Retarding progression of Diabetic Kidney Disease

MEDICINE REVIEW COURSE 2015

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Learning objectives

- Diagnosis of DM nephropathy
- Screening for renal disease in patients with DM
- Managing DM nephropathy

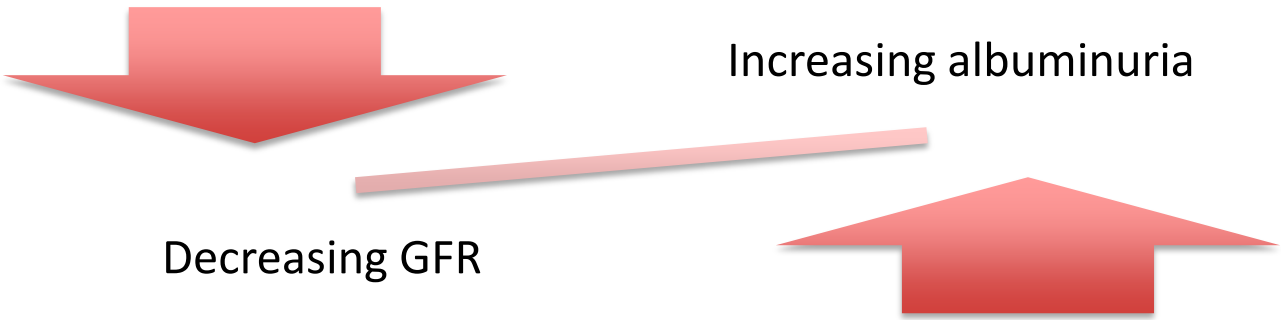
Firstly to diagnose DM Kidney Disease

CKD in Diabetes =

ACR ≥2.0 mg/mmol

and / or

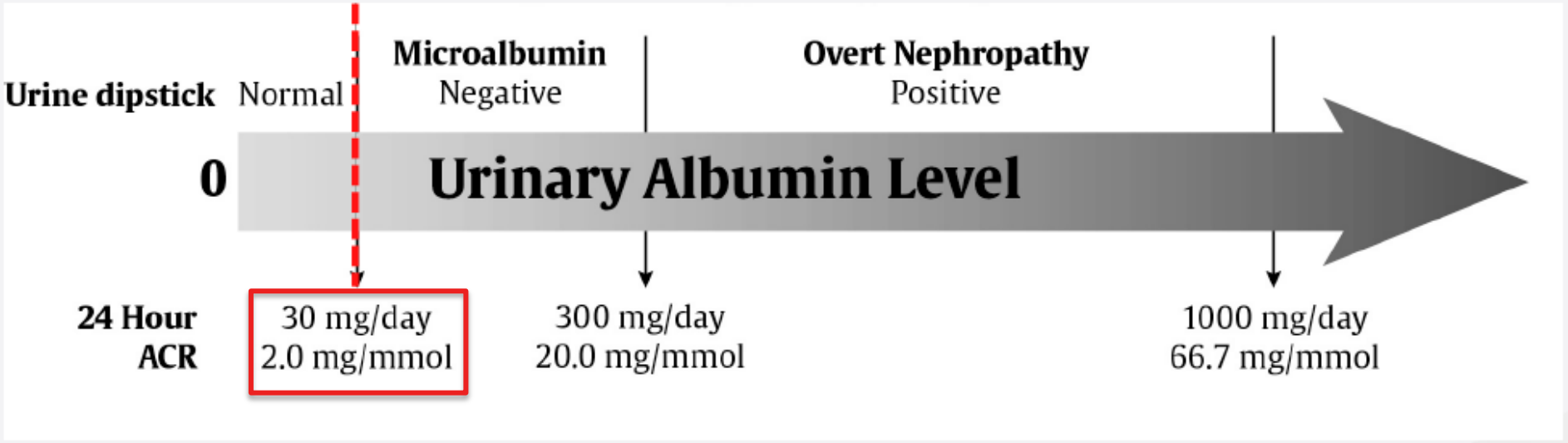
eGFR <60 mL/min



Either one of the above or both defines presence of DM nephropathy

*ACR = Albumin : Creatinine ratio

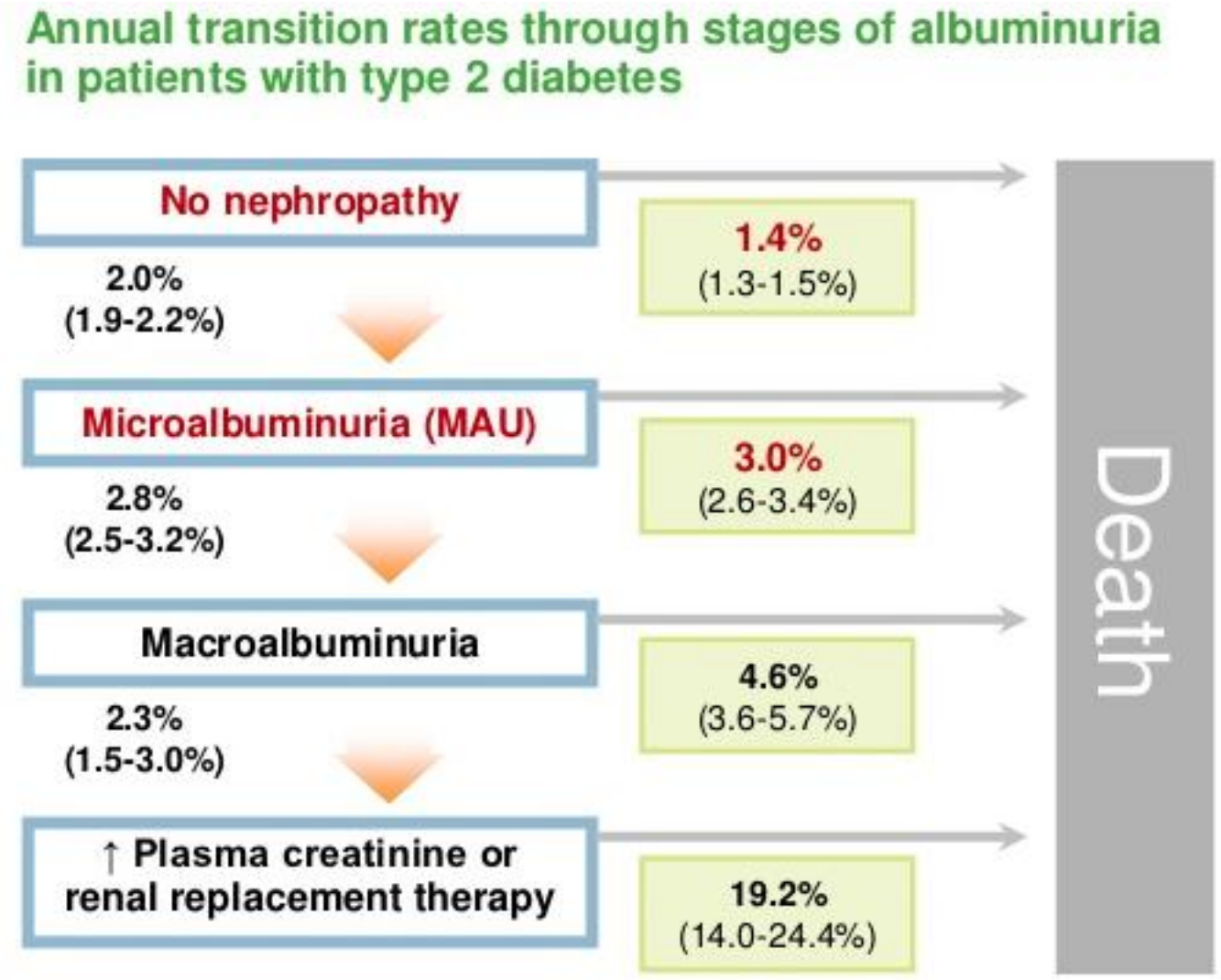
Stages of Diabetic Kidney Disease



Renal impairment

As albuminuria becomes heavier, the renal function will also be correspondingly lower

Remember that the progression of DM CKD is also accompanied by increasing risk of death



Best to do urine screening using UACR and not regular urine dipstick

Stages of Diabetic Nephropathy by Level of Urinary Albumin Level			
Stage of nephropathy	**Urine dipstick for protein**	**Urine ACR (mg/mmol)**	**24 hour urine collection for albumin**
Normal	Negative	<2	<30 mg/day
Microalbuminuria	Negative	2-20	30-300 mg/day
Overt nephropathy	Positive	>20 >67	>300 mg/day >1000 mg/day
Values are for urinary albumin, not total urinary protein, which will be higher than urinary albumin levels. ACR results may be elevated with conditions other than diabetic nephropathy (see text and Table 4)			

Regular urine dipstick will only detect high level of albuminuria (overt proteinuria) and will miss lower level of albuminuria [= early DM nephropathy]

When and how to screen?

Screen annually when no transient causes of albuminuria or low eGFR are present, and when acute kidney injury or non-diabetic kidney disease is not suspected

Type 1 diabetes: Annually in postpubertal individuals with duration of diabetes ≥5 years
Type 2 diabetes: At diagnosis and annually thereafter

