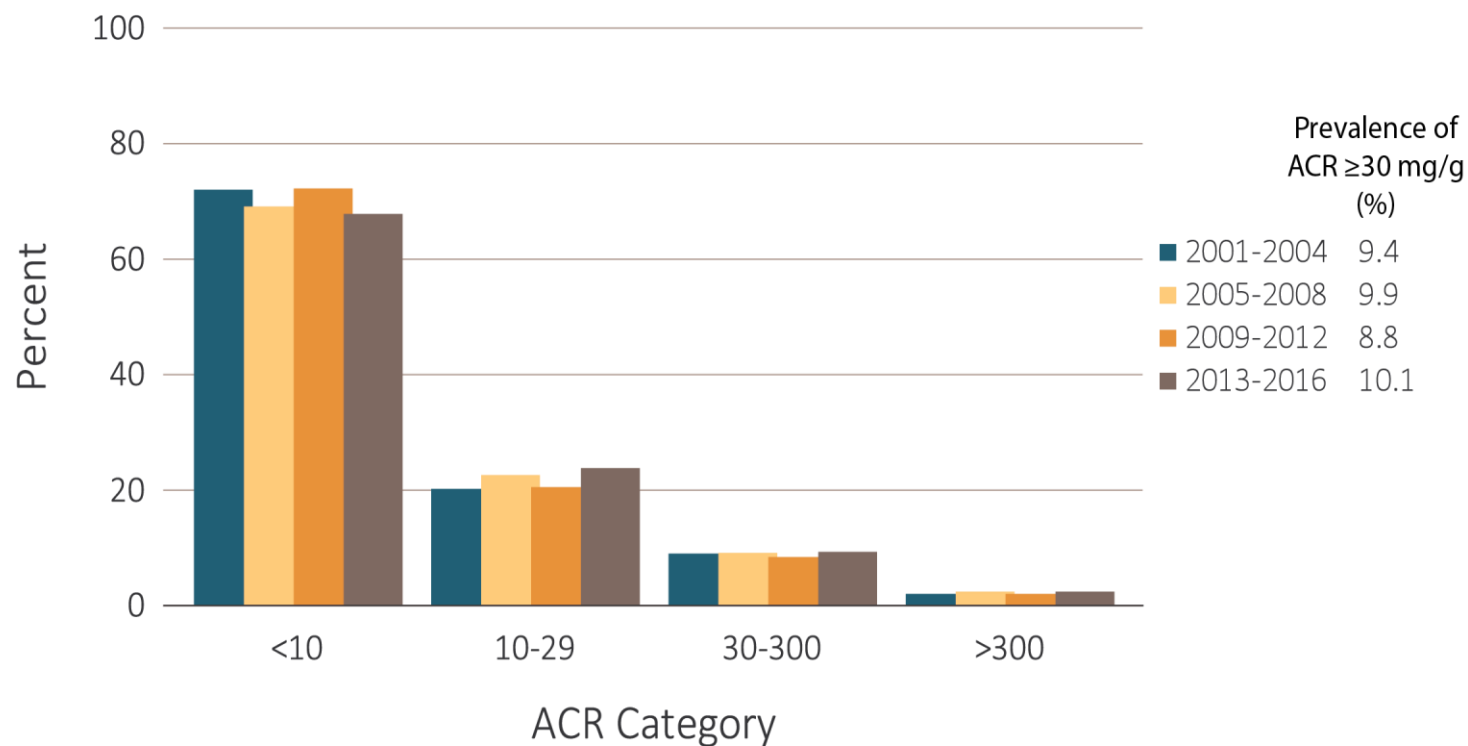
Prevalence of CKD in US Adults



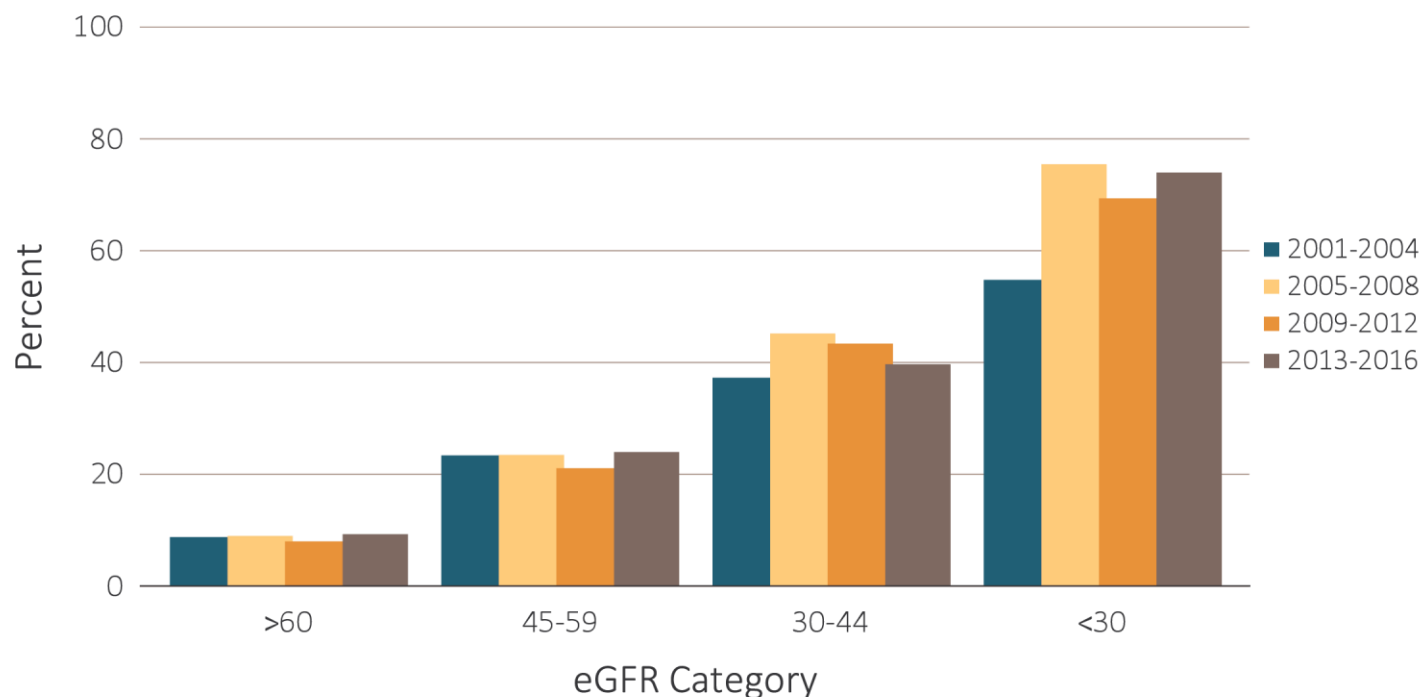
14% prevalence of CKD in adults in most recent NHANES survey



Prevalence of albuminuria



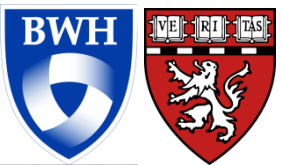
Prevalence of albuminuria by CKD category



