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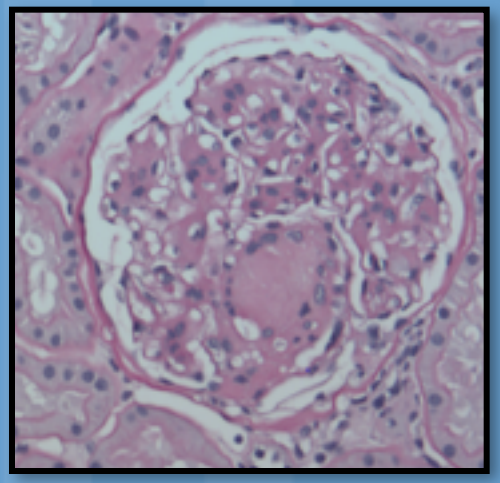
Diabetes and the Kidney

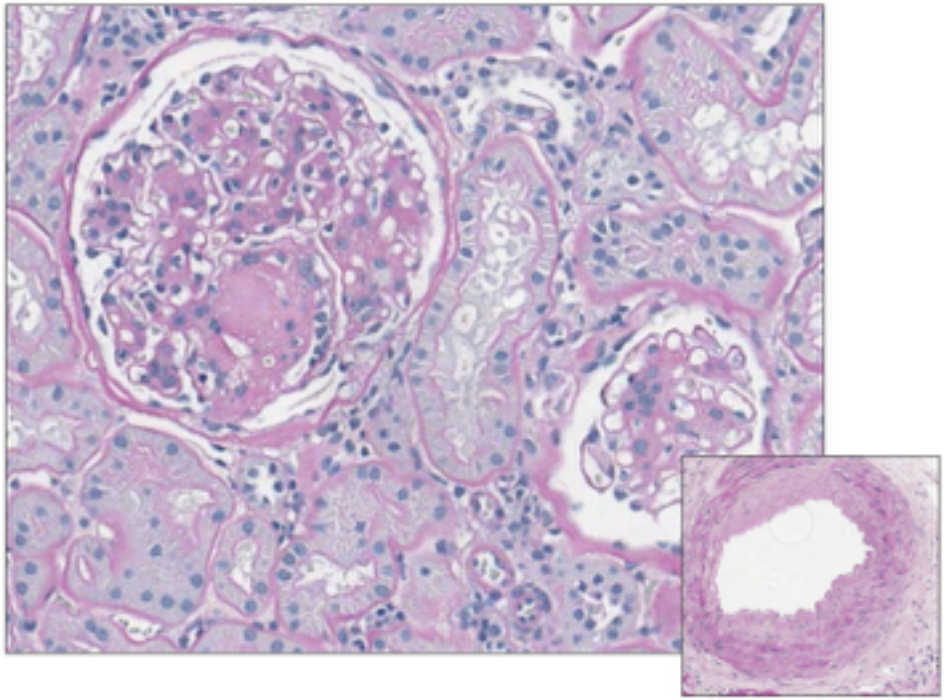


Amy K. Mottl, MD MPH FASN

April 22, 2017

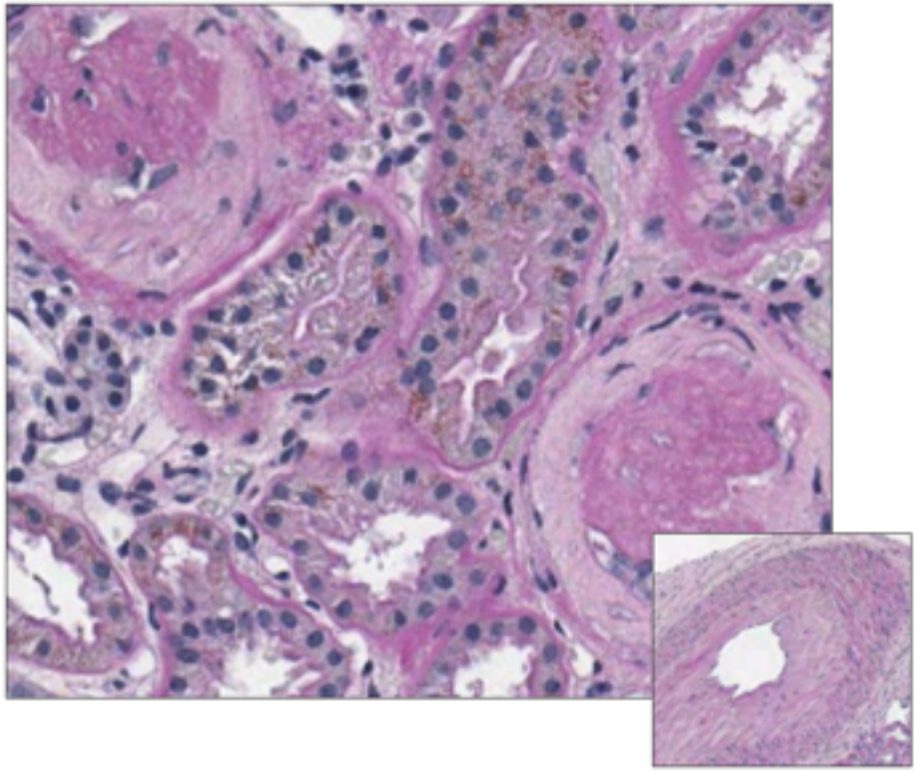
Diagnosis of DKD: Case 1

- 38 yo BF
- T2DM x 19 yr
- HbA1c 6.2
- Random UACR 88 mg/gm
  - FMV ACR 20mg/gm
- SCr 0.76



Diagnosis of DKD: Case 2

- 64 yo BF
- T2DM x 13yr
- HbA1c 7.9
- Random UACR 292
  - FMV UACR 90
- SCr 1.54



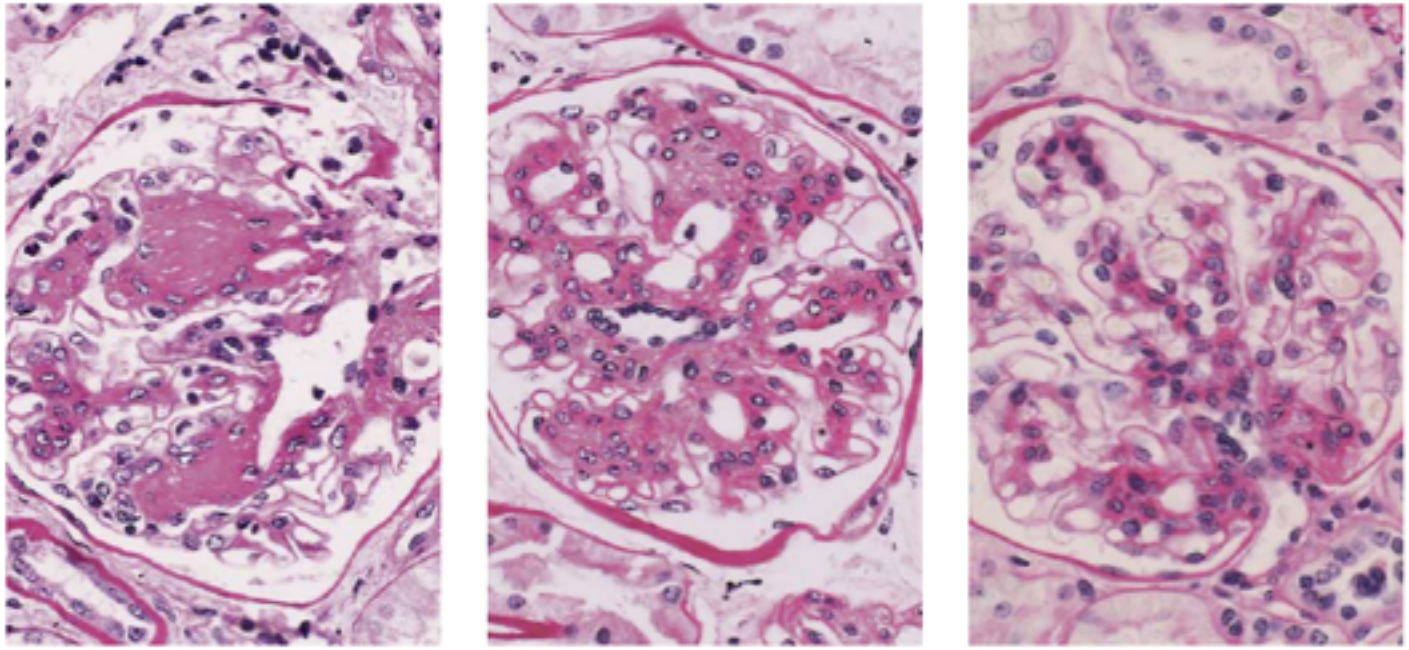
Diabetes and the Kidney

I. Clinical course of disease
- Microalbuminuria
- Normoalbuminuric chronic kidney disease
- Physiologic and pathogenic heterogeneity

II. Competing Risks
- ESRD
- Cardiovascular death

III. Treatment
- Glycemic and blood pressure control
- Renin Angiotensin Aldosterone Inhibition
- Pleiotropic effects of diabetes drugs

Hope: Diabetic Kidney Disease can be reversed!



Renal biopsy specimens obtained before and after pancreas transplantation from a 33 y.o. female with type I DM x 17 years.

A: base-line biopsy specimen characterized by diffuse and nodular diabetic glomerulopathy.

B: 5 years after transplantation shows persistence of diffuse and nodular lesions.

C: 10 years after transplantation: marked resolution of diffuse and nodular lesions and more open glomerular capillary lumina.

Fioretto P et al. N Engl J Med 1998; 339: 69-75

The changing natural history of diabetic kidney disease

Clinical course of disease

Microalbuminuria

Normoalbuminuric chronic kidney disease

Physiologic and Pathologic Heterogeneity

Diabetic kidney disease: U.S. Numbers

- Over 20 years, kidney disease is increasing, as diabetes prevalence increases. But...
  - Albuminuria is decreasing
  - Low eGFR is increasing

- 7.2 million people with diabetes (35%) have kidney disease (albuminuria and/or decreased eGFR)
  - 3.3 million with albuminuria (ONLY)
  - 2.3 million with low eGFR (ONLY)
  - 1.3 million with both albuminuria and low eGFR
  - 0.3 million with ESRD on dialysis or with transplant