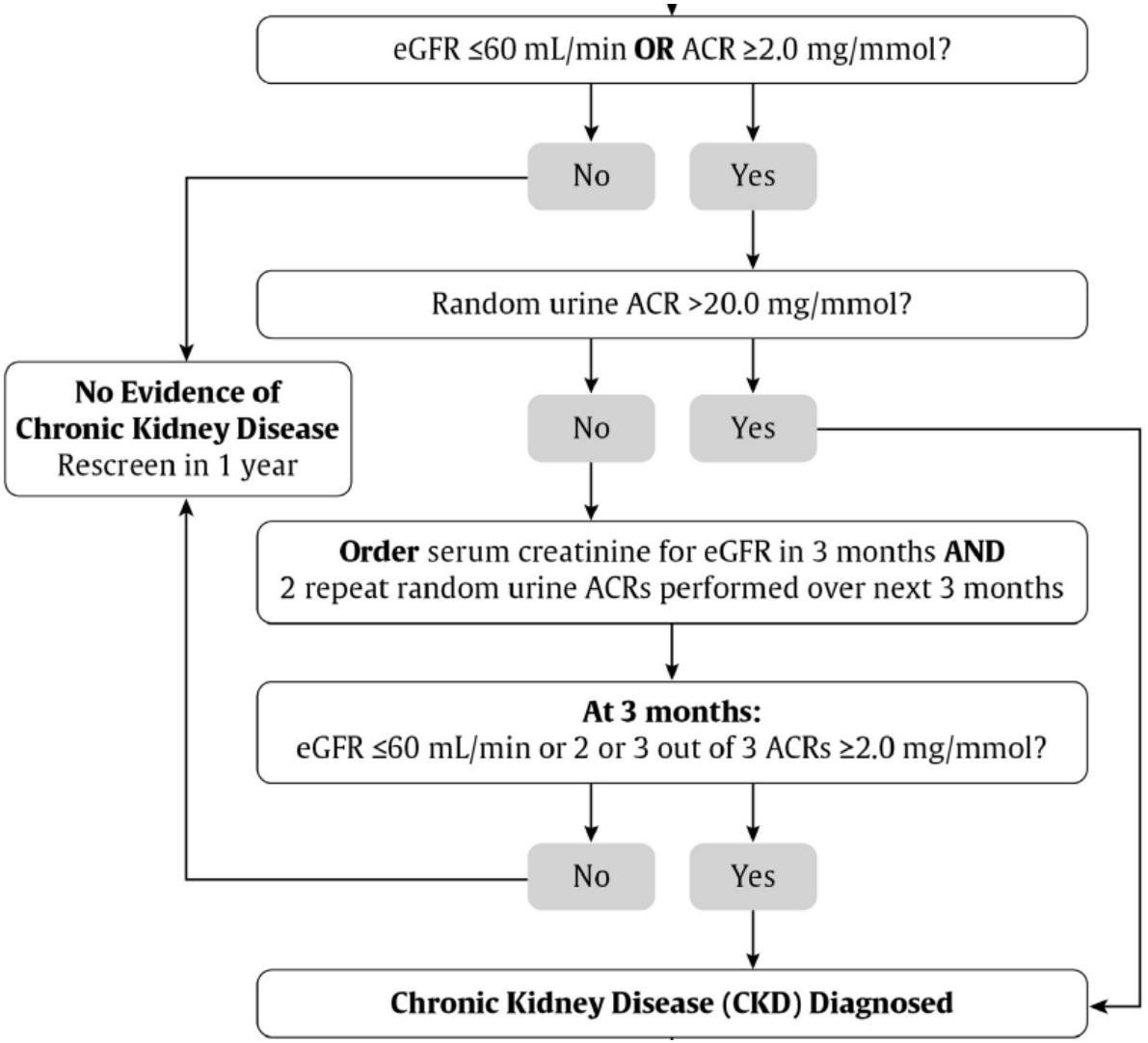
↓

Order random urine ACR and serum creatinine for eGFR

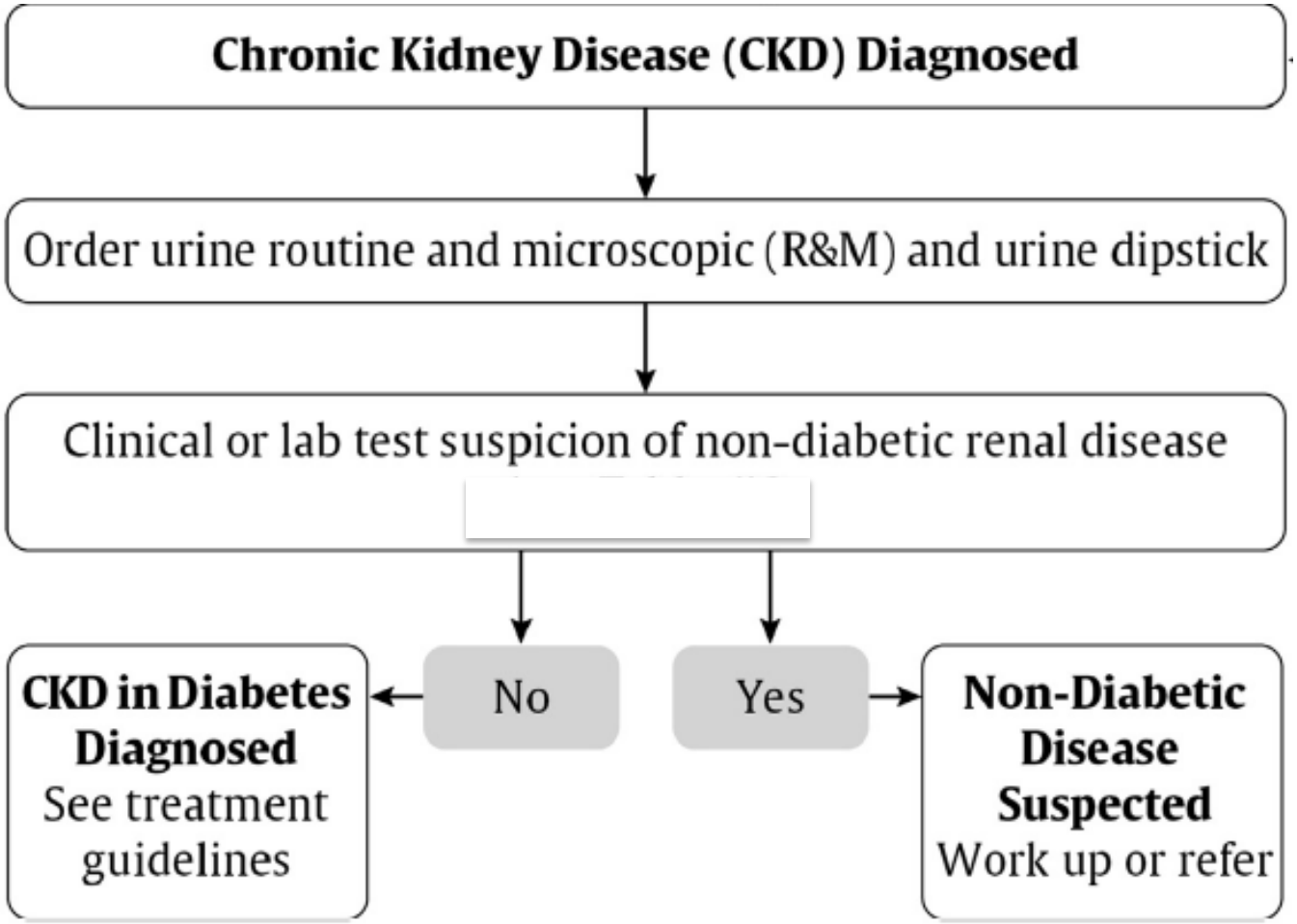
Beware of transient albuminuria from various other causes

Potential Causes for Transient Albuminuria
Recent major exercise
Urinary tract infection
Febrile illness
Decompensated congestive heart failure
Menstruation
Acute severe elevation in blood glucose
Acute severe elevation in blood pressure