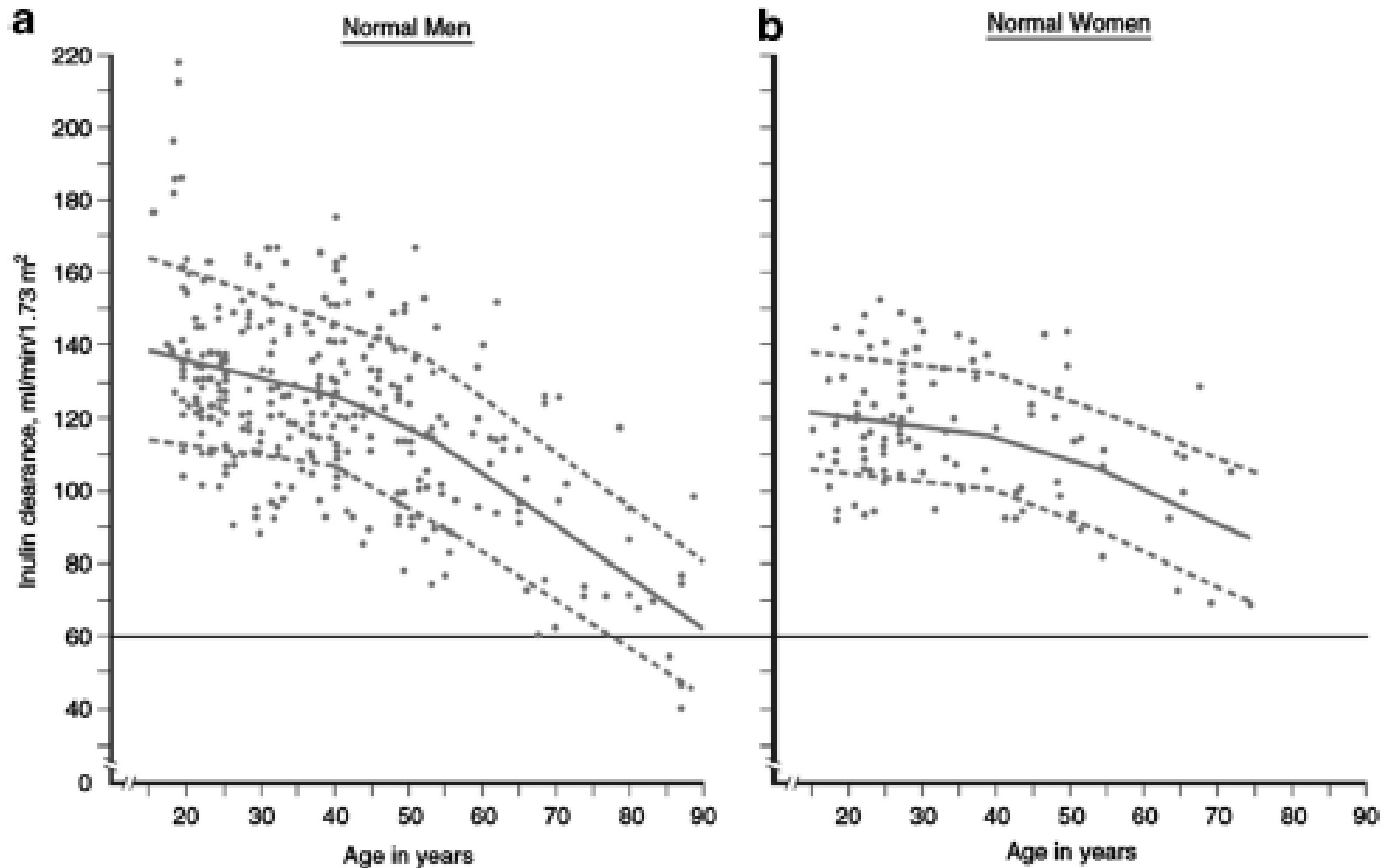
Prevalence of CKD

Percentage of US Population by eGFR and Albuminuria Category: KDIGO 2012 and NHANES 1999-2006				Persistent albuminuria categories Description and range			
				A1	A2	A3	
				Normal to mildly increased	Moderately increased	Severely increased	
				<30 mg/g <3 mg/mmol	30-300 mg/g 3-30 mg/mmol	>300 mg/g >30mg/mmol	
GFR categories (ml/min/ 1.73m ²) Description and range	G1	Normal or high	≥90	55.6	1.9	0.4	57.9
	G2	Mildly decreased	60-89	32.9	2.2	0.3	35.4
	G3a	Mildly to moderately decreased	45-59	3.6	0.8	0.2	4.6
	G3b	Moderately to severely decreased	30-44	1.0	0.4	0.2	1.6
	G4	Severely decreased	15-29	0.2	0.1	0.1	0.4
	G5	Kidney failure	<15	0.0	0.0	0.1	0.1
				93.2	5.4	1.3	100.0

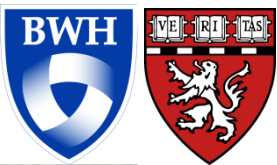
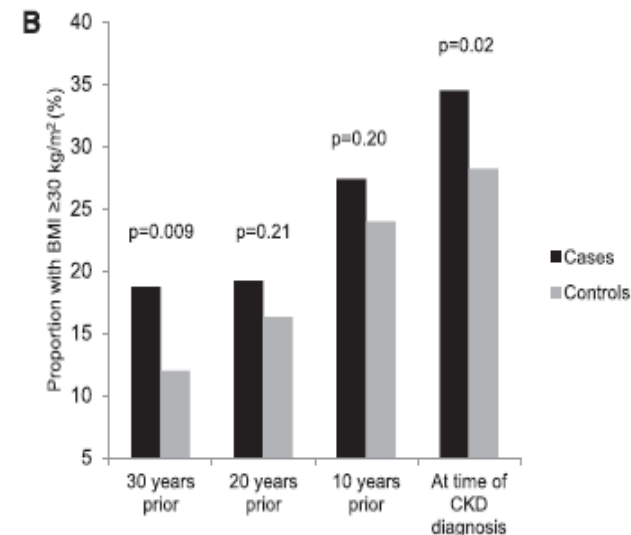
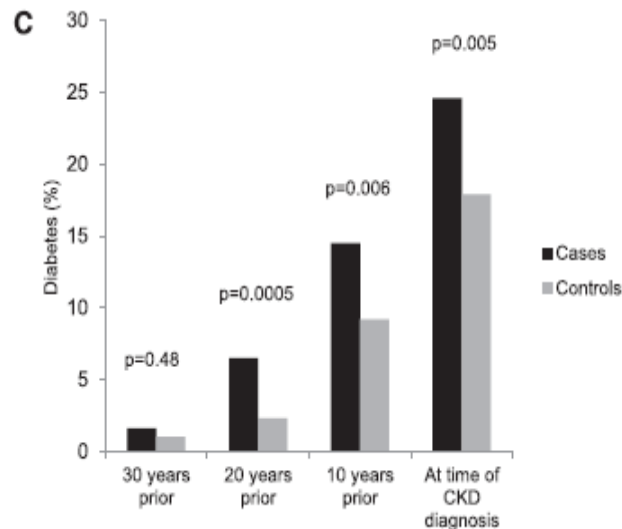
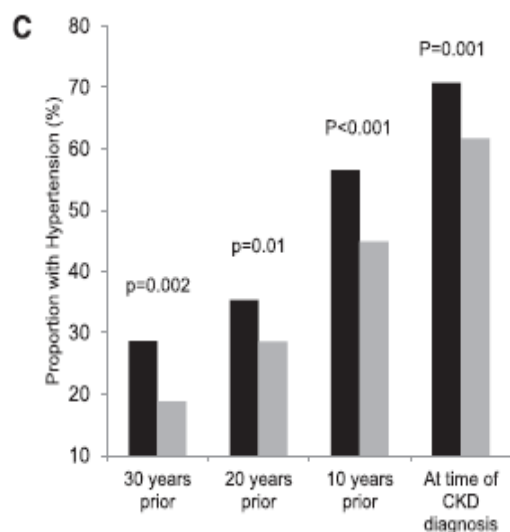
Is early CKD important?