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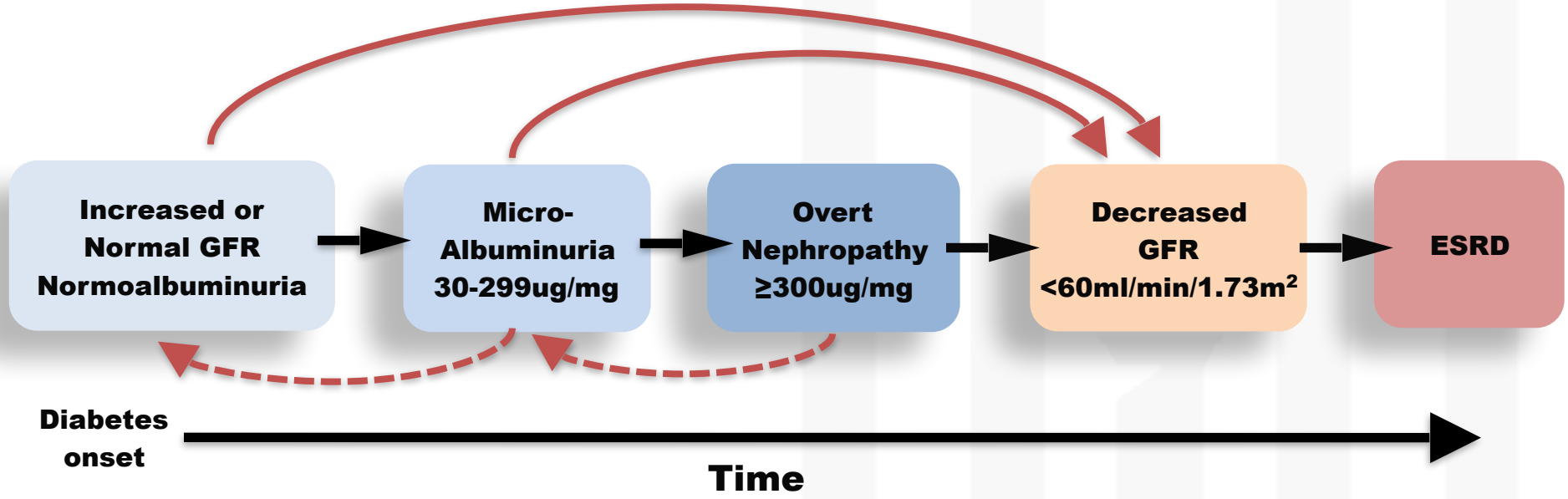
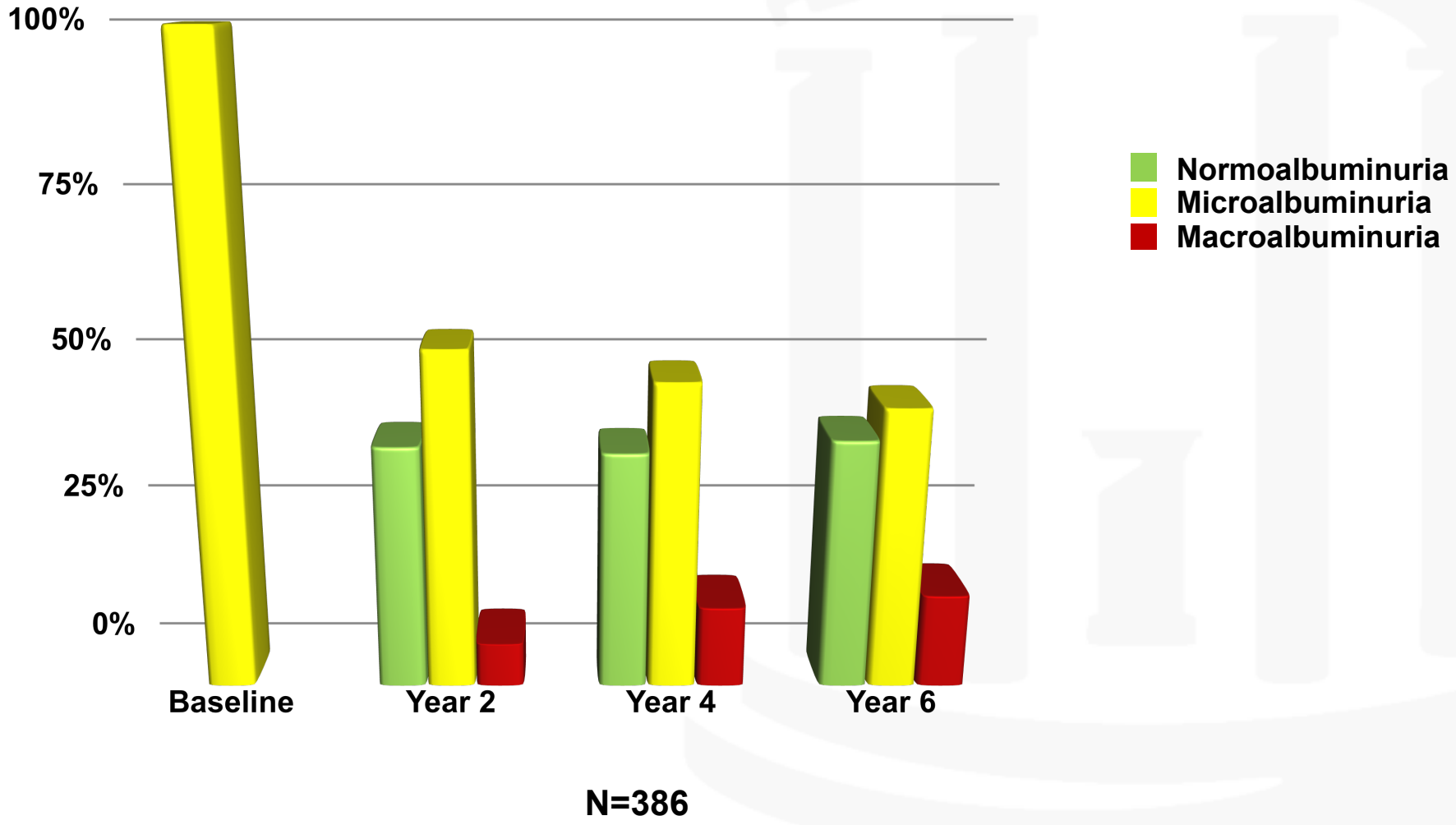
de Boer, et al. JAMA 2011; 305(24): 2532-2539

Diabetic Kidney Disease
Variability in Clinical Course



Course of Albuminuria in Type 1 Diabetes

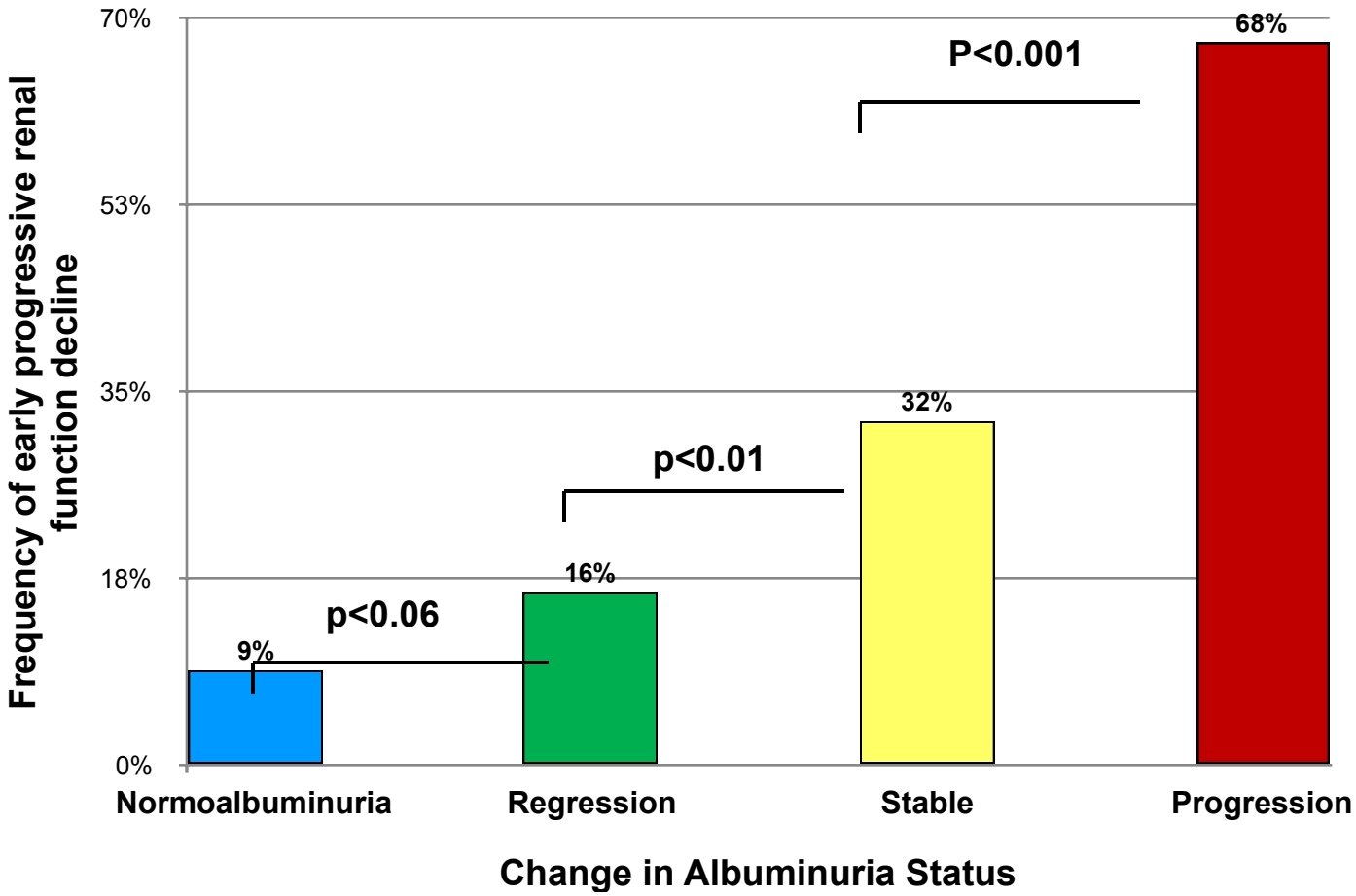
Regression More Common than Progression



N=386

Perkins BA et al. N Engl J Med 2003; 348: 2285-93

Course of Albuminuria and Risk of GFR Loss in Type 1 Diabetes Mellitus



Perkins BA et al. J Am Soc Nephrol 2007; 18(4): 1353-61

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Rising prevalence of normoalbuminuric CKD

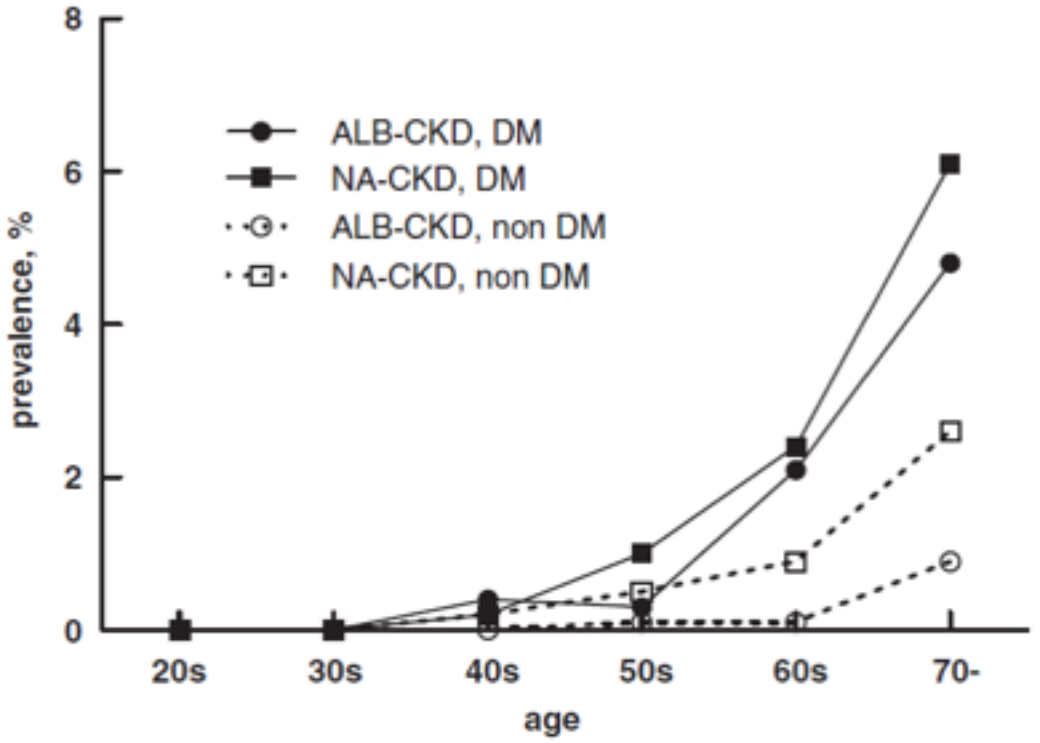

Fig. 2. Age-specific prevalence of chronic kidney disease (CKD) defined as eGFR <60 ml/min/1.73 m^2 according to diabetes status and albuminuria (ALB) ≥30 mg/g or normoalbuminuria (NA) <30 mg/g on a random urine specimen from NHANES 2001–2008.

Mottl et al. J Diabetes Complications 2013; 27(2):123-127.

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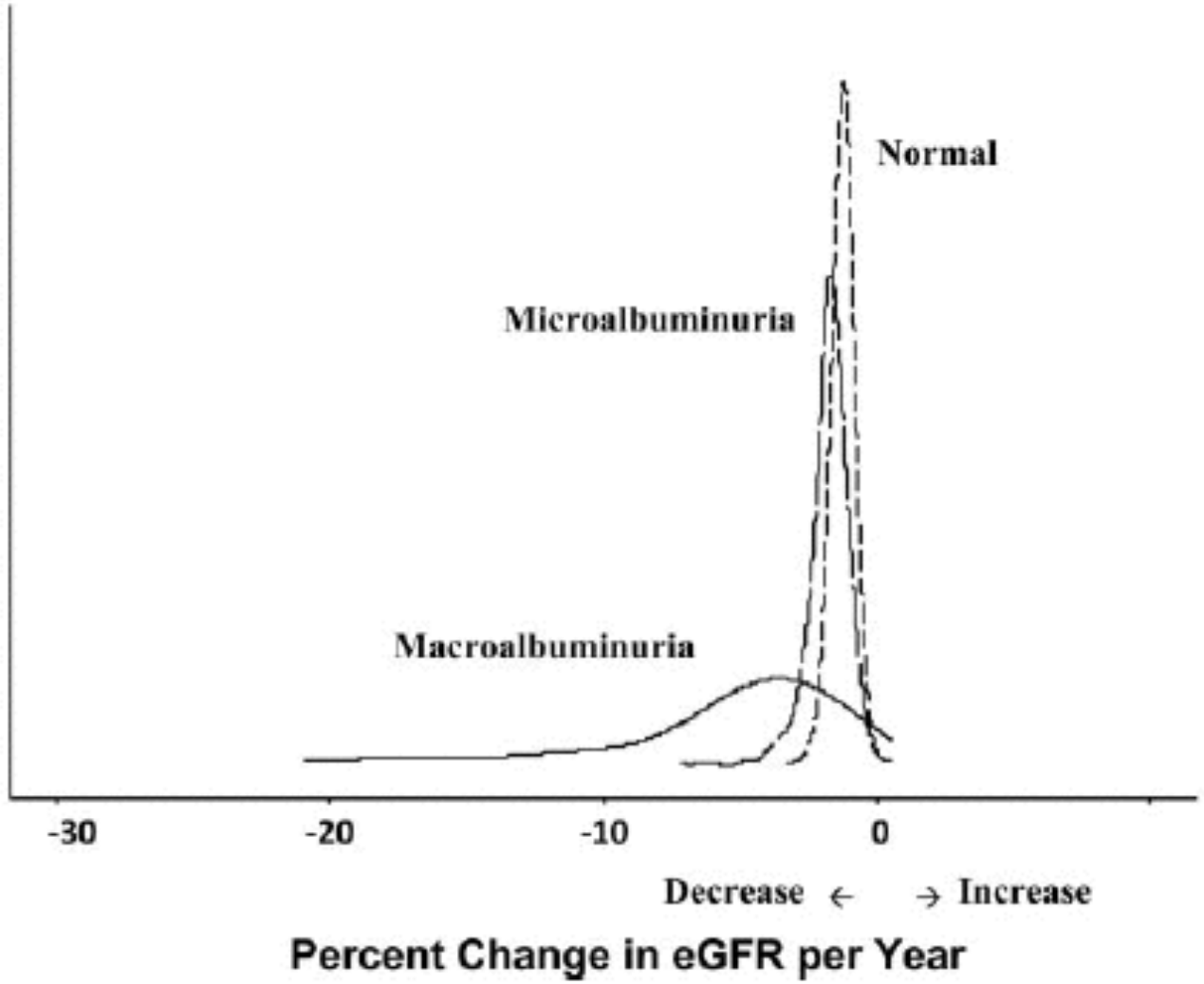
Rate of renal function decline with eGFR < 60 according to albuminuric status