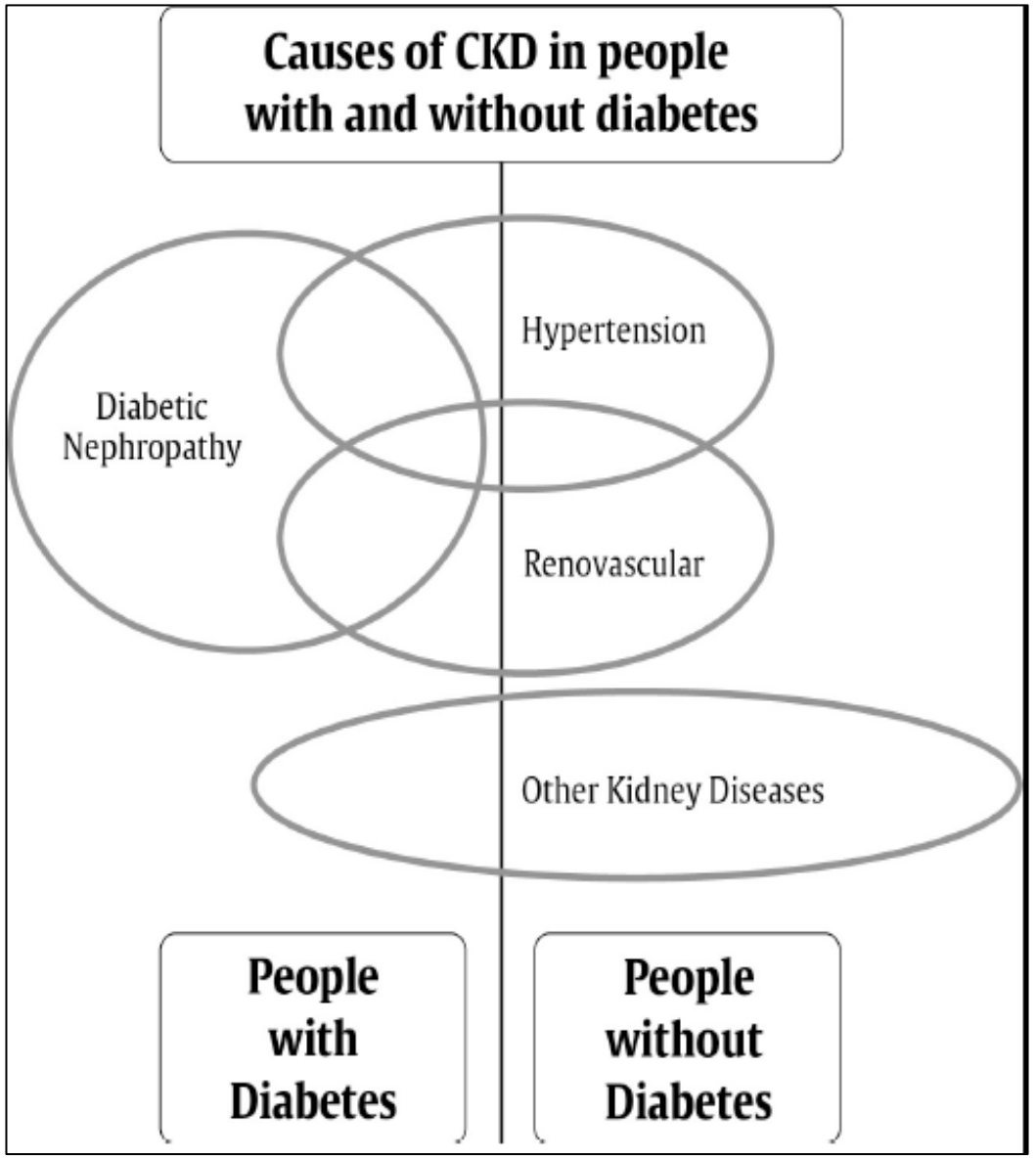
Screening algorithm



Clinical diagnosis of DM nephropathy is a diagnosis of exclusion



CKD in someone with DM is **not always** DM nephropathy



When to consider other causes of CKD in diabetic patients?

Factors Favouring Classical Diabetic Nephropathy vs. Alternate Diagnoses (17-20)	
Favours Diabetic Nephropathy	**Favours Alternate Renal Diagnosis**
Persistent albuminuria	Extreme proteinuria (>6 g/d)
Bland urine sediment	Persistent hematuria (micro- or macroscopic) or active urinary sediment
Slow progression of disease	Rapidly falling eGFR
Low eGFR associated with overt proteinuria	Low eGFR with little or no proteinuria
Other complications of diabetes present	Other complications of diabetes not present or relatively not as severe
Know duration of DM >5 years	Known duration of diabetes <5 years
	Family history or nondiabetic renal disease (e.g. polycystic kidney disease)
	Signs or symptoms of systemic disease

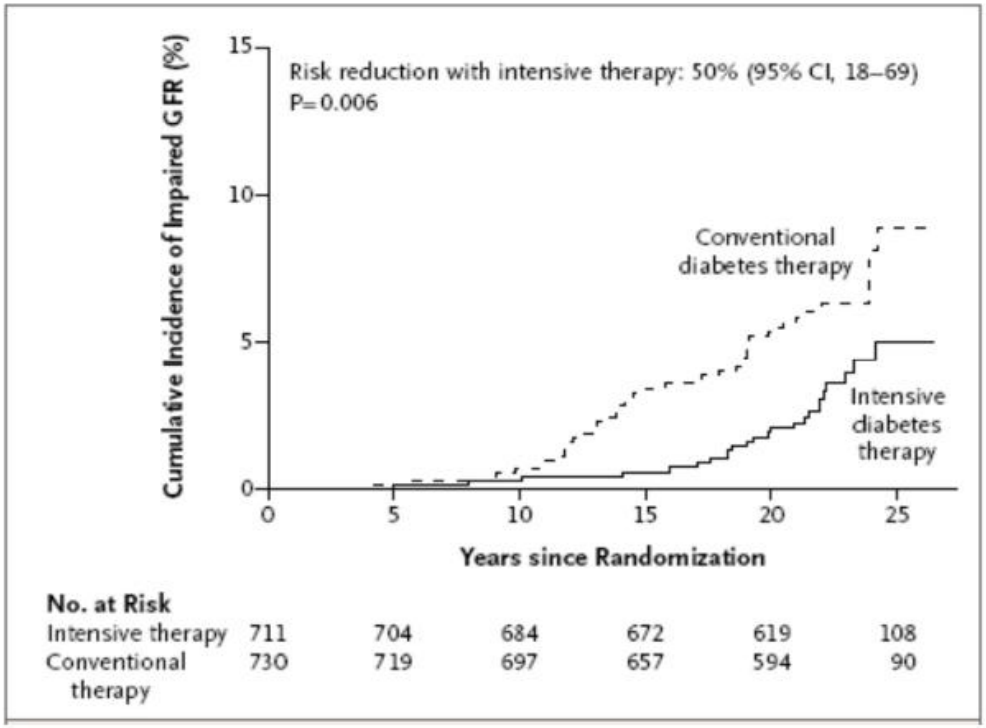
When to refer to renal specialist clinic?