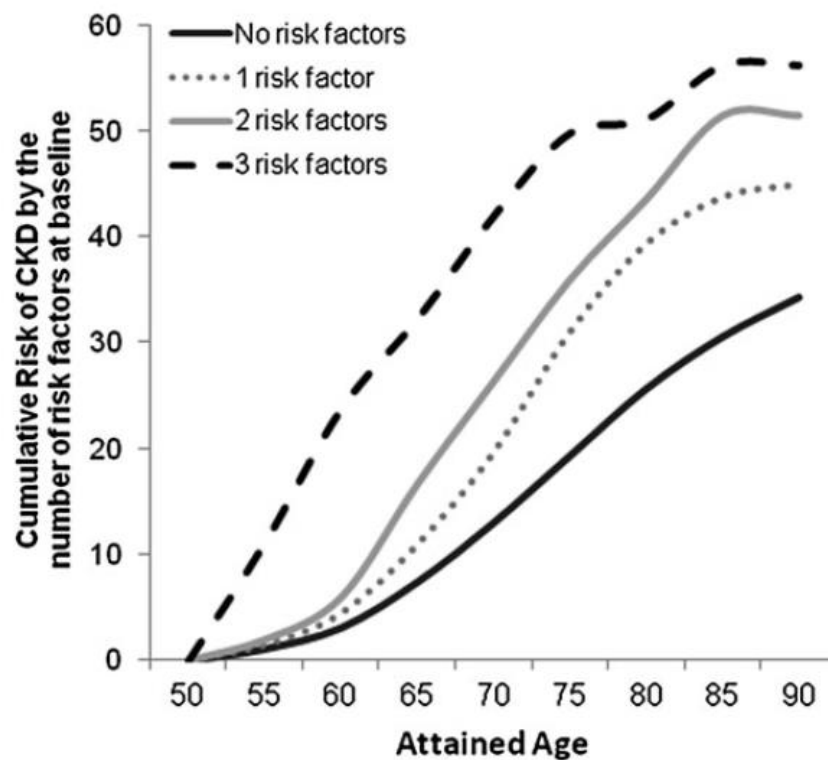
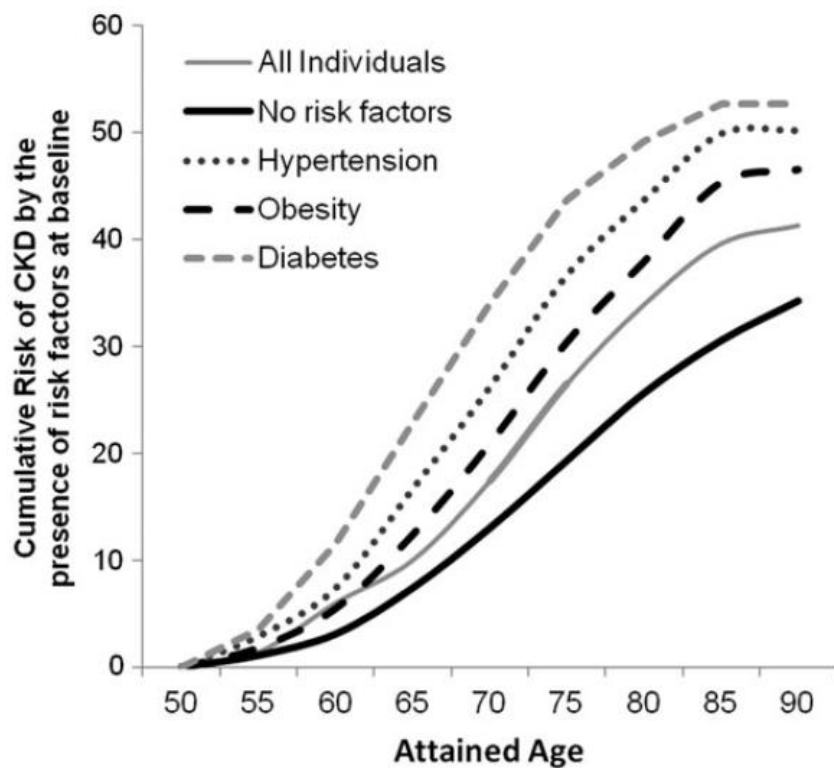
Increasing Prevalence of CKD with Age