Molitch et al. Diabetes Care 2010; 33(7):1536-43

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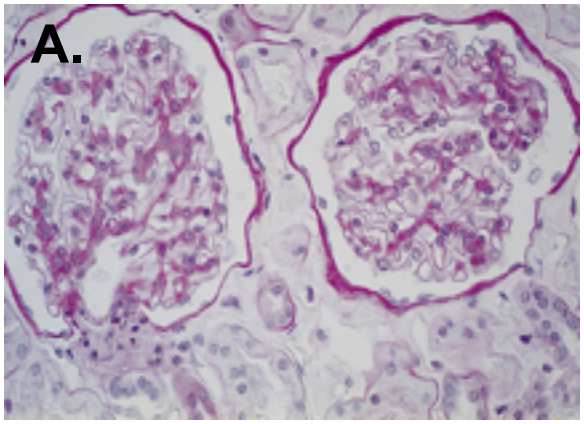
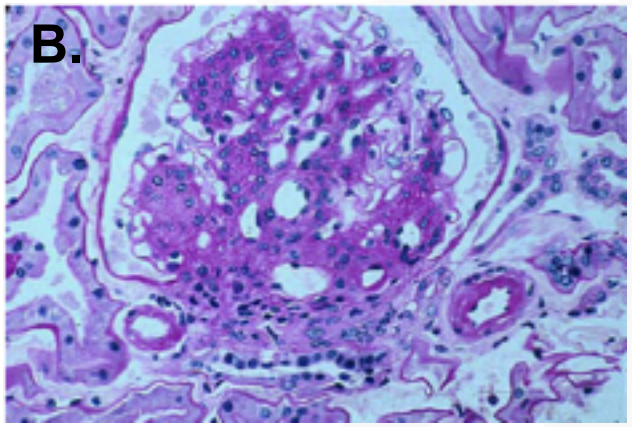
Heterogeneity in Pathology of Type 2 Diabetic Kidney Disease

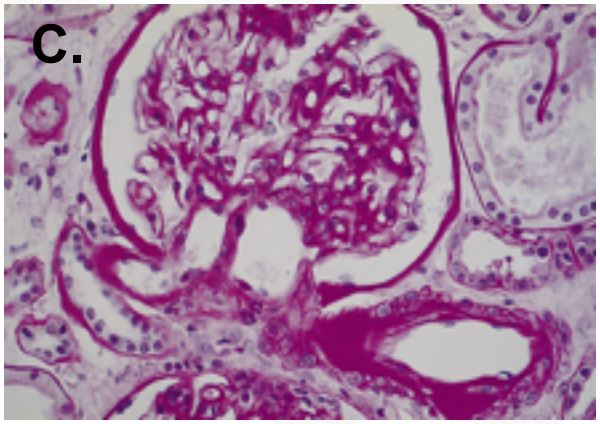


(A) normal/ near normal structure



(B) typical diabetes histopathology

- **Nodular mesangial expansion**
- **Thickened GBM**
- **Arteriolar hyalinosis**



(C) atypical patterns of renal injury

- **Tubular atrophy**
- **Thickened tubular BM**
- **Interstitial fibrosis**
- **Advanced arteriolar hyalinosis**

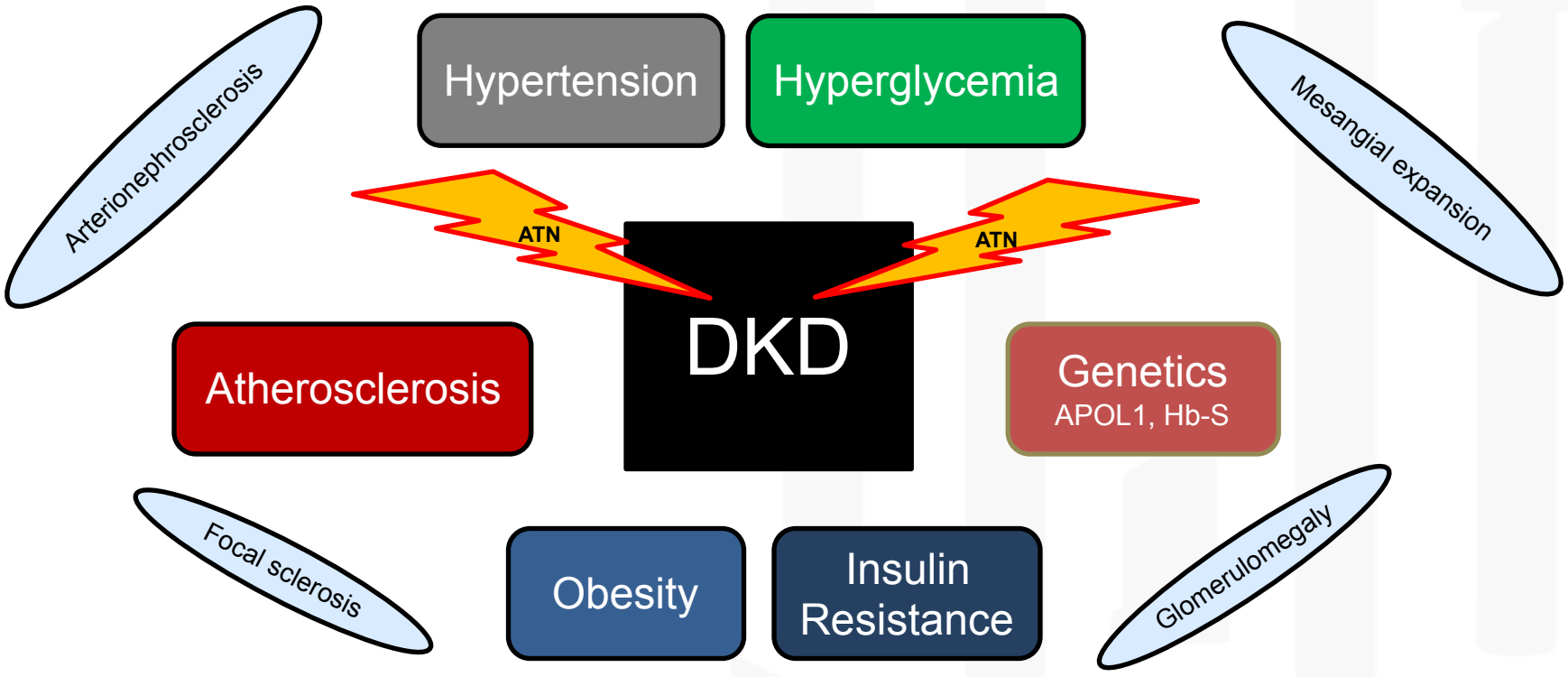
Fioretto P et al. Diabetologia 2008; 51: 1347-1355

Histopathology by Clinical Indices

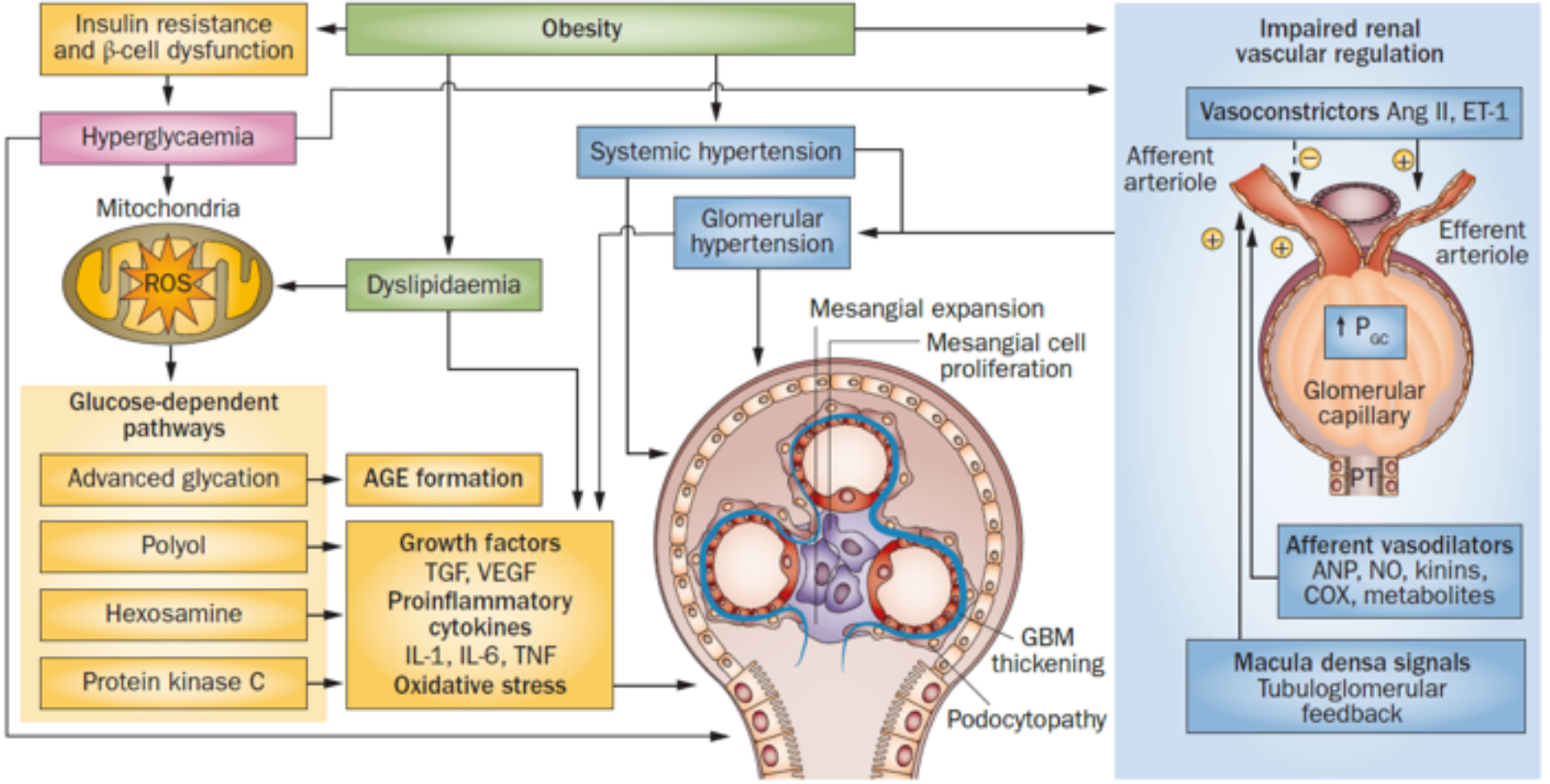
Structural Category	eGFR ≥60ml/min/ 1.73m² Microalbuminuria	eGFR <60ml/min/1.73m² Normoalbuminuria	eGFR <60ml/min/ 1.73m² Microalbuminuria	eGFR <60ml/min/ 1.73m² Macroalbuminuria
Normal Structure	10	2	0	0
Predominant Diabetic Glomerulosclerosis	10	3	5	17
Disproportionately Severe Interstitial and Arteriosclerosis	14	3	1	0

Ekinci EI, et al. Diabetes Care 2013

Pathogenetic factors in DKD



Renal Physiology in Diabetes



Acute kidney injury and the risk of progressive kidney disease

Thakar CV et al. CJASN 2011; 6: 2567-72.