- Chronic, progressive loss of kidney function
- ACR persistently very high (>60 mg/mmol)
- eGFR <30 mL/min (stage 4 CKD or worse)
- Unable to remain on renal-protective therapies due to adverse effects such as hyperkalemia or a >30% increase in serum Cr within 3 months of starting ACEi or ARB
- Unable to achieve target BP (could be referred to any specialist in hypertension)
- Reasons to suspect the CKD is not DM nephropathy

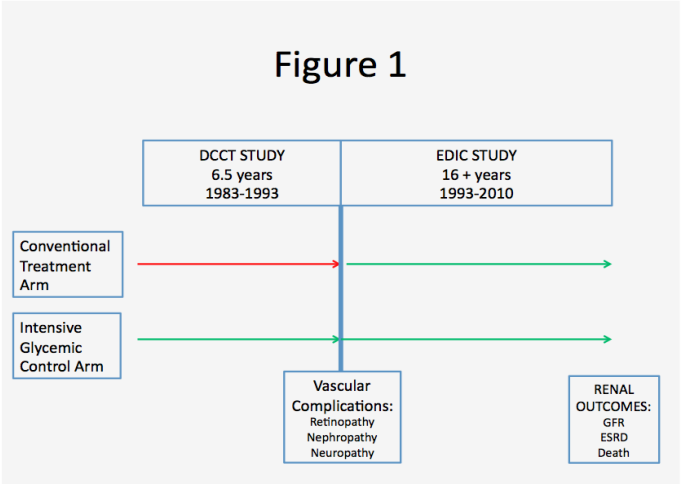
Retarding progression of DM nephropathy

- Optimal glycemic control
- Optimal blood pressure control
- ACE-inhibitor (ACEi) or Angiotensin Receptor Blocker (ARB)
- Moderating dietary protein intake

Optimal glycemic control in type I DM



Impaired GFR was defined as GFR <60 ml/min/1.73m2

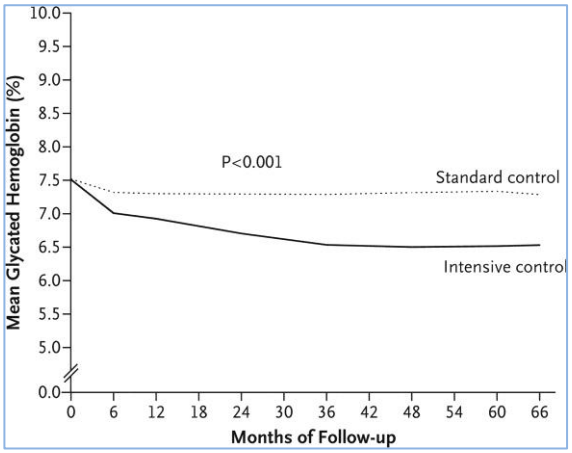


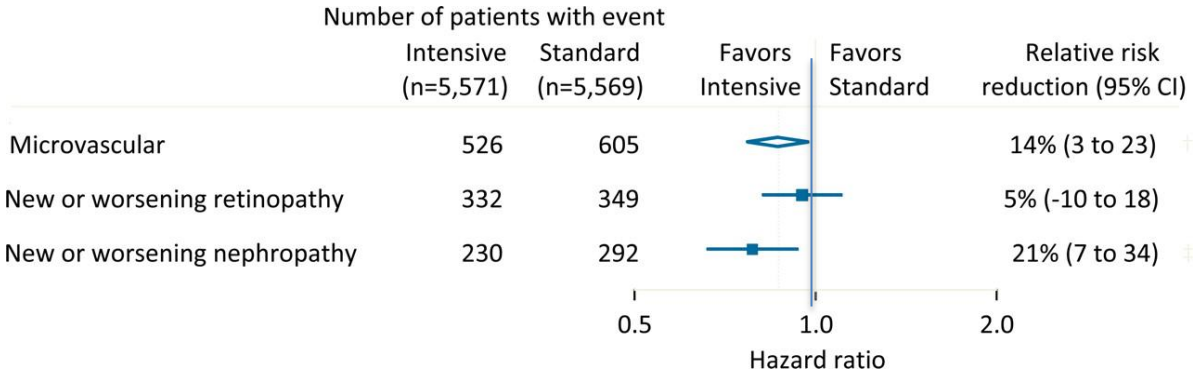
In the DCCT, the mean HbA1C achieved was 7.2 + 0.9% versus 9.1+1.3% in intensive arm and conventional arm respectively. Epidemiology of Diabetes Interventions and Complications (EDIC) study was the subsequent observational follow-up period of the DCCT cohort

DCCT/EDIC Research Group

N Engl J Med 2011; 365: 2366-76

Intensive glycemic control in type II DM and DM nephropathy (surrogate)