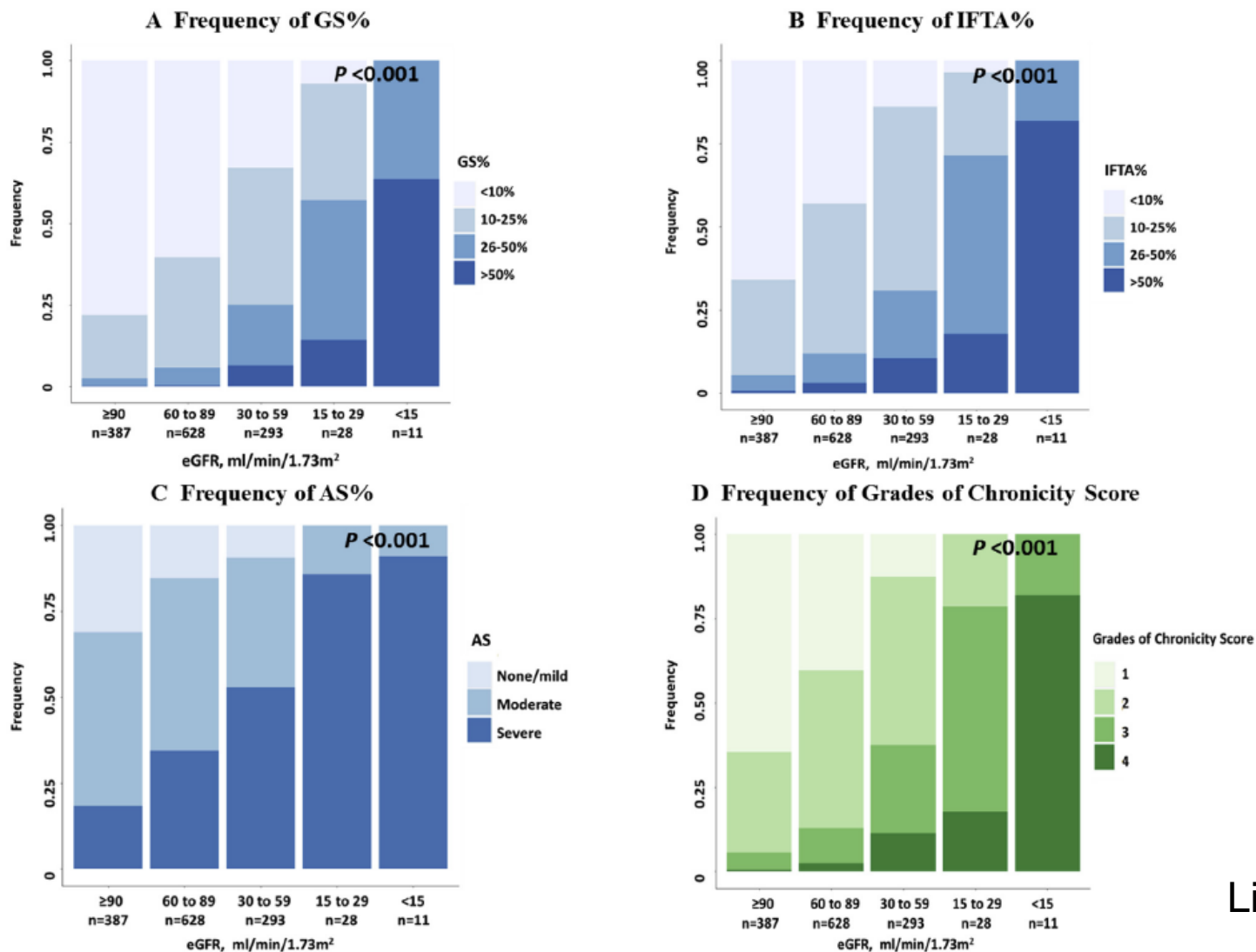
Long-term Risk Factors for CKD



Residual Lifetime Risk of CKD



Distinct pathologic profile in patients with early CKD



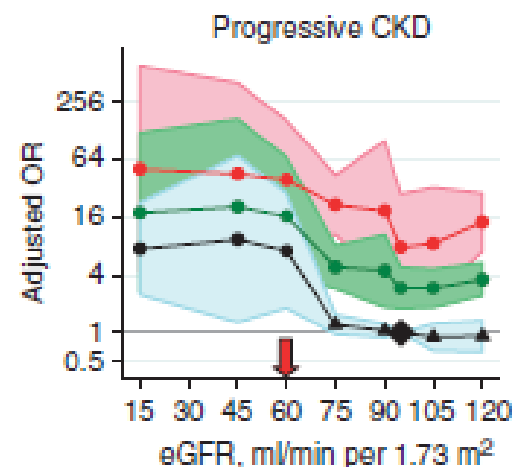
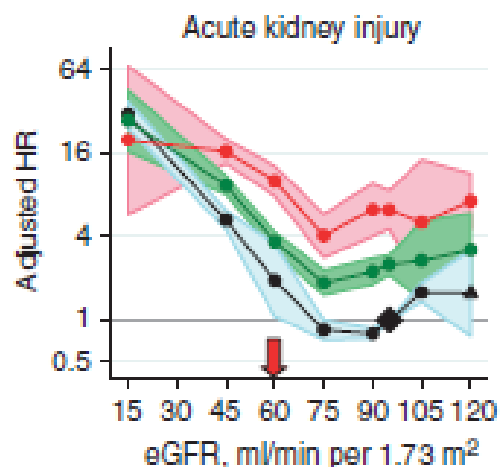
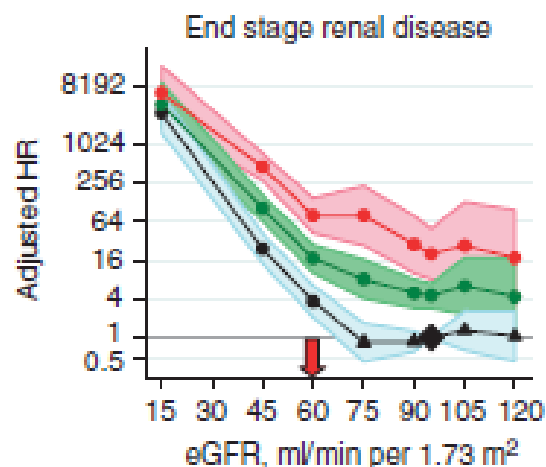
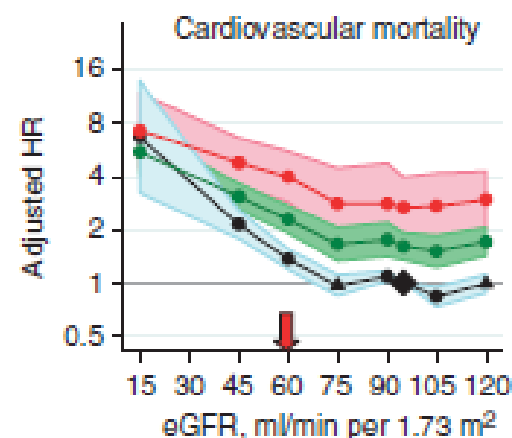
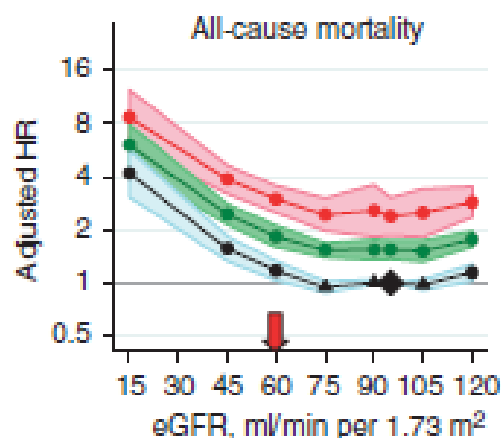
Complications develop early in CKD

Table 27 | Prevalence of CKD complications by GFR category* derived from CKD cohorts

Complication	GFR category (ml/min/1.73 m ²)					Reference
	≥ 90	60-89	45-59	30-44	< 30	
Anemia ¹	4.0%	4.7%	12.3%	22.7%	51.5%	366
Hypertension ²	18.3%	41.0%	71.8%	78.3%	82.1%	366
25(OH) Vit D deficiency ³	14.1%	9.1%	10.7%		27.2%	367
Acidosis ⁴	11.2%	8.4%	9.4%	18.1%	31.5%	366
Hyperphosphatemia ⁵	7.2%	7.4%	9.2%	9.3%	23.0%	366
Hypoalbuminemia ⁶	1.0%	1.3%	2.8%	9.0%	7.5%	366
Hyperparathyroidism ⁷	5.5%	9.4%	23.0%	44.0%	72.5%	366

CKD is a risk factor for poor outcomes

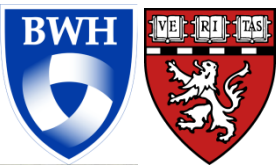
Summary of
relative risks
from
continuous
meta-analysis



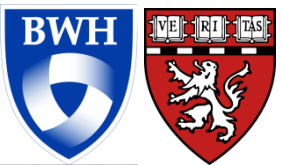
CKD Progression and Risk of All-cause mortality and ESRD

Definition of progression	All-cause mortality HR** (95% CI)	ESRD* HR** (95% CI)
Certain rise	1.51 (1.46–1.56)	0.33 (0.26–0.42)
Uncertain rise	1.12 (1.08–1.16)	0.39 (0.30–0.51)
Stable (reference)	Ref	Ref
Uncertain drop	0.98 (0.95–1.01)	2.13 (1.84–2.47)
Certain drop	1.89 (1.83–1.95)	5.11 (4.56–5.71)

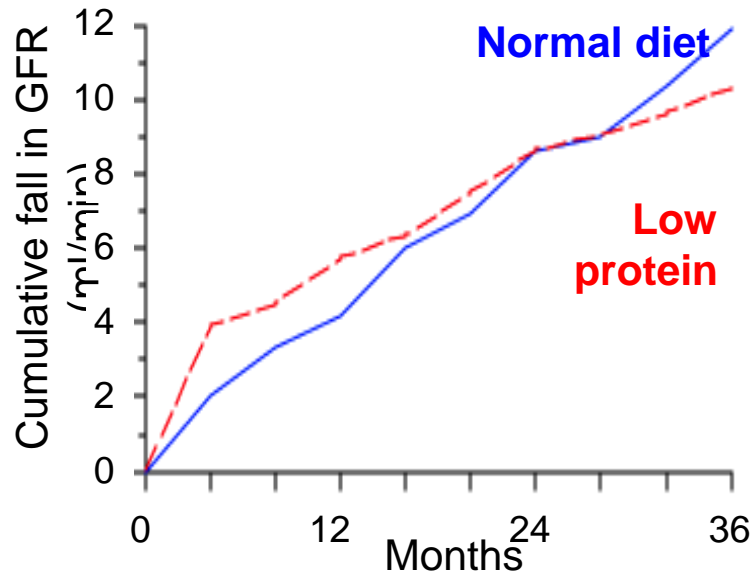
- ~600,000 adults with at least two outpatient creatinine measures spaced 6 months apart.
- Certain change = change in GFR category + 25% change in eGFR.
- Increased risk of mortality and ESRD with progression



How do we prevent CKD
progression?



Dietary Protein Restriction in CKD



MDRD study

585 patients with nondiabetic CKD

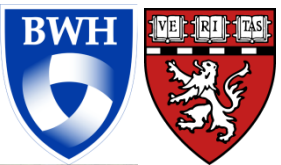
Mean GFR = 39

Randomized to 1.3 or 0.58 g/kg (achieved 0.6-0.8) protein per day

Little or no overall benefit

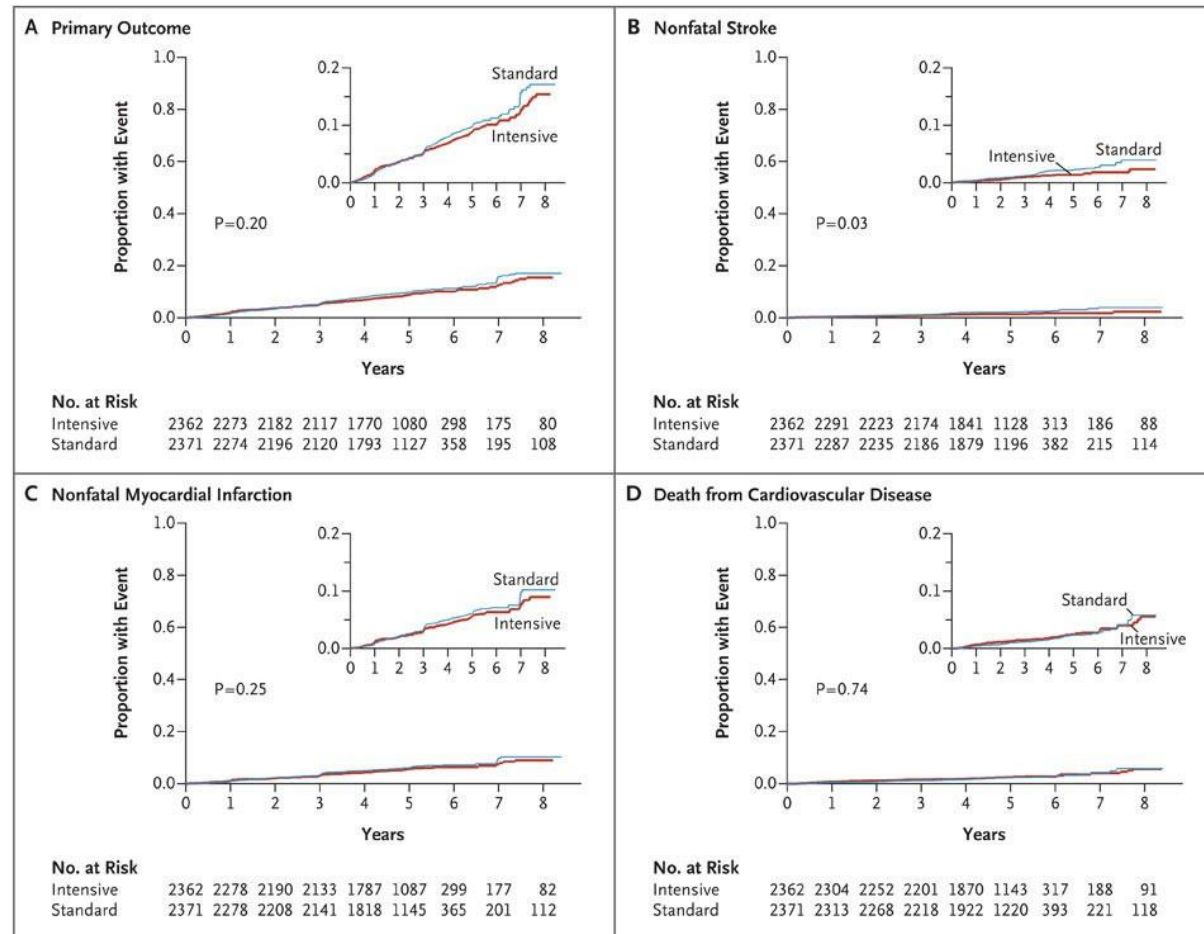
Conclusions:

- Dietary protein restriction *may* protect against the progression of CKD in humans by reducing intra-glomerular pressure
- Benefits of dietary protein restriction to 0.6-0.8 g/kg per day on CKD progression **is controversial**
- At best, a small reduction in the rate of GFR decline can be observed with low protein diet

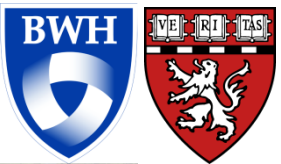


Blood pressure and CKD progression

ACCORD – no CV benefit
 for intense BP control
 (<120 vs <140) in T2DM
 Reduction in albuminuria
 but no reduction in ESRD
 (underpowered)



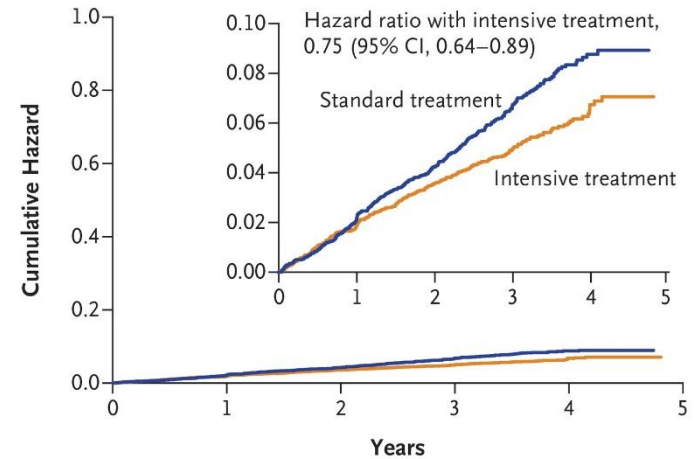
ACCORD Study Group, NEJM 2008



Blood pressure and CKD progression

- Previous guidelines suggested higher BP targets in non-proteinuric CKD
- SPRINT has changed this – now all high-risk patients should have a lower BP target to reduce CV risk
- No effect on CKD progression
- Increased risk of AKI in patients with CKD

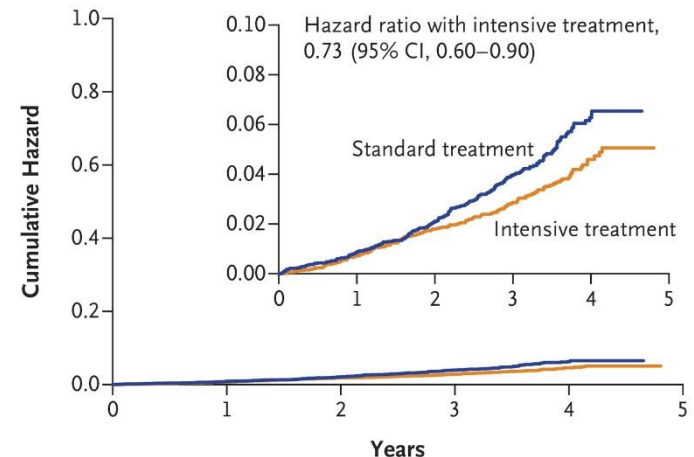
A Primary Outcome



No. at Risk

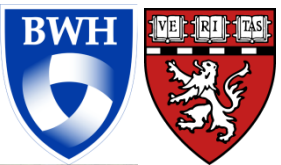
Standard treatment	4683	4437	4228	2829	721
Intensive treatment	4678	4436	4256	2900	779

B Death from Any Cause



No. at Risk

Standard treatment	4683	4528	4383	2998	789
Intensive treatment	4678	4516	4390	3016	807



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

Hazard ratio with intensive treatment,
1.64 (95% CI: 1.30-2.10), $p < 0.0001$

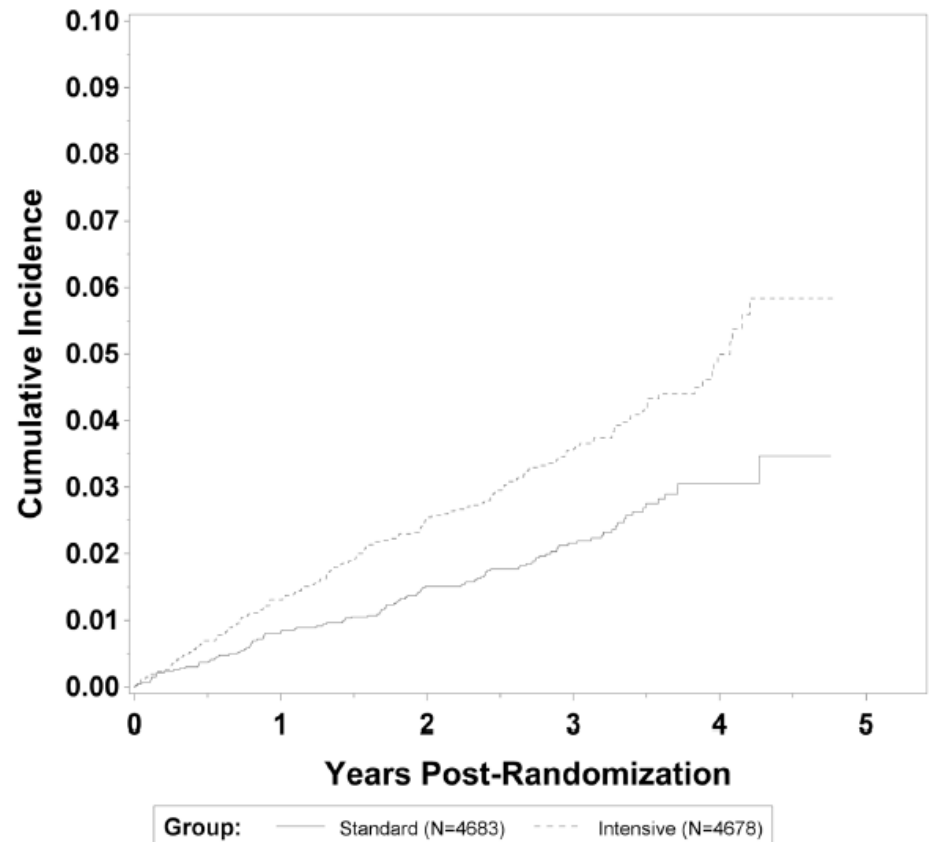
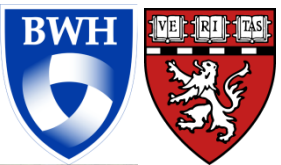
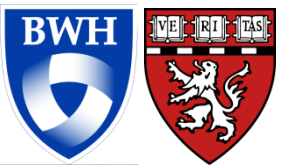
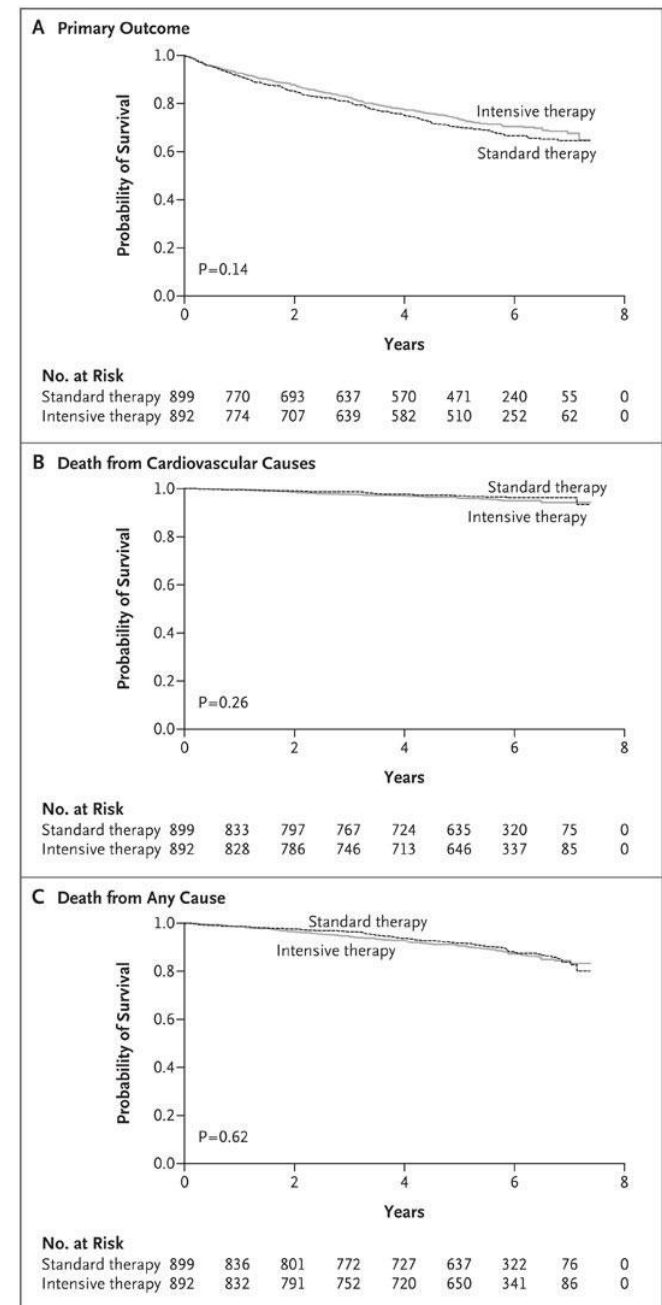