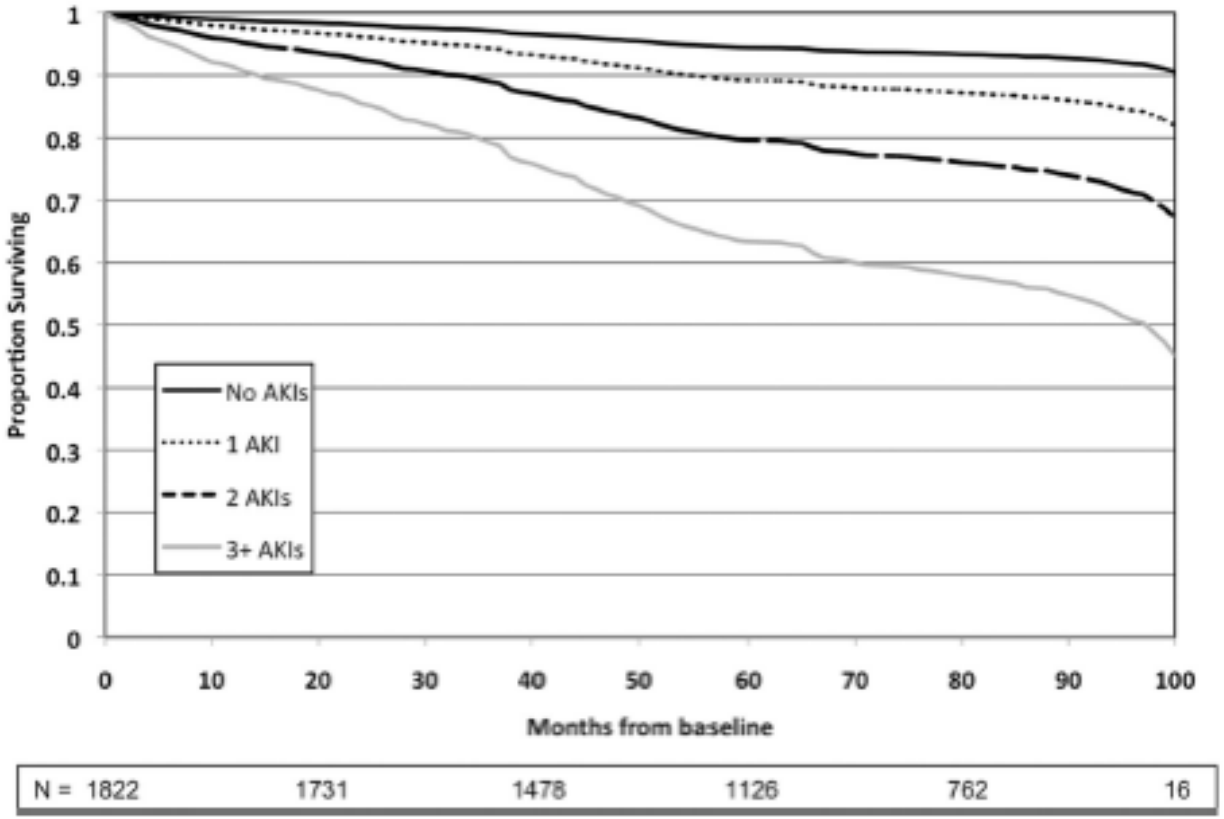


Figure 2. | **(A) Survival to stage 4 CKD in no AKI *versus* AKI groups.** (B) Survival to stage 4 CKD in no AKI *versus* multiple AKI episode group. CKD, chronic kidney disease; AKI, acute kidney injury.

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The changing natural history of diabetic kidney disease

Competing Risks

ESRD

Death

Annual transition rates of type 2 diabetic kidney disease

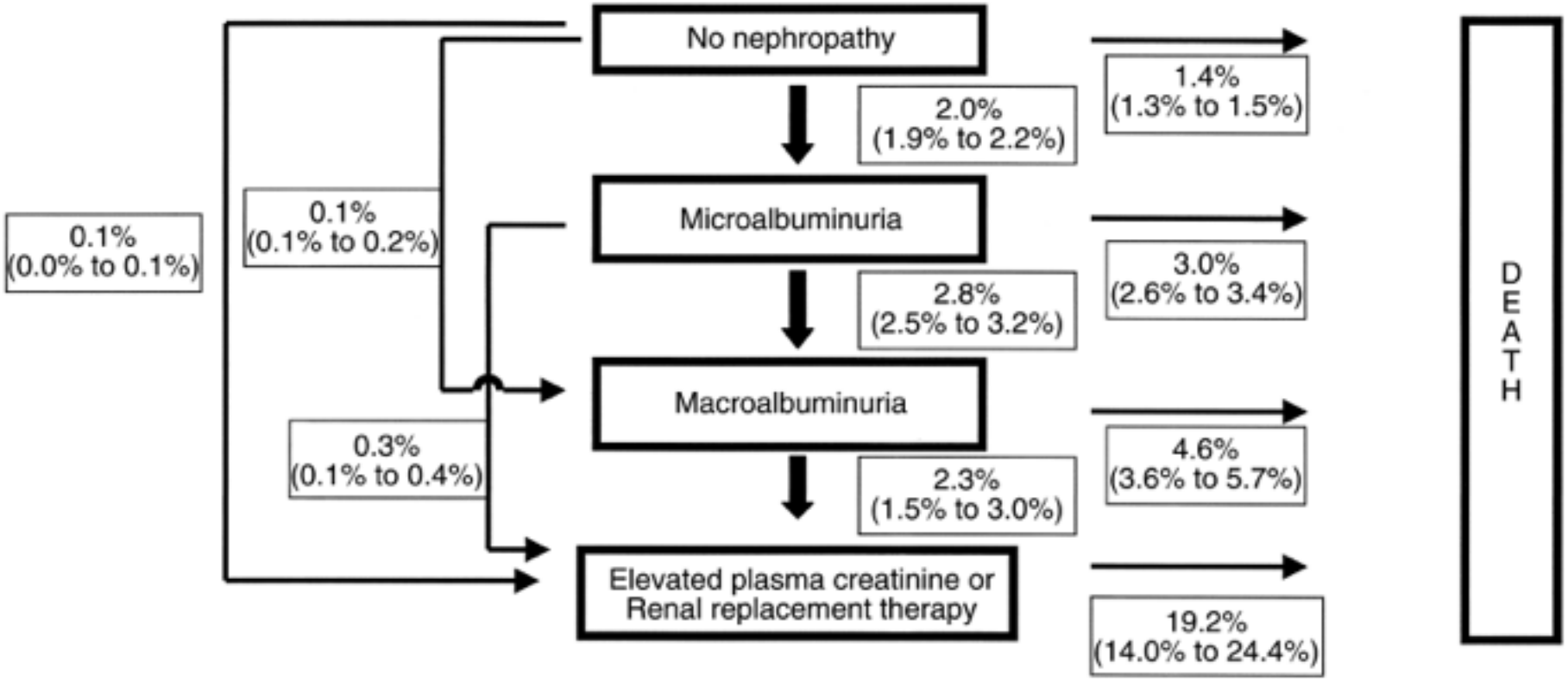
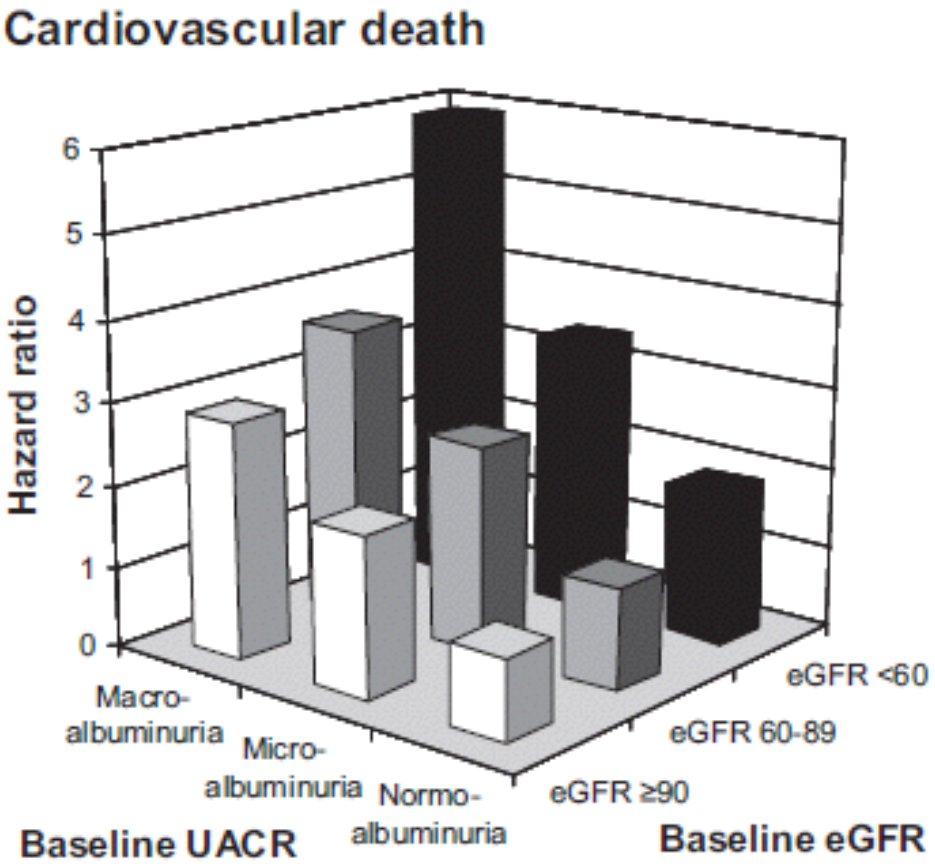
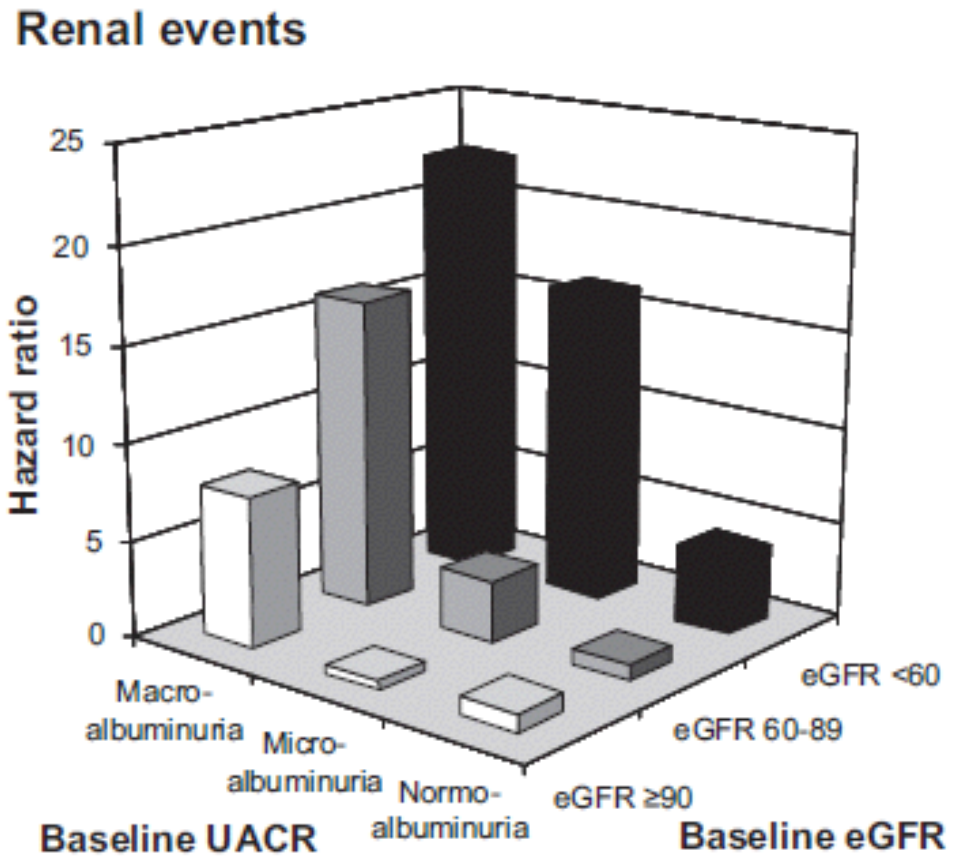


Fig. 1. Annual transition rates with 95% confidence intervals through the stages of nephropathy and to death from any cause.

Adler, et al. Kidney International 2003; 63: 223-32.