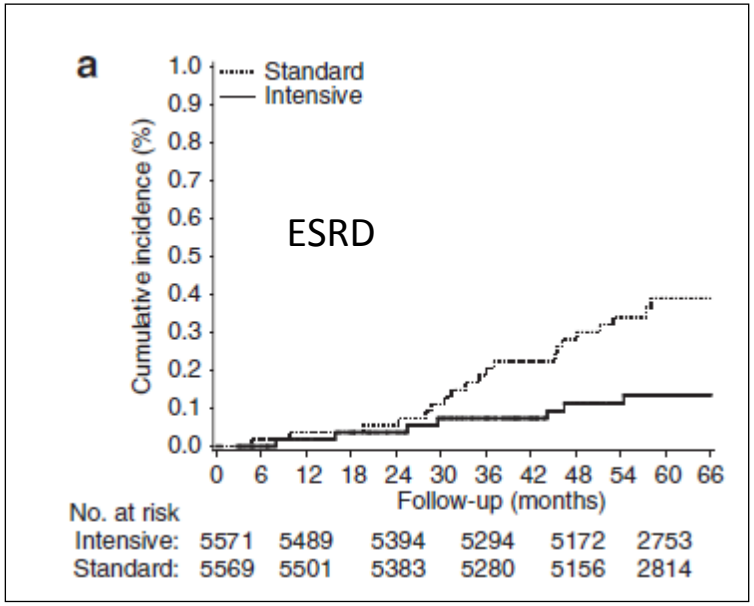


ADVANCE trial randomly assigned 11,140 DM type II participants to an intensive glucose-lowering strategy (hemoglobin A1c target 6.5% or less) or standard glucose control

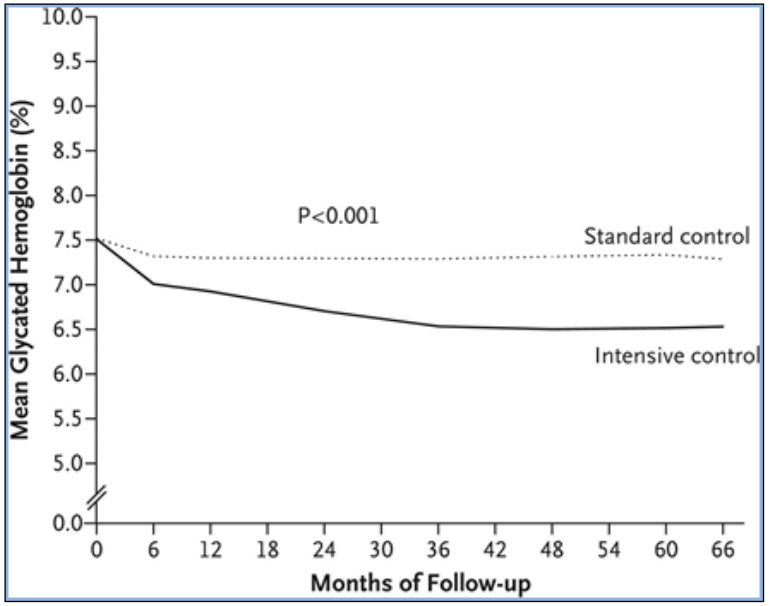
Relative effects of glucose-control strategy on microvascular disease

N Engl J Med 2008; 358:2560–2572

Intensive glycemic control and ESRD



Kaplan–Meier curves depicting the incidence of end-stage kidney disease (ESRD)



ADVANCE trial randomly assigned 11,140 DM type II participants to an intensive glucose-lowering strategy (hemoglobin A1c target 6.5% or less) or standard glucose control

Kidney International (2013) 83, 517–524

In a nutshell

Glycemic control is an important element of therapy that can reduce incidence of DM nephropathy and ESRD. This is best done early on in the disease and less beneficial later on.

About KDIGO

KDIGO Clinical Practice Guideline
for the Management of Blood Pressure in
Chronic Kidney Disease

KDIGO: BP TARGET FOR DM CKD

KDIGO: BP management in CKD (non dialysis) patients with DM

4.1: We recommend that adults with diabetes and CKD ND with urine albumin excretion *<30 mg per 24 hours* (or equivalent*) whose office BP is consistently >140 mm Hg systolic or >90 mm Hg diastolic be treated with BP lowering drugs to maintain a BP that is consistently ≤140 mm Hg systolic and ≤90 mm Hg diastolic. (1B)