Figure 2.
Cumulative Hazard Plot for Acute Kidney Injury (CI denotes confidence interval).



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

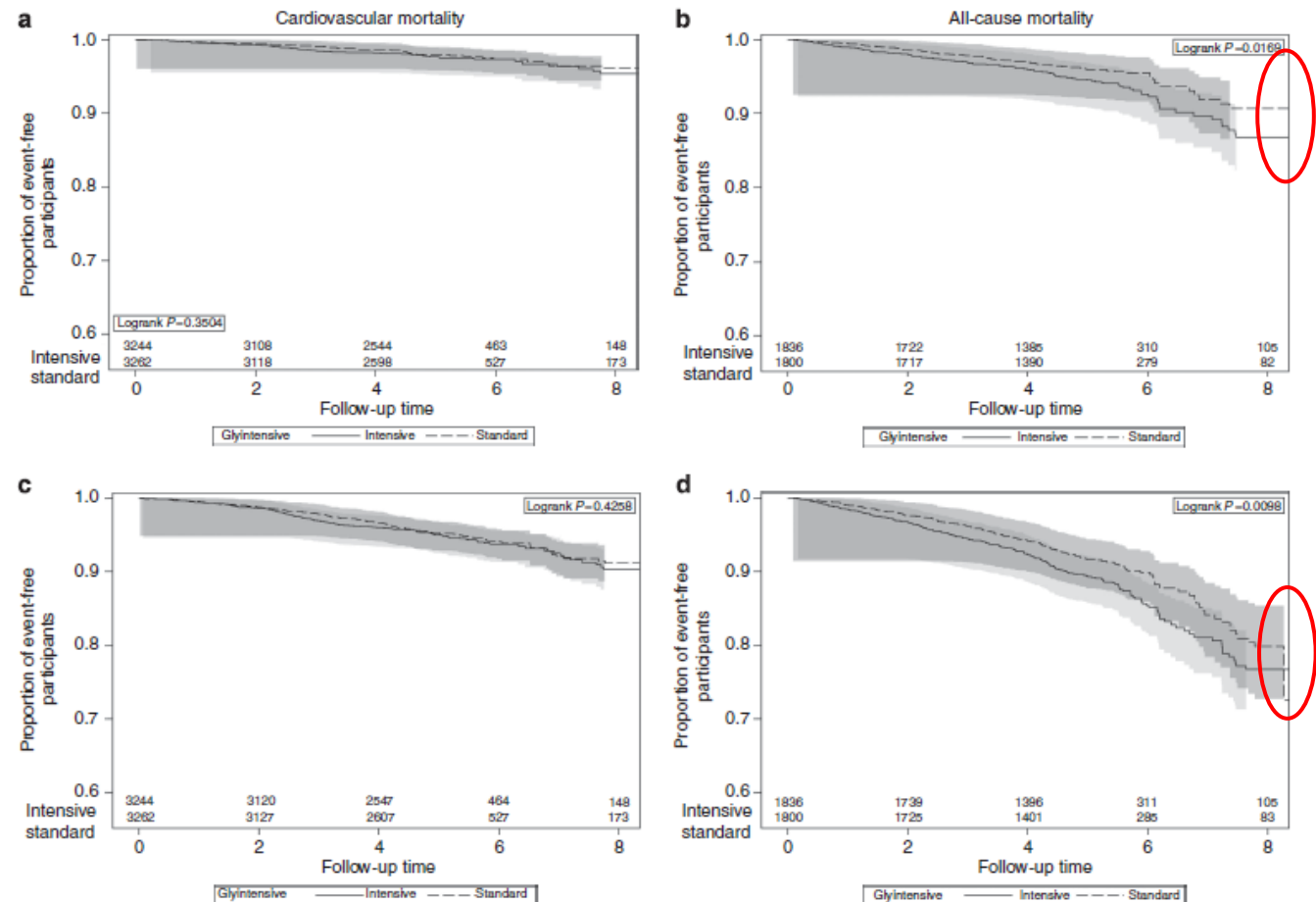
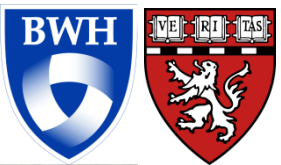


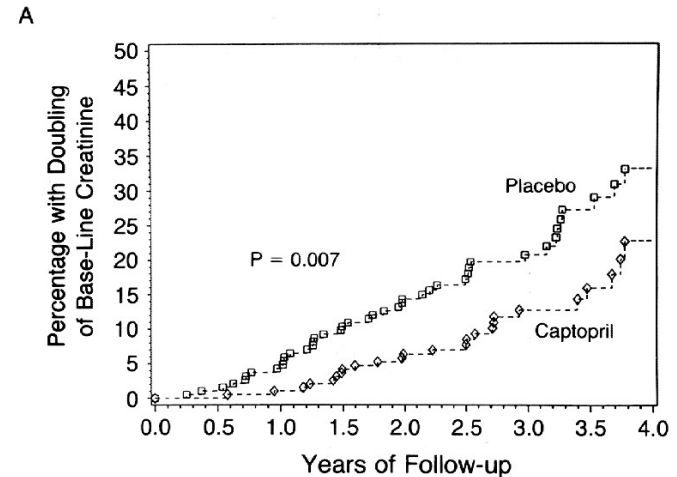
Figure 5 | Cardiovascular and all-cause mortality stratified by intensive or standard treatment group and by chronic kidney disease (CKD) status. Cardiovascular and all-cause mortality with intensive versus standard glycemic control in patients without CKD (a, c) and with CKD (b, d).