Competing risks in diabetic kidney disease

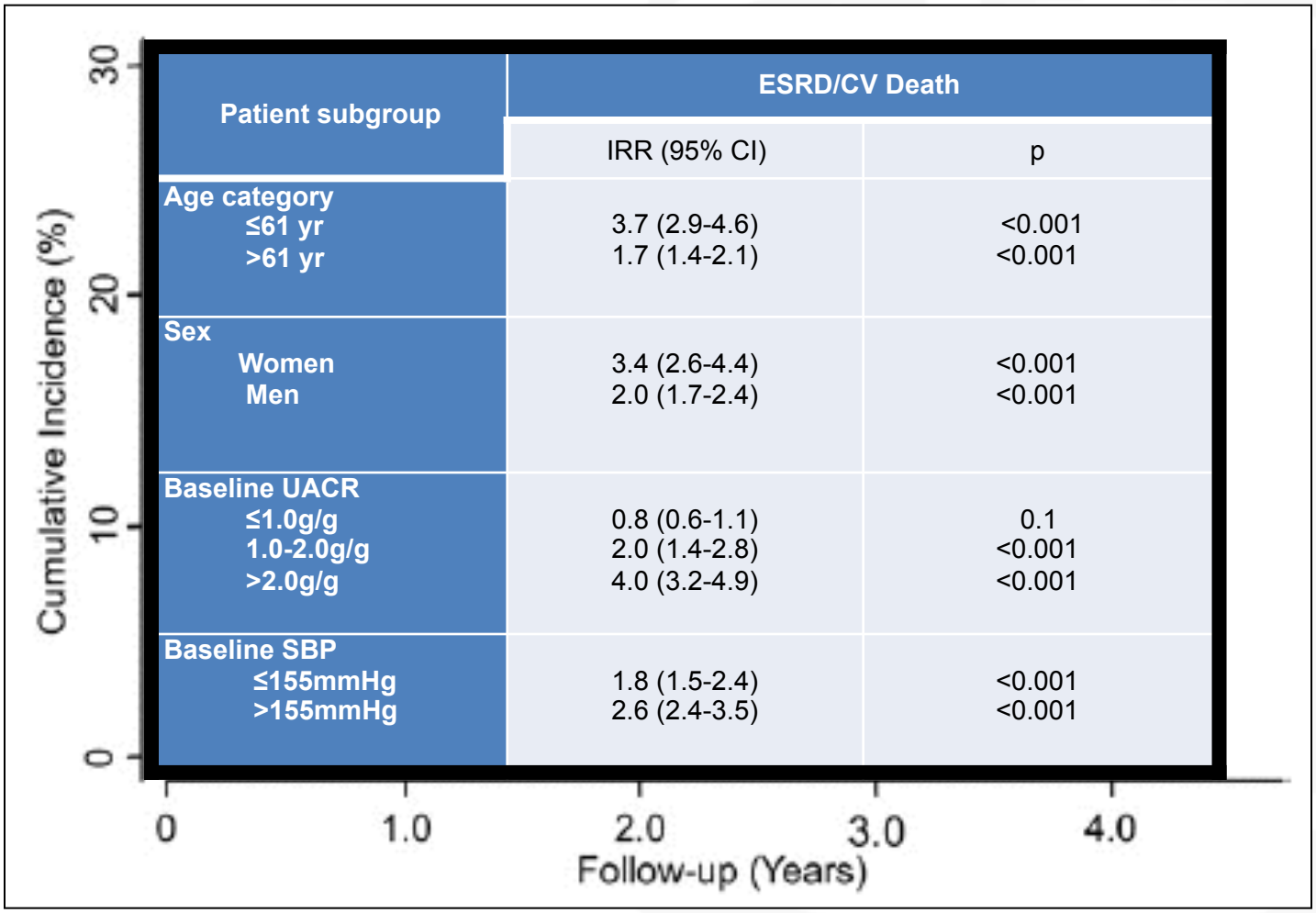




ADVANCE.JASN 2009; 20: 1813-1821.

When the risk of ESRD supercedes the risk of Cardiovascular Death

Patient subgroup	ESRD/CV Death	
	IRR (95% CI)	p
Age category		
≤61 yr	3.7 (2.9-4.6)	<0.001
>61 yr	1.7 (1.4-2.1)	<0.001
Sex		
Women	3.4 (2.6-4.4)	<0.001
Men	2.0 (1.7-2.4)	<0.001
Baseline UACR		
≤1.0g/g	0.8 (0.6-1.1)	0.1
1.0-2.0g/g	2.0 (1.4-2.8)	<0.001
>2.0g/g	4.0 (3.2-4.9)	<0.001
Baseline SBP		
≤155mmHg	1.8 (1.5-2.4)	<0.001
>155mmHg	2.6 (2.4-3.5)	<0.001



Packham et al. AJKD 2012; 59(1): 75-83.

The changing natural history of diabetic kidney disease

Treatment

Glycemic and Blood Pressure Control

Renin Angiotensin Aldosterone Inhibition

Pleiotropic Effects of Diabetes Drugs
Thiazolidinediones
SGLT2 inhibitors
Incretins

Glycemia targets for reducing renal outcomes

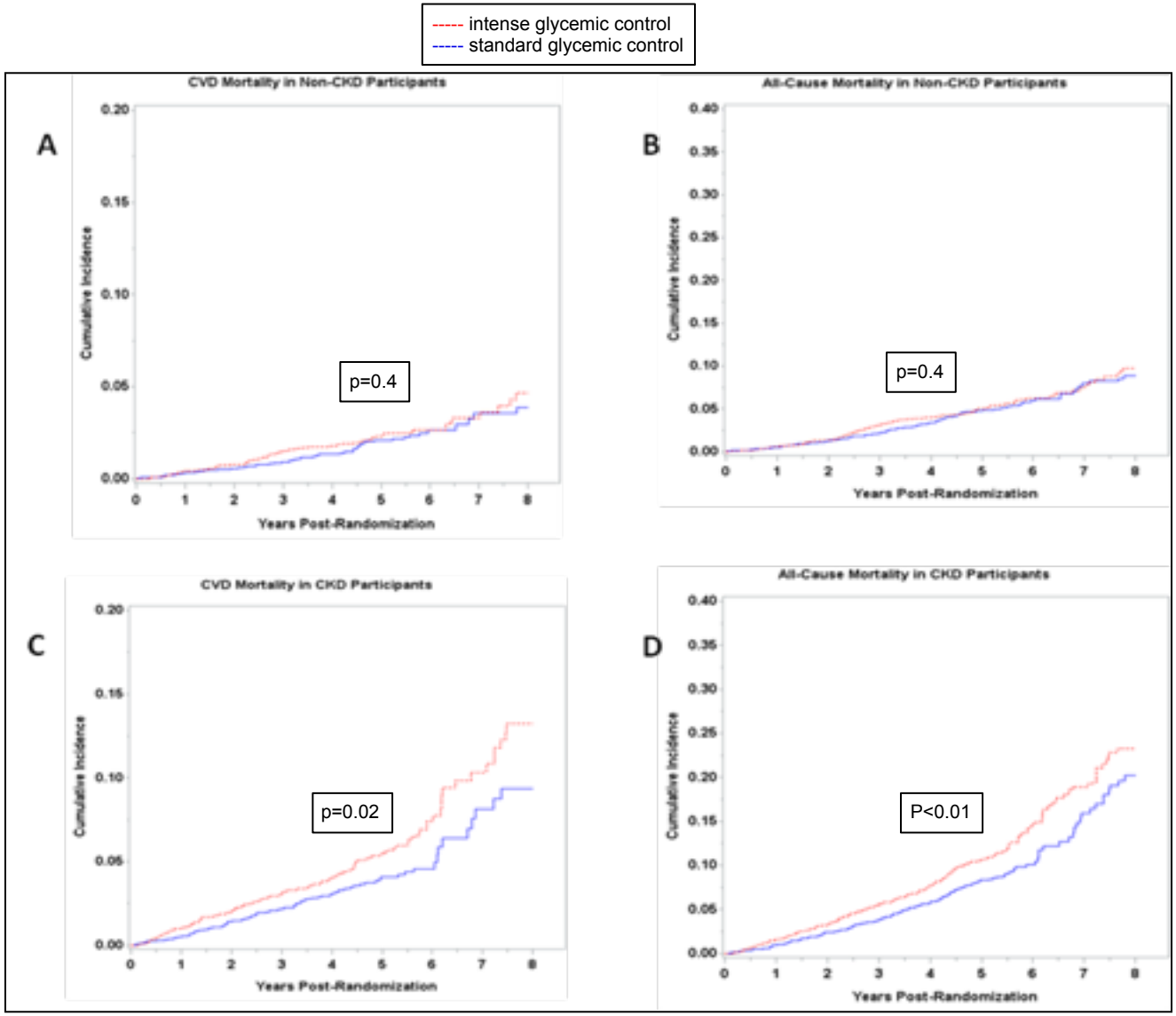
Table 3. Large (N>100), extended (> 2 yrs duration)randomized, controlled trials of the effect of glycemic control on renal outcomes in type 1 and type 2 diabetes.

Study	Diabetes Type	Mean Age (Years)	Sample Size	Median Study Duration (Years)	Intervention	Mean A1C (%)	Renal Outcomes	Relative Risk (95% CI)
DCCT[1]	Type 1	27	1441	6.5 yrs	A1C < 6% vs. Asymptomatic	7.0 8.9	macroalbuminuria	**0.5 (0.3, 0.9)**
EDIC[2]	Type 1	34	1349	8 yrs (from DCCT close)	None: extension of DCCT cohort	8.0 8.2	macroalbuminuria SCr >2mg/dl	**0.8 (0.7, 0.9)** **0.3 (0.1, 0.7)**
UKPDS[3]	Type 2	54	3867	10 yrs	FPG < 108mg/dl vs. FPG < 280mg/dl	7.0 7.9	macroalbuminuria doubling of SCr	0.6 (0.3, 1.3) **0.5 (0.3, 0.7)**
ADVANCE[4]	Type 2	66	11140	5 yrs	A1C <6.5% vs. "Local Guidelines"	6.5 7.2	macroalbuminuria doubling of SCr RRT or renal-related death	**0.7 (0.6, 0.9)** 1.2 (0.8, 1.6) 0.6 (0.4, 1.1)
VADT[5]	Type 2	60	1791	5.6 yrs	A1C < 6% vs. A1C < 9%	6.9 8.4	macroalbuminuria doubling of SCr eGFR < 15mg/dl/m^2	**0.6 (0.3, 1.0)** 1.0 (0.7, 1.4) 0.6 (0.2, 1.6)
ACCORD[6]	Type 2	62	10251	3.4 yrs	A1C <6% vs. A1C 7-7.9%	6.3 7.6	macroalbuminuria double SCr or loss of 20U eGFR SCr >3.3mg/dl or RRT	**0.7 (0.6, 0.9)** 1.1 (1.0, 1.1) 1.0 (0.7, 1.2)

DCCT: Diabetes Control and Complications Trial; EDIC: Epidemiology of Diabetes Intervention and Complications; VADT: Veterans Affairs Diabetes Trial; A1C: Hemoglobin A1C; FPG: Fasting Plasma Glucose; SCr: Serum Creatinine; RRT: Renal Replacement Therapy

Mottl and Tuttle. Management of Kidney Risk in Diabetes. In: Evidence Based Management of Diabetes; UK: Tfm Publishing Ltd 2012

More… or Less aggressive glycemic control with CKD?



Papademetriou, Mottl, et al. Kidney Int 2015 Mar; 87(3): 649-659

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Blood Pressure Targets in Diabetes

Study	Intervention	Attained Blood Pressures	Renal Outcomes	Macrovascular Outcomes
UKPDS	<150/85 + ACEI/BB <180/105	144/82 154/87	Micro: RR=0.71 (p<0.001) Macro: NS	MI: NS Stroke: RR=0.56 (p<0.05) All cause mortality: NS
HOT	DBP < 80 DBP < 90	144/81 148/85	N/A	MI: NS Stroke: NS CV death: RR=0.33 (p<0.05)
ABCD (hypertensive)	DBP = 75 DBP = 80-89	132/78 138/86	Micro: NS Macro NS CrCl: NS	MI: NS Stroke: NS All cause mortality: 0.51 (p<0.05)
ABCD (normotensive)	↓DBP 10 + ACEI maintain DBP 80-89	128/75 137/81	Micro: p=0.04 Macro: p=0.02 CrCl: NS	MI: NS Stroke: 0.31 (p< 0.05) All cause mortality: NS
ACCORD	SBP <120 SBP < 140	119/64 133/70	eGFR < 30: RR=1.9 (<0.001) Micro: NS Macro: RR 0.76 (<0.001)	Composite outcome: CV event or death: NS

Micro: microalbuminuria; Macro: macroalbuminuria; NS: not significant; CrCl: creatinine clearance; eGFR: estimated glomerular filtration rate; MI: myocardial infarction;

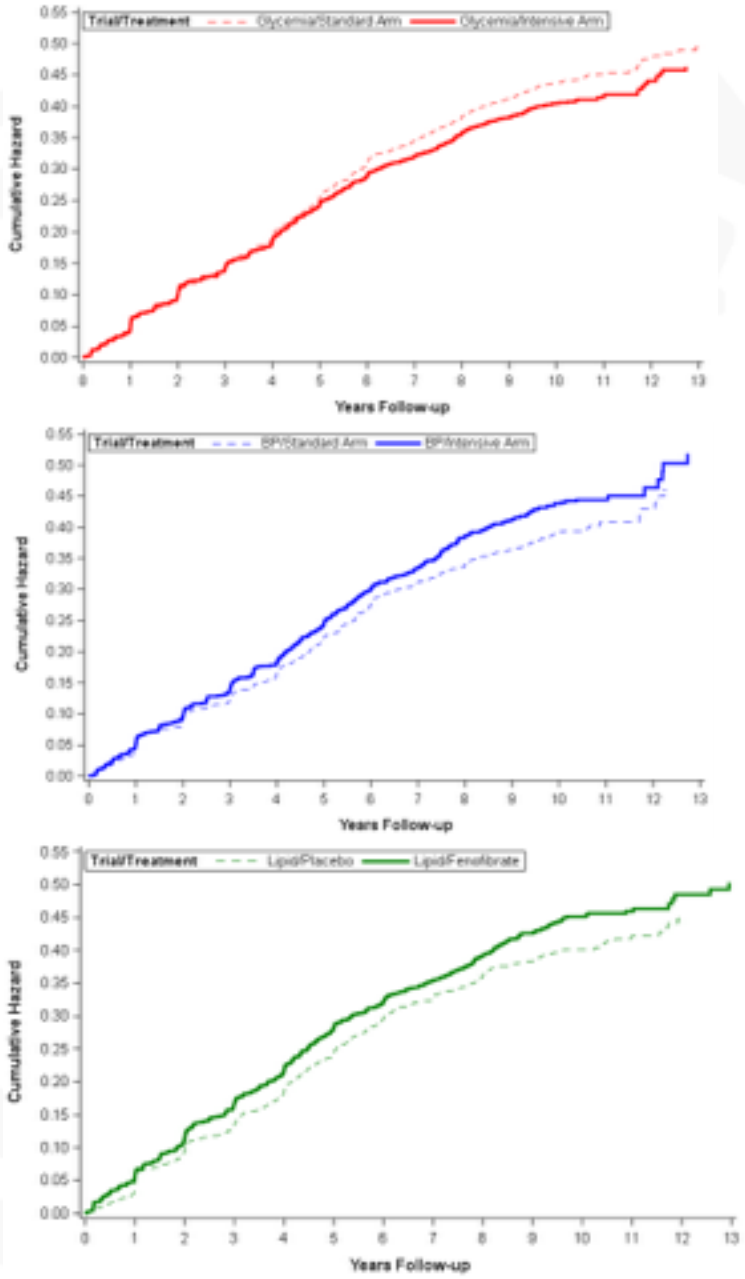
Mottl and Tuttle. Management of Kidney Risk in Diabetes; In: Evidence Based Management of Diabetes; UK: Tfm Publishing Ltd.