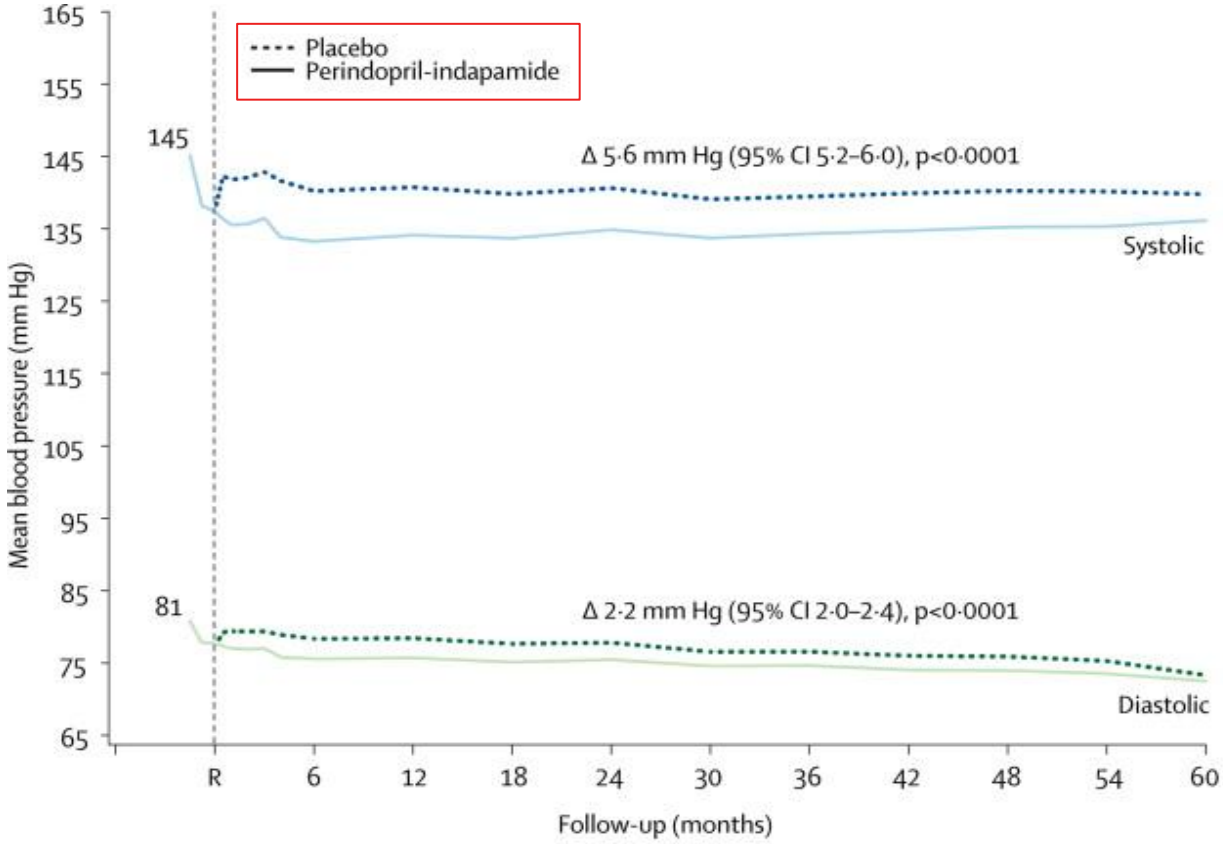
4.2: We suggest that adults with diabetes and CKD ND with urine albumin excretion >30 mg per 24 hours (or equivalent*) whose office BP is consistently >130 mm Hg systolic or >80 mm Hg diastolic be treated with BP lowering drugs to maintain a BP that is consistently ≤130 mm Hg systolic and ≤80 mm Hg diastolic (2D)

4.3: We suggest that an ARB or ACE-I be used in adults with diabetes and CKD ND with urine albumin excretion of 30 to 300 mg per 24 hours (or equivalent*). (2D)