Papademetriou, Kid Int 2015

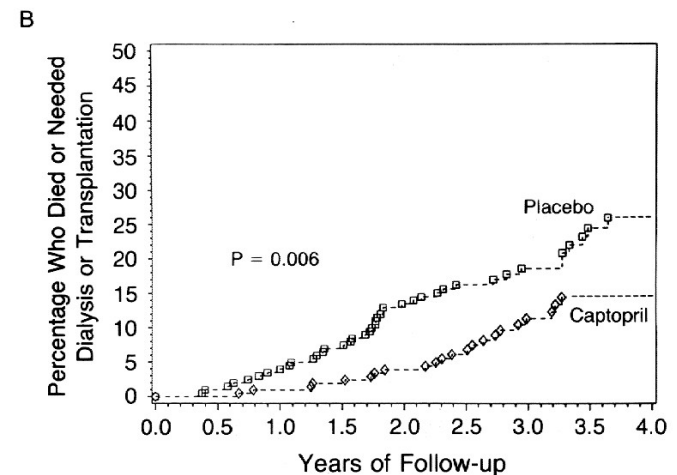


RAAS Blockade

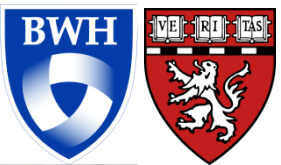
- ACEi, ARB, Direct Renin Inhibitors and mineralocorticoid antagonists.
- Single most effective therapy for slowing down the progression of diabetic nephropathy.
- Seminal Captopril Trial
 - Reduction in doubling of creatinine
 - 50% reduction in death/ESRD



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

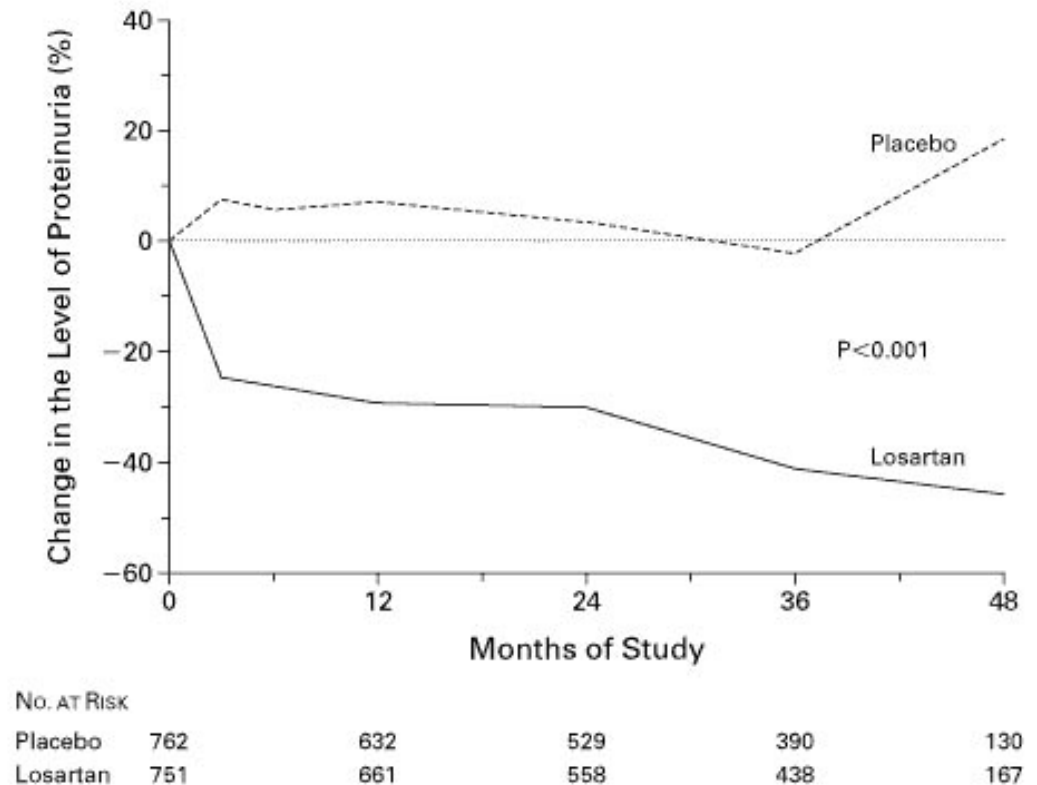


Placebo	202	198	192	186	171	121	100	59	26
Captopril	207	207	204	201	195	140	103	64	37



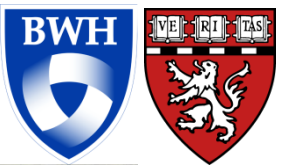
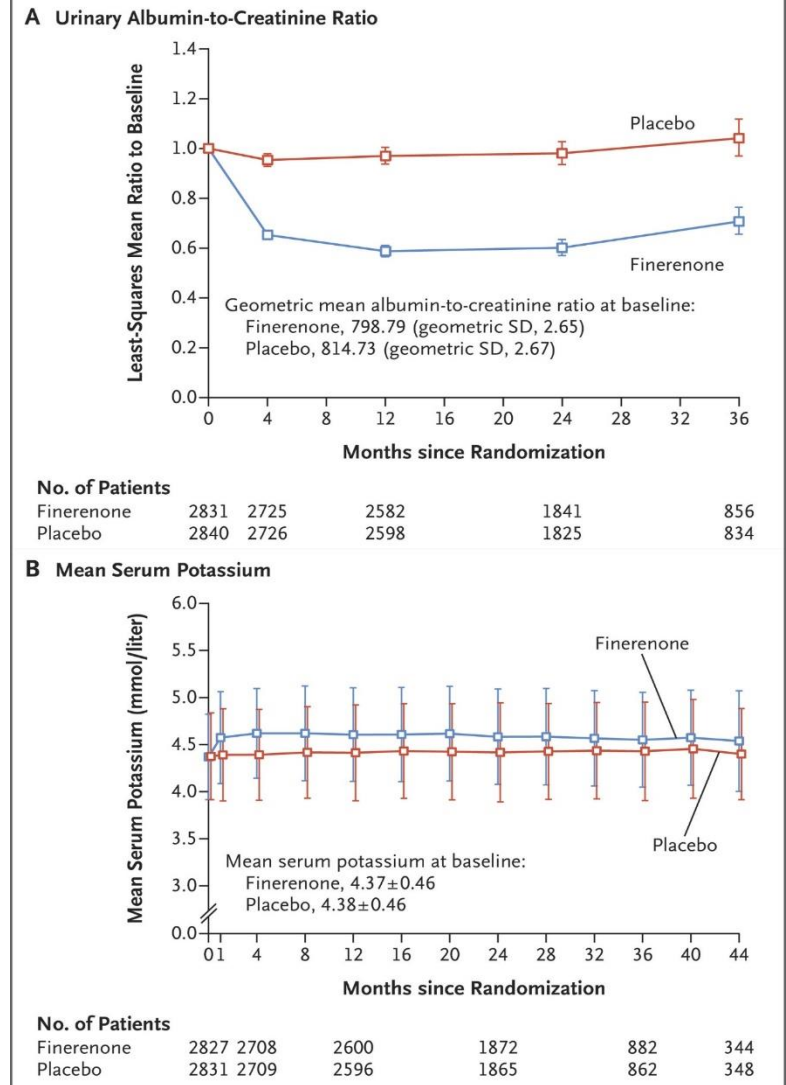
ARBs as effective as ACEi

- 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



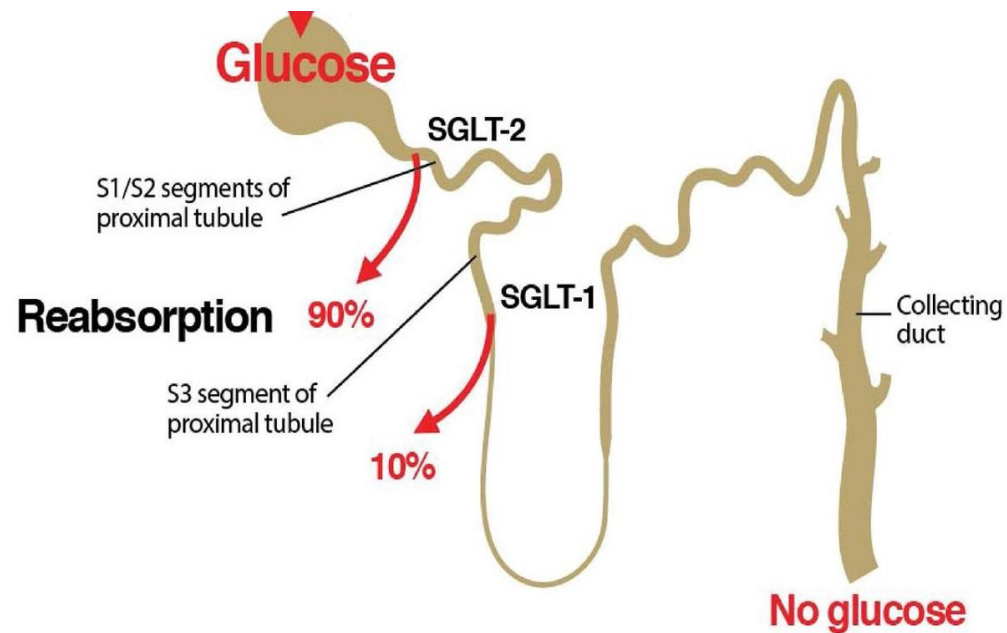
Non-Steroidal MRA

- 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)