Long term outcomes from ACCORDion

Table 2. Incidence of long-term (10 year) kidney outcomes according to initial randomization to intensive glycemic control (HbA1c <6.0%), blood pressure control (systolic blood pressure <120 mmHg) or treatment with fenofibrate in the ACCORD study.

Outcome	Glycemia Trial N = 10,139 HR (95% CI)	Blood Pressure Trial N = 4,682 HR (95% CI)	Fenofibrate Trial N = 5,457 HR (95% CI)
Univariate Analyses:			
Composite Outcome	**0.92 (0.86, 0.99)**	**1.15 (1.04, 1.27)**	**1.15 (1.05, 1.26)**
Macroalbuminuria	**0.72 (0.64, 0.82)**	1.00 (0.83, 1.21)	1.19 (1.00, 1.40)
Creatinine Doubling	1.05 (0.93, 1.20)	**1.52 (1.25, 1.85)**	**1.83 (1.54, 2.18)**
ESRD	0.84 (0.68, 1.04)	0.91 (0.61, 1.25)	0.97 90.74, 1.29)
All-cause mortality	1.00 (0.91, 1.09)	1.03 (0.90, 1.18)	0.95 (0.84, 1.06)
Multivariate Analyses*:			
Composite Outcome	**0.92 (0.86, 0.98)**	**1.16 (1.05, 1.28)**	**1.16 (1.06, 1.27)**
Macroalbuminuria	**0.68 (0.59, 0.77)**	0.97 (0.79, 1.17)	1.11 (0.93, 1.33)
Creatinine Doubling	1.09 (0.94, 1.27)	**1.64 (1.30, 2.06)**	**2.00 (1.61, 2.49)**
ESRD	0.92 (0.72, 1.16)	0.90 (0.63, 1.28)	1.09 (0.80, 1.50)
All-cause mortality	1.00 (0.91, 1.10)	1.01 (0.88, 1.17)	0.96 (0.85, 1.08)

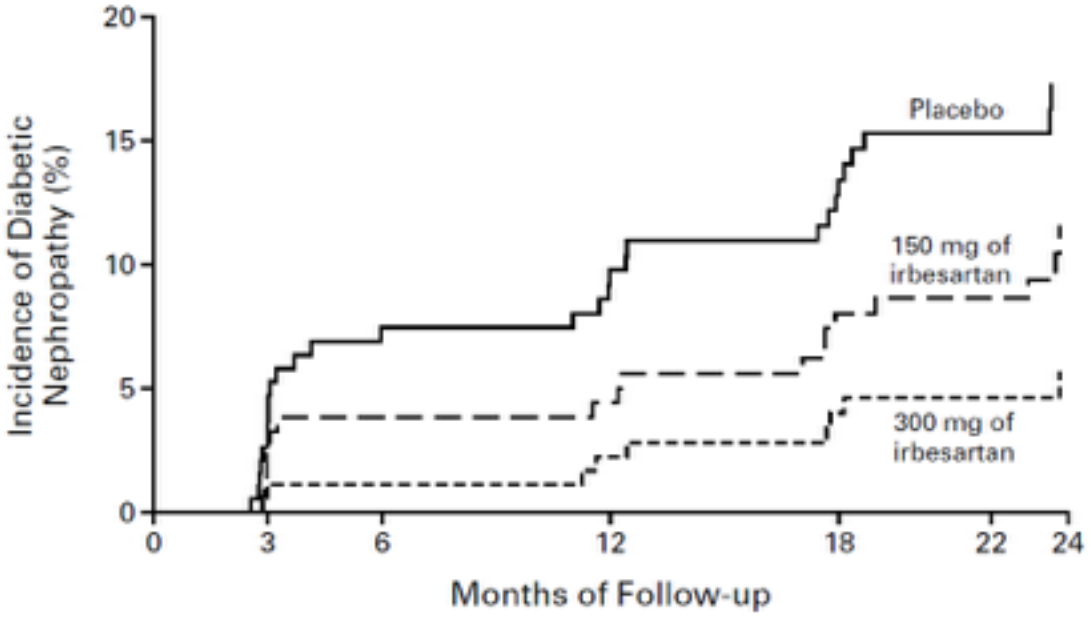
*Multivariate models included: age, sex, NHW ethnicity, site, HbA1c, SBP, baseline eGFR and UACR, ACEI/ARB use. Models for creatinine doubling and ESRD also included time-varying incident macroalbuminuria as covariate.



Mottl et al, unpublished.

ACEI/ARB Therapies

Reduction in Proteinuria



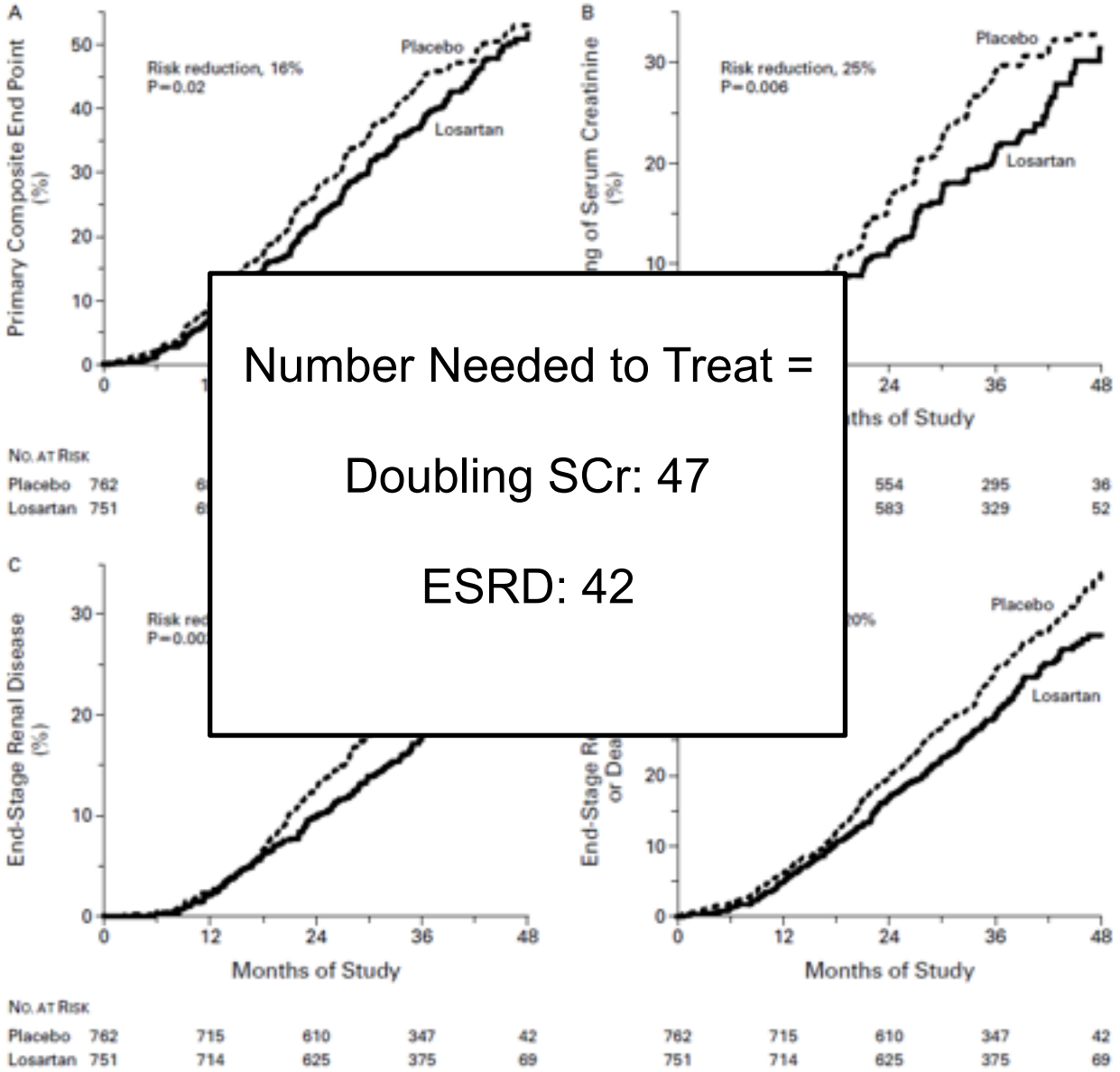
No. at Risk							
Placebo	201	201	164	154	139	129	36
150 mg of irbesartan	195	195	167	161	148	142	45
300 mg of irbesartan	194	194	180	172	159	150	49

Figure 2. Incidence of Progression to Diabetic Nephropathy during Treatment with 150 mg of Irbesartan Daily, 300 mg of Irbesartan Daily, or Placebo in Hypertensive Patients with Type 2 Diabetes and Persistent Microalbuminuria.

The difference between the placebo group and the 150-mg group was not significant ($P=0.08$ by the log-rank test), but the difference between the placebo group and the 300-mg group was significant ($P<0.001$ by the log-rank test).

Parving et al. NEJM 2001; 345 (12): 870-878.

ARBs for Overt Nephropathy: RENAAL



Number Needed to Treat =

Doubling SCr: 47

ESRD: 42

Brenner et al. NEJM 2001; 345(12): 861-69

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Relative benefit from ARB Therapy
ROADMAP versus RENAAL

Characteristic	Olmesartan Mean (SD) N=2232	Placebo Mean (SD) N=2215	Losartan Group Mean (SD) N=751	Placebo Group Mean (SD) N=762
Age, yr	58 (9)	58 (9)	60 (7)	60 (7)
Male Gender	47%	47%	62%	65%
BMI	31 (5)	31(5)	30 (6)	29 (6)
SBP, mmHg	137 (16)	136 (15)	152 (19)	153 (20)
DBP, mmHg	81 (10)	80 (9)	82 (10)	82 (11)
HbA1c, %	7.7 (1.6)	7.7 (1.6)	8.5 (1.7)	8.4 (1.6)
Creatinine, mg/dl	0.9 (0.2)	0.9 (0.2)	1.9 (0.5)	1.9 (0.5)
Median UACR, ug/mg	4	4	1237	1261

Haller et al. NEJM 2011; 364: 907-17

Brenner et al. NEJM 2001; 345(12): 861-69

Primary Prevention of microalbuminuria: ROADMAP

5-fold higher risk of cardiovascular death

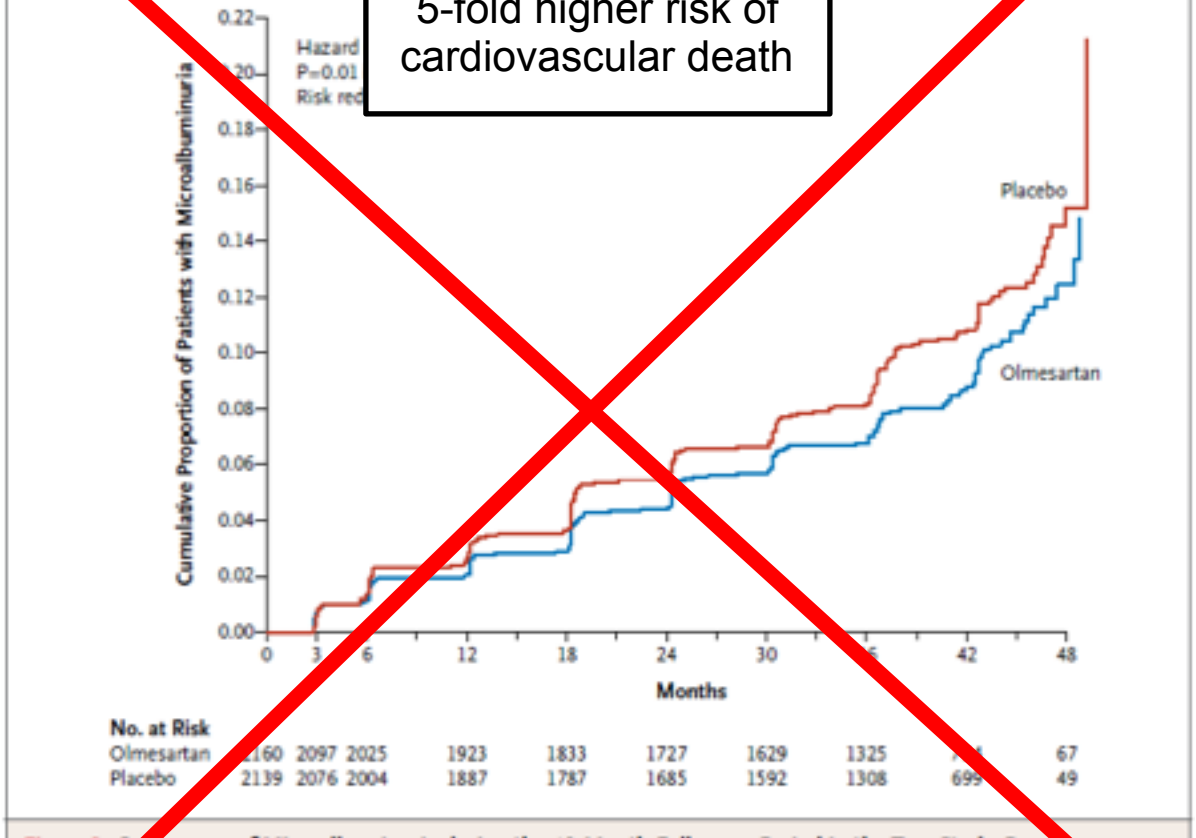

Figure 1. Occurrence of Microalbuminuria during the 48-Month Follow-up Period in the Two Study Groups.
The restricted full analysis set was used for this analysis. This set comprises all patients from the full analysis set (i.e. patients in the intention-to-treat population) with the exception of patients who had confirmed microalbuminuria at baseline (visit 1) and patients without any follow-up measurements of microalbuminuria that could be evaluated.