4.4: We recommend that an ARB or ACE-I be used in adults with diabetes and CKD ND with urine albumin excretion >300 mg per 24 hours (or equivalent*). (1B)

Kidney International Supplements (2012) 2, 343–346

ADVANCE: Intensive BP lowering in DM type 2



Placebo	137/78	140/78	141/78	140/78	141/78	139/77	139/77	140/76	140/76	140/75	140/73
Per-ind	137/78	133/76	134/76	134/75	135/75	134/75	134/75	135/74	135/74	135/74	136/73

Lancet. 2007 Sep 8;370(9590):829-40

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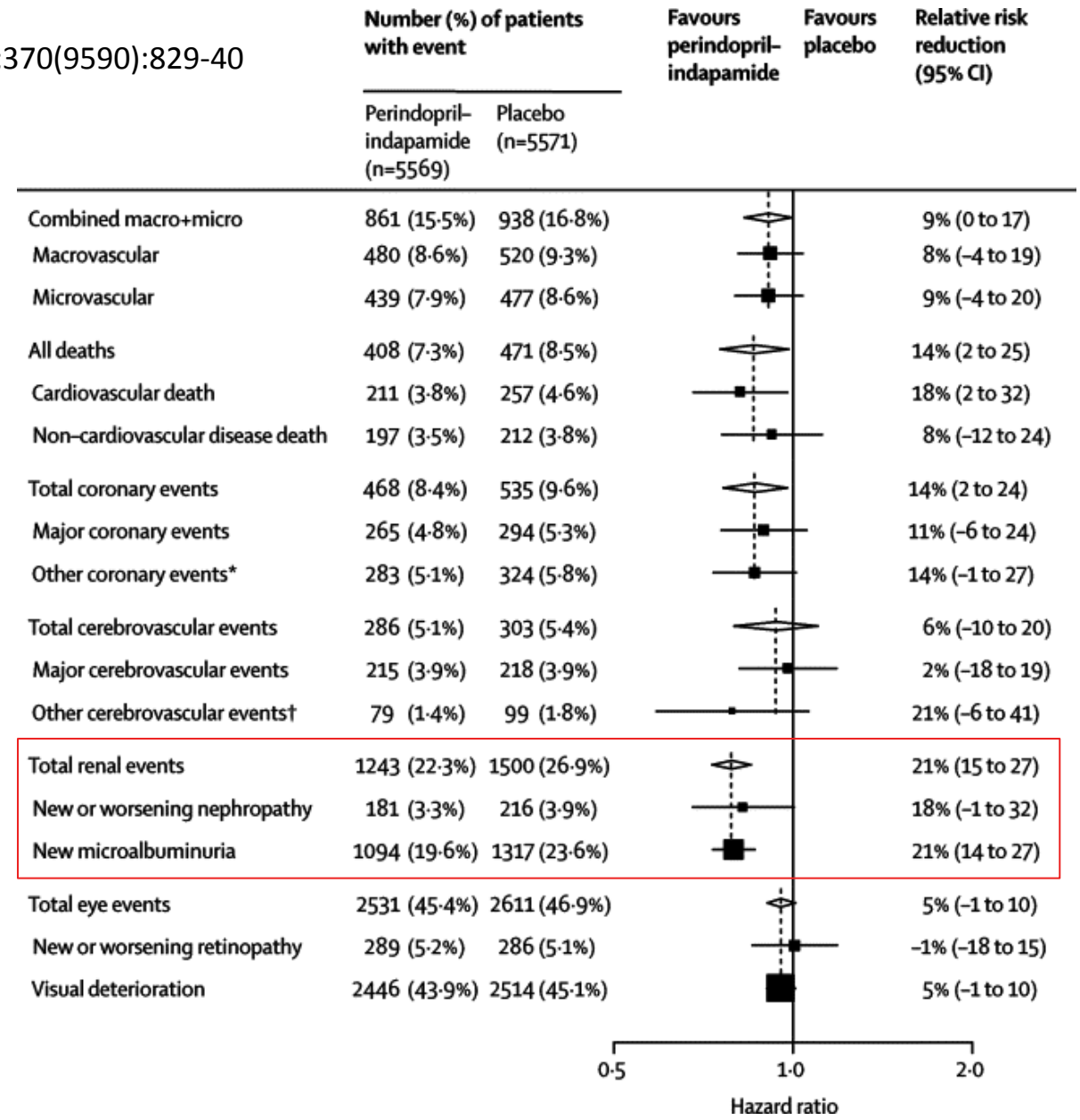
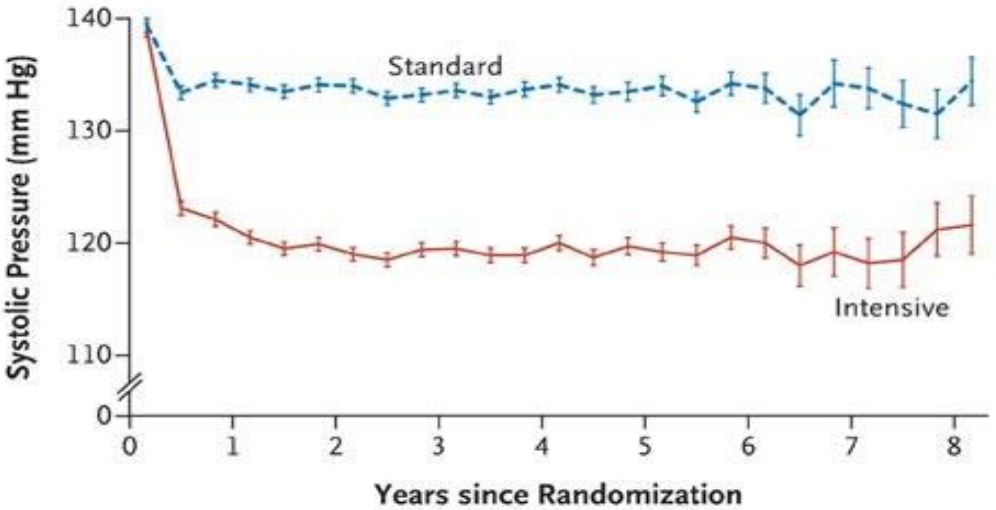