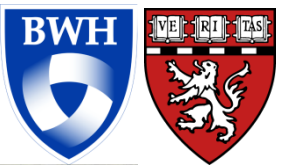
SGLT2 Inhibitors

- 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



CREDENCE – Study Design

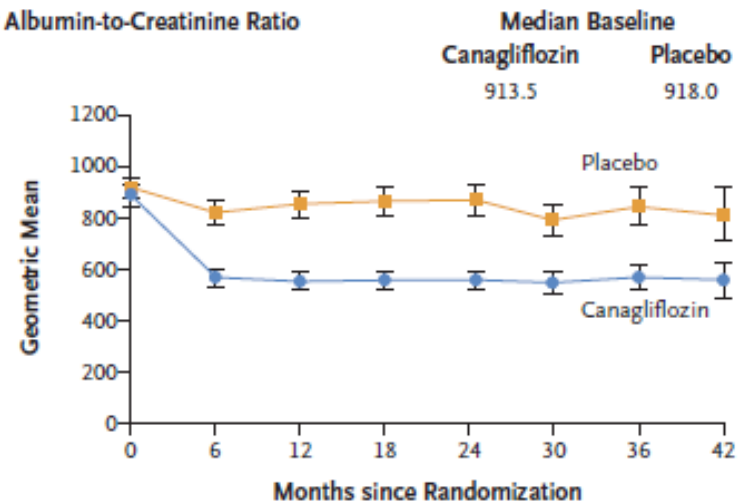
- Randomized trial of canagliflozin 100 mg daily versus placebo
- 4401 patients randomized
- Inclusion criteria:
 - Albumin/creatinine > 300 to 5000
 - eGFR 30 to < 90
 - Treatment with RAS blockade
- Primary outcomes:
 - Composite of ESRD and
 - Doubling of the serum creatinine
 - Death from renal or 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
- Most important discovery in nephrology in the past 10 years!

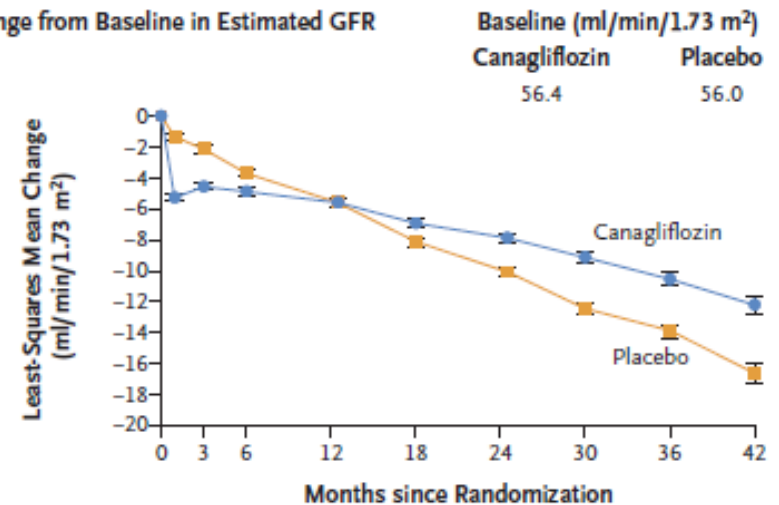
A Urinary Albumin-to-Creatinine Ratio



No. of Patients

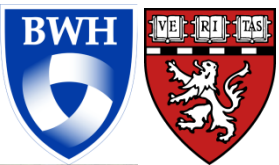
Placebo	2113	2061	1986	1865	1714	1158	685	251
Canagliflozin	2114	2070	2019	1917	1819	1245	730	271

B Change from Baseline in Estimated GFR

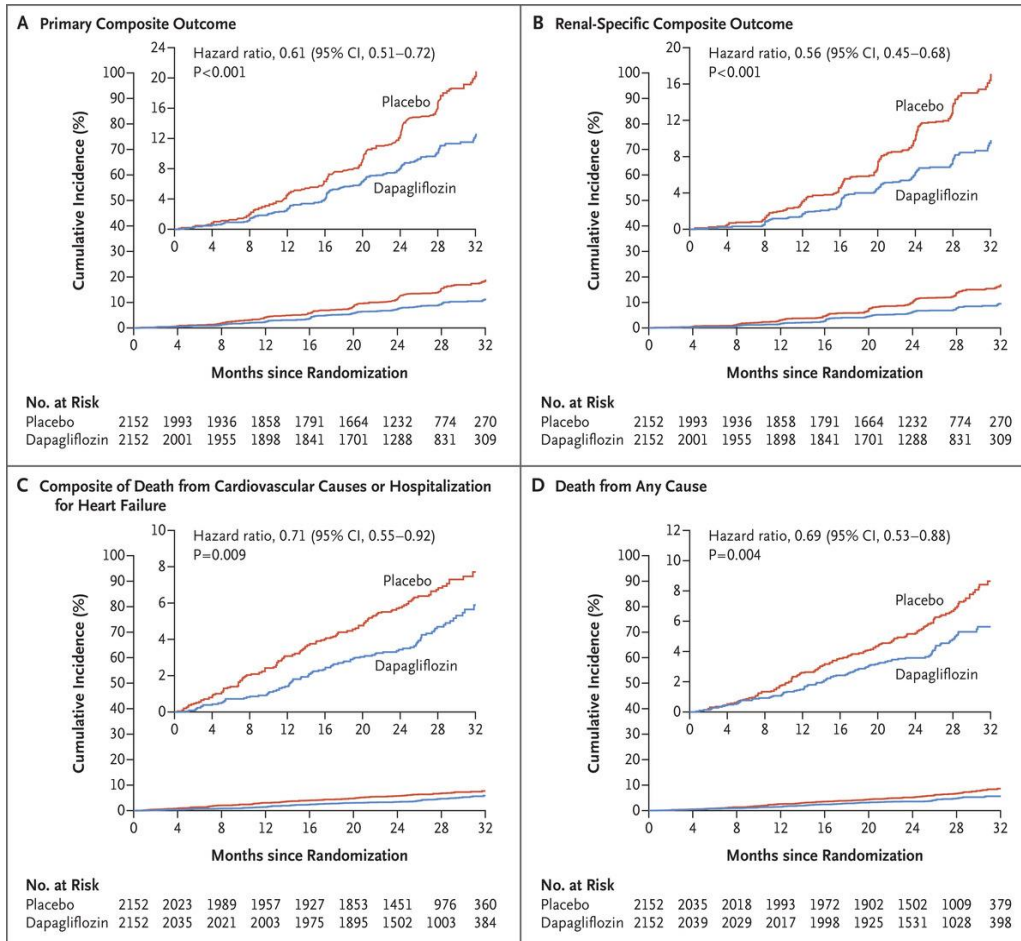


No. of Patients

Placebo	2178	1985	1882	1720	1536	1006	583	210
Canagliflozin	2179	2005	1919	1782	1648	1116	652	241



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

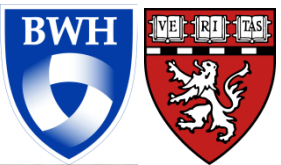


4200 patients with CKD stage 2-4 with albuminuria
Mix of patients with and without T2DM
Composite endpoint
ESRD
Cardiovascular or renal death
50% reduction in GFR

Study stopped early for overwhelming evidence of efficacy

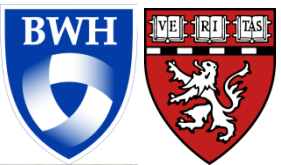
Case

- 74yo with CKD, mild albuminuria, hypertension and DM.
 - Is at increased risk of CV disease and CKD progression
 - Target A1c <8%
 - Target BP <130/80 to reduce CV risk
 - Add SGLT2i for renoprotection
 - Continue ACEi
 - No current indication for MRA



Take Home Points

- Early CKD is important and is associated with adverse outcomes including cardiovascular disease
- Delaying progression of CKD is hard as it is likely that significant structural changes have already occurred by the time the GFR has fallen
- Early intervention is likely more effective.
- We have more options for CKD delay now than ever before:



References

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