Haller et al. NEJM 2011; 364: 907-17

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Dual ACEI/ARB Therapy

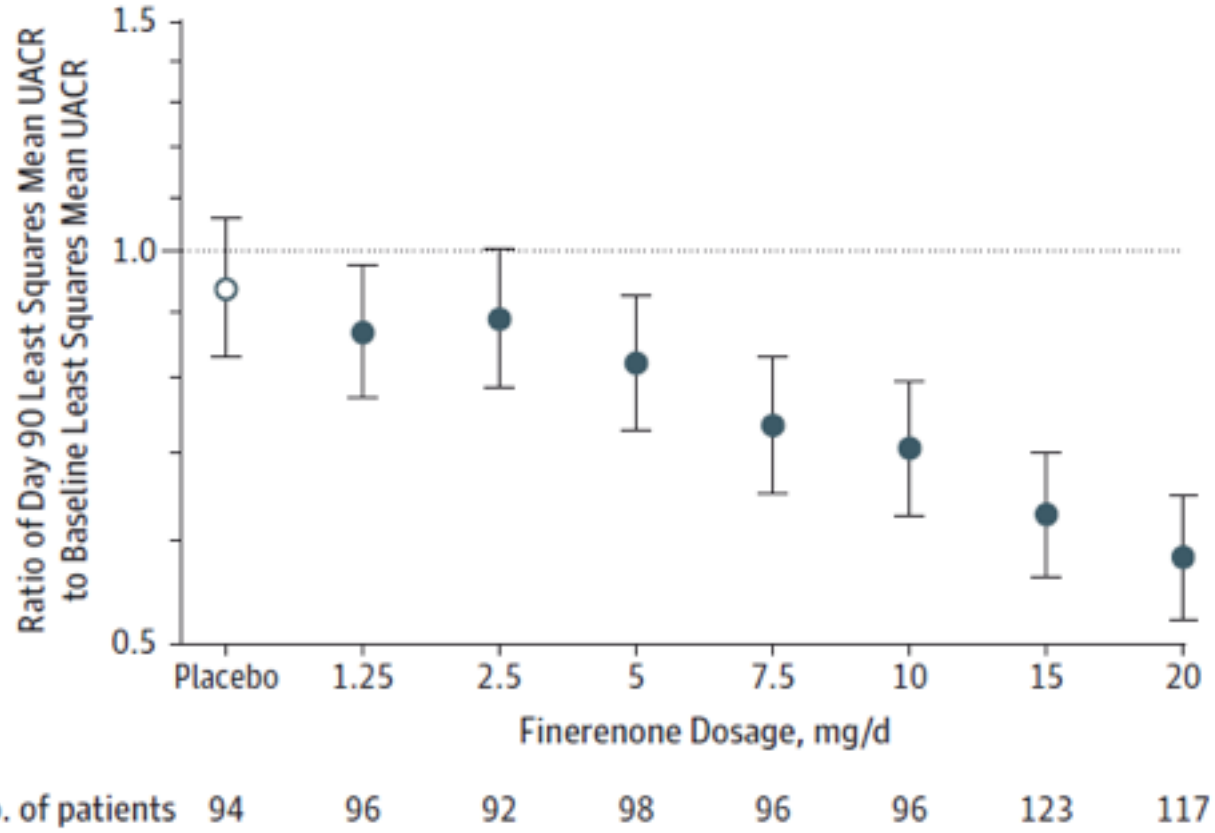
- Studies demonstrating benefit:
  - small size, short duration, soft endpoints
- ONTARGET (1/3 with diabetes) subanalysis by renal risk
  - No renal or CVD event benefit
  - Mortality dependent on albuminuria status
    - Normal UACR: possible harm – HR 1.13 (1.02, 1.24)
    - UACR > 300: possible benefit - HR 0.8 (0.64, 1.01)
  - Adverse Events in dual therapy: AKI, hyperkalemia
- VA NEPHRON-D stage 2/3 CKD and macroalbuminuria
  - Stopped early due to safety concerns – Hyperkalemia, AKI
  - Possible benefit for ESRD/GFR decline; No benefit CVD/Death outcomes

Tobe et al. Circulation 2011; 123: 1098-1107
Fried et al. NEJM 2013; 369(20): 1892-1903

Mineralocorticoid Receptor Blockers

Bakris et al. JAMA 2015; 312(9): 884-894

Figure 2. Change in Least Squares Mean UACR at Day 90 Relative to Baseline in Patients Treated With Finerenone, 1.25-20 mg/d, or Placebo



Error bars indicate 90% confidence intervals. UACR indicates urinary albumin-creatinine ratio. Data are from the full analysis set (n=812).

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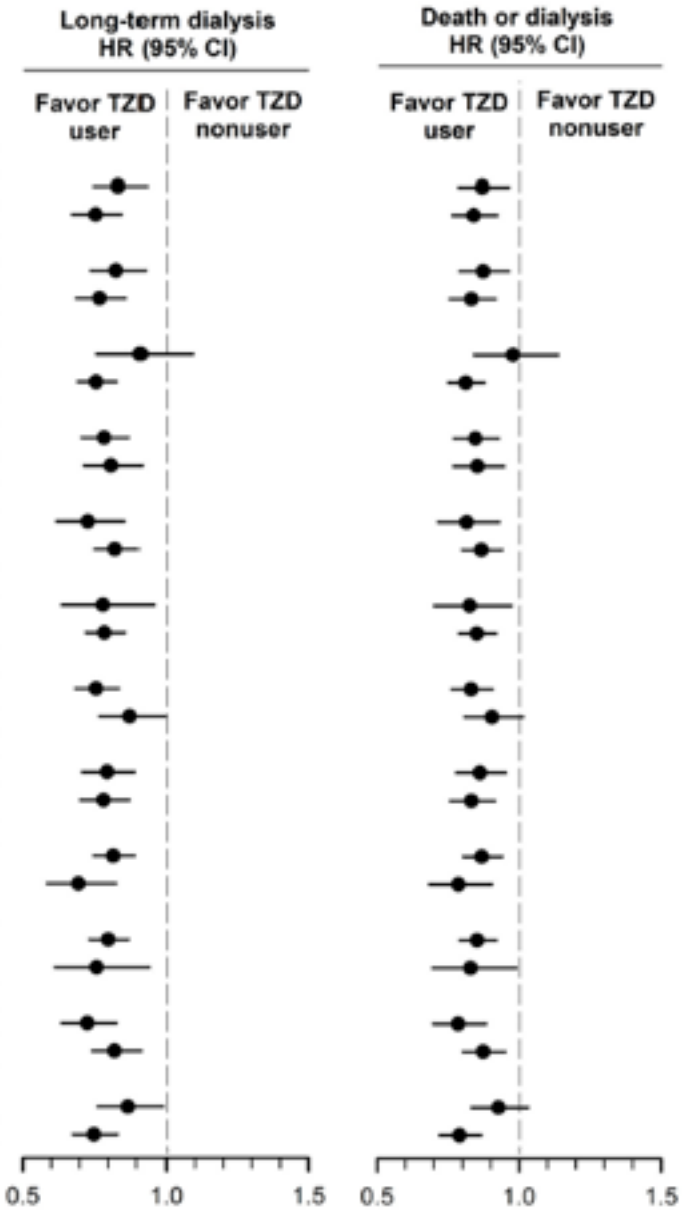
Thiazolidinediones

Characteristic	No. of Patients
Age, y	
< 65	2181
≥ 65	2623
Sex	
Male	2349
Female	2455
Heart failure	
Yes	1060
No	3744
Dyslipidemia	
Yes	2672
No	2132
CAD	
Yes	1338
No	3466
Nephrologist visit	
0	923
> 1	3881
ACEIs/ARBs	
User	3028
Nonuser	1776
Beta-blockers	
User	2301
Nonuser	2503
CCBs	
User	3592
Nonuser	1212
Diuretics	
User	4022
Nonuser	782
Statin	
User	1742
Nonuser	3062
Insulin	
User	2048
Nonuser	2756

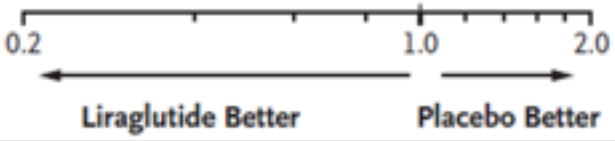


Chen et al. PLOS One 2015; Jun 17; 10 (6): e0129922

UNC KIDNEY CENTER

CV outcomes in GLP-1 agonists
Obese and CKD strata

Subgroup	No. of Patients	Liraglutide	Placebo	Hazard Ratio (95% CI)
		no. of events/no. of patients (%)		
Primary analysis	9340	608/4668 (13.0)	694/4672 (14.9)	0.87 (0.78–0.97)
Body-mass index				
≤30	3574	241/1743 (13.8)	261/1831 (14.3)	0.96 (0.81–1.15)
>30	5757	367/2920 (12.6)	431/2837 (15.2)	0.82 (0.71–0.94)
Renal function				
Severe or moderate disease				
<60 ml/min/1.73 m^2	2158	172/1116 (15.4)	223/1042 (21.4)	0.69 (0.57–0.85)
≥60 ml/min/1.73 m^2	7182	436/3552 (12.3)	471/3630 (13.0)	0.94 (0.83–1.07)
Severe disease				
<30 ml/min/1.73 m^2	224	25/117 (21.4)	26/107 (24.3)	0.89 (0.51–1.54)
≥30 ml/min/1.73 m^2	9116	583/4551 (12.8)	668/4565 (14.6)	0.87 (0.77–0.97)



Marso… Buse. NEJM July 2016; 375(4): 311-323.

Table 3. Incidence, Incidence Rates, and Time at Risk of Primary and Secondary Outcomes

	Linagliptin (n = 3,505)			Placebo (n = 1,961)		
	Incidence	IR	Time at Risk	Incidence	IR	Time at Risk
Primary Composite Outcome[a]						
Overall	448 (12.8)	268.4	1,669.4	306 (15.6)	311.7	981.6
Age						
<65 y	297 (12.2)	259.4	1,145.0	213 (16.1)	331.0	643.5
≥65 y	151 (14.0)	287.9	524.4	93 (14.5)	275.1	338.1
Race						
White	280 (12.4)	247.1	1,133.0	207 (15.6)	296.4	698.3
Asian	161 (13.7)	323.6	497.6	90 (16.0)	359.7	250.2
Black	7 (9.2)	180.3	38.8	9 (13.4)	272.2	33.1
Antihypertensive treatment						
Without ACEi/ARB	224 (11.3)	247.5	904.9	149 (13.9)	289.4	514.8
With ACEi/ARB	224 (14.7)	293.0	764.4	157 (17.7)	336.3	466.8
Secondary Outcomes						
Albuminuria						
Moderate elevation	326 (9.3)	191.1	1,705.7	213 (10.9)	210.9	1,009.8
Severe elevation	84 (2.4)	48.0	1,751.4	62 (3.2)	59.0	1,051.7
Reduction in kidney function	4 (0.1)	2.3	1,774.6	11 (0.6)	10.3	1,065.1
Halving of eGFR	2 (0.1)	1.1	1,776.7	2 (0.1)	1.9	1,069.3
Acute renal failure	52 (1.5)	29.5	1,764.9	37 (1.9)	34.9	1,060.5
Death	5 (0.1)	2.8	1,777.3	4 (0.2)	3.7	1,069.9

Note: Incidence values are given as number (percentage). IRs expressed per 1,000 person-years; time at risk, in person-years.

Abbreviations: ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; eGFR, estimated glomerular filtration rate; IR, incidence rate.

[a]The primary outcome is a composite of 6 kidney disease end points, listed under the secondary outcomes.

GLP1 agonists and kidney outcomes in patients with diabetes

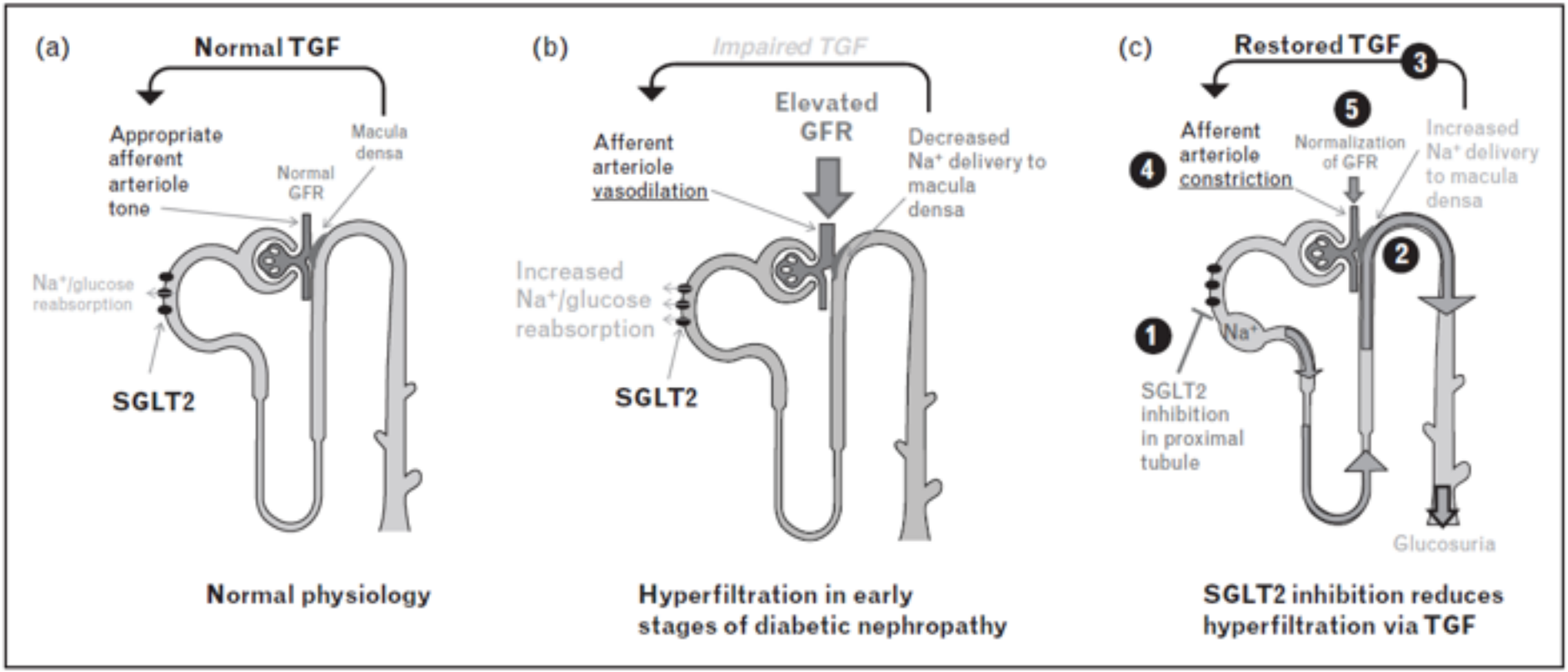
	GLP-1 patients (%)	GLP-1 incidence rate (events/100pt-yr)	Placebo Patients (%)	Placebo incidence rate (events/100pt-yr)	Hazard Ratio (95% CI)
Liraglutide* N=9,340	268 (5.7)	1.5	337 (7.2)	1.9	0.78 (0.67-0.92)
Semaglutide* N=3,297	62 (3.8)	1.86	100 (6.1)	3.06	0.64 (0.46-0.88)

*Persistent macroalbuminuria, doubling serum creatinine (and CrCl<45ml/min/1.73m^2) or need for RRT.

Marso et al. NEJM July 2016; 375(4): 311-323.

Marso et al. NEJM Nov 2016; 375(19): 1834-1844.

SGLT2 inhibition and tubuloglomerular feedback



Skrtic and Cherney; Curr Opin Nephrol Hypertens 2015; 24 (1): 96-103

SGLT2 inhibitors in CKD 3

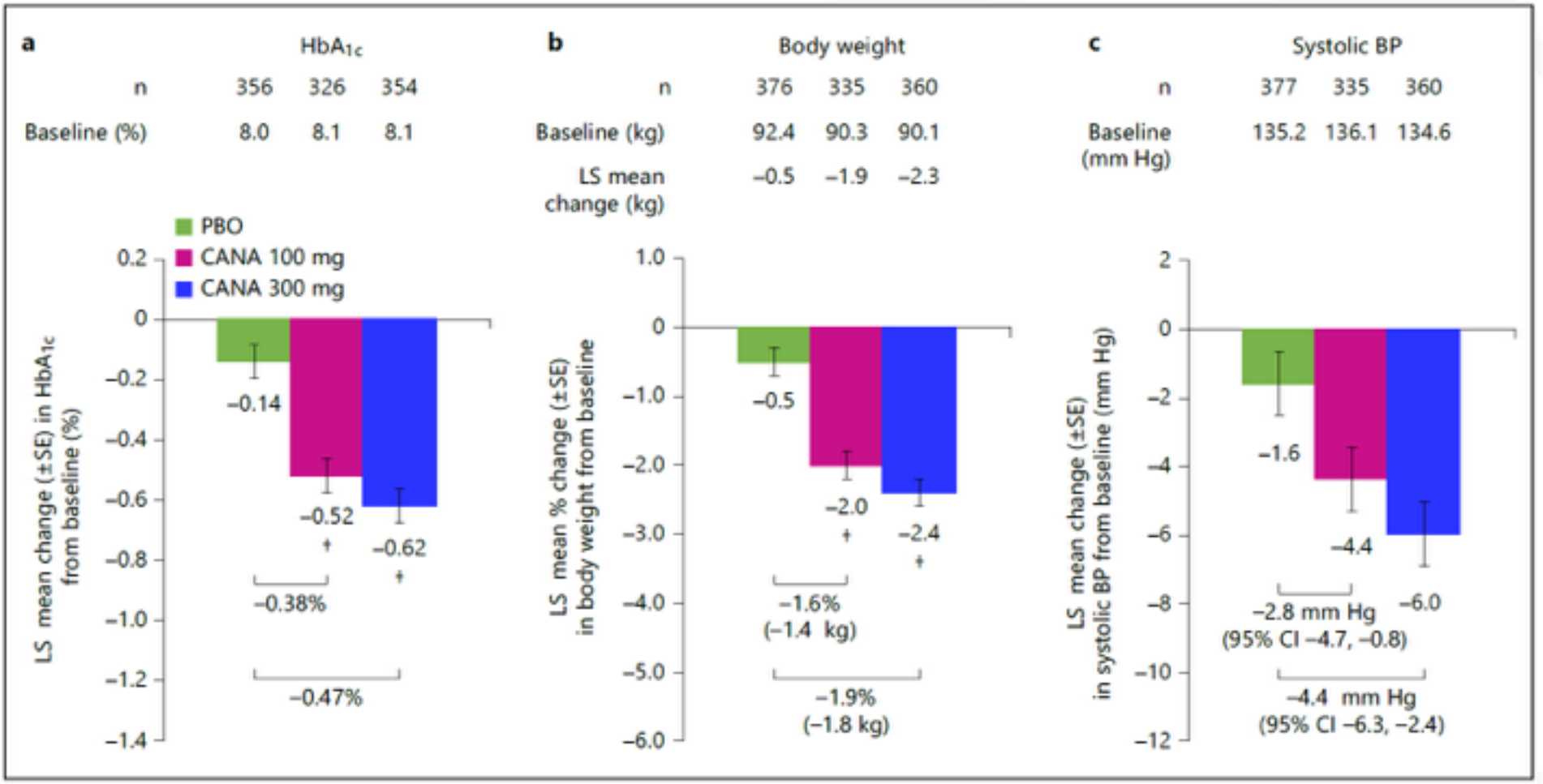
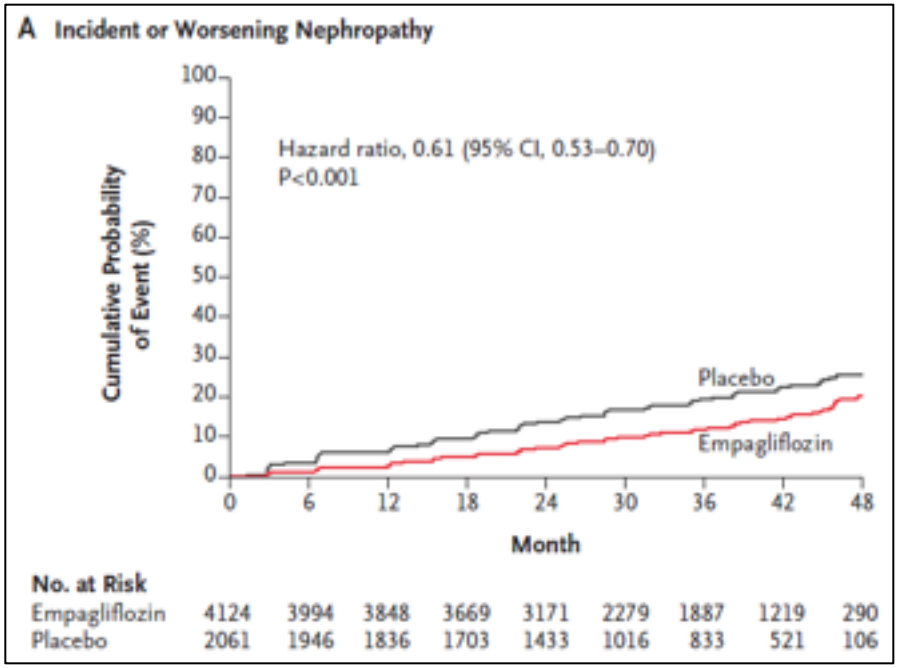
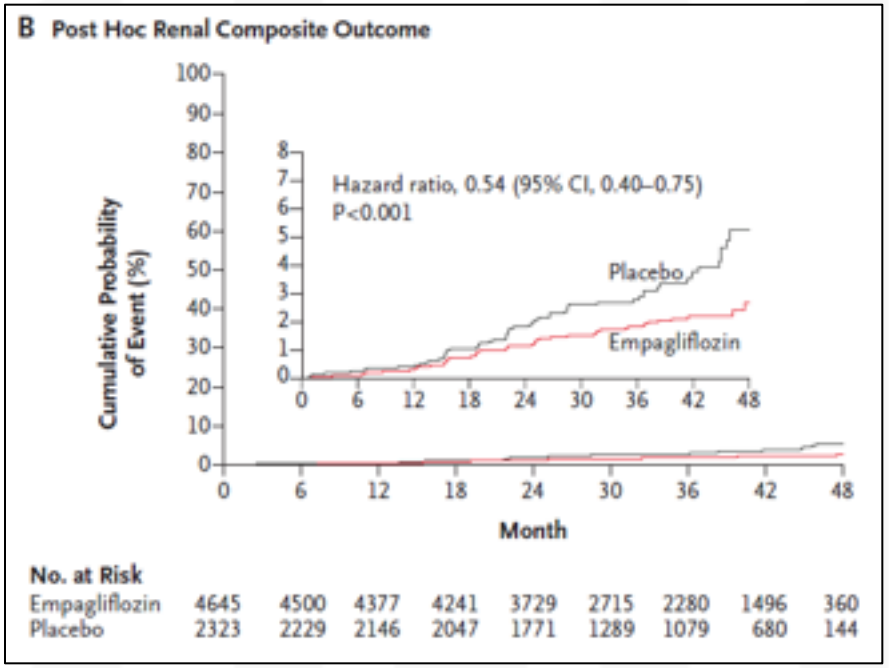


Fig. 1. Changes in (**a**) HbA_{1c}, (**b**) body weight, and (**c**) systolic BP for the overall stage 3 CKD population. SE = Standard error; PBO = placebo; CANA = canagliflozin. Note: Statistical comparison for changes in systolic BP with CANA 100 and 300 mg vs. PBO not performed (not pre-specified). † $p < 0.001$ vs. PBO.

Yamout et al; Am Jnl Nephrol 2014; 40: 64-74

SGLT2-inhibitors in diabetic kidney disease





EMPA-REG Investigators. NEJM 2016; 375: 323-334.

Diabetes and the Kidney

- Pathogenetic Heterogeneity
- ESRD vs CVD death risk evolves over life course
- Individually tailor therapy
  - Personalization of glycemic and BP targets
  - ACEI/ARB therapy for HTN and/or albuminuria
  - MRB with severe proteinuria/HTN
  - SGLT2 inhibitors and incretins especially in the obese patient or with uncontrolled diabetes
- Pathology-based translational studies lend hope for the future… stay tuned.