RENAL

The Action in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled Evaluation (ADVANCE) study

Effects of intensive BP in DM type 2: ACCORD

The Action to Control Cardiovascular Risk in Diabetes (ACCORD)



Mean No. of Medications Prescribed								
Intensive	3.2	3.4	3.4	3.5	3.5	3.5	3.4	3.4
Standard	1.9	2.1	2.1	2.2	2.2	2.3	2.3	2.3
No. of Patients								
Intensive	2174	2071	1973	1792	1150	445	156	156
Standard	2208	2136	2077	1860	1241	504	203	201

N Engl J Med 2010;362:1575-85

The Action to Control Cardiovascular Risk in Diabetes (ACCORD)

Table 3. Primary and Secondary Outcomes.

Outcome	Intensive Therapy (N=2363)		Standard Therapy (N=2371)		Hazard Ratio (95% CI)	P Value
	no. of events	*%/yr*	*no. of events*	*%/yr*		
Primary outcome*	208	1.87	237	2.09	0.88 (0.73–1.06)	0.20
Prespecified secondary outcomes						
Nonfatal myocardial infarction	126	1.13	146	1.28	0.87 (0.68–1.10)	0.25
Stroke						
Any	36	0.32	62	0.53	0.59 (0.39–0.89)	0.01
Nonfatal	34	0.30	55	0.47	0.63 (0.41–0.96)	0.03
Death						
From any cause	150	1.28	144	1.19	1.07 (0.85–1.35)	0.55
From cardiovascular cause	60	0.52	58	0.49	1.06 (0.74–1.52)	0.74

No benefit seen in the primary outcome measure (composite of nonfatal myocardial infarction, nonfatal stroke, or death from cardiovascular causes).

N Engl J Med 2010;362:1575-85

Table 2. Serious Adverse Events and Clinical Measures after Randomization.*

Variable	Intensive Therapy (N=2362)	Standard Therapy (N=2371)	P Value
Serious adverse events — no. (%)†			
Event attributed to blood-pressure medications	77 (3.3)	30 (1.27)	<0.001
Hypotension	17 (0.7)	1 (0.04)	<0.001
Syncope	12 (0.5)	5 (0.21)	0.10
Bradycardia or arrhythmia	12 (0.5)	3 (0.13)	0.02
Hyperkalemia	9 (0.4)	1 (0.04)	0.01
Angioedema	6 (0.3)	4 (0.17)	0.55
Renal failure	5 (0.2)	1 (0.04)	0.12
End-stage renal disease or need for dialysis	59 (2.5)	58 (2.4)	0.93
Adverse laboratory measures — no. (%)			
Potassium <3.2 mmol/liter	49 (2.1)	27 (1.1)	0.01
Potassium >5.9 mmol/liter	73 (3.1)	72 (3.0)	0.93
Elevation in serum creatinine			
>1.5 mg/dl in men	304 (12.9)	199 (8.4)	<0.001
>1.3 mg/dl in women	257 (10.9)	168 (7.1)	<0.001
Estimated GFR <30 ml/min/1.73 m^2	99 (4.2)	52 (2.2)	<0.001
Microalbuminuria — no./total no. (%)	656/2174 (30.2)	712/2205 (32.3)	0.13
Macroalbuminuria — no. /total no. (%)	143/2174 (6.6)	192/2205 (8.7)	0.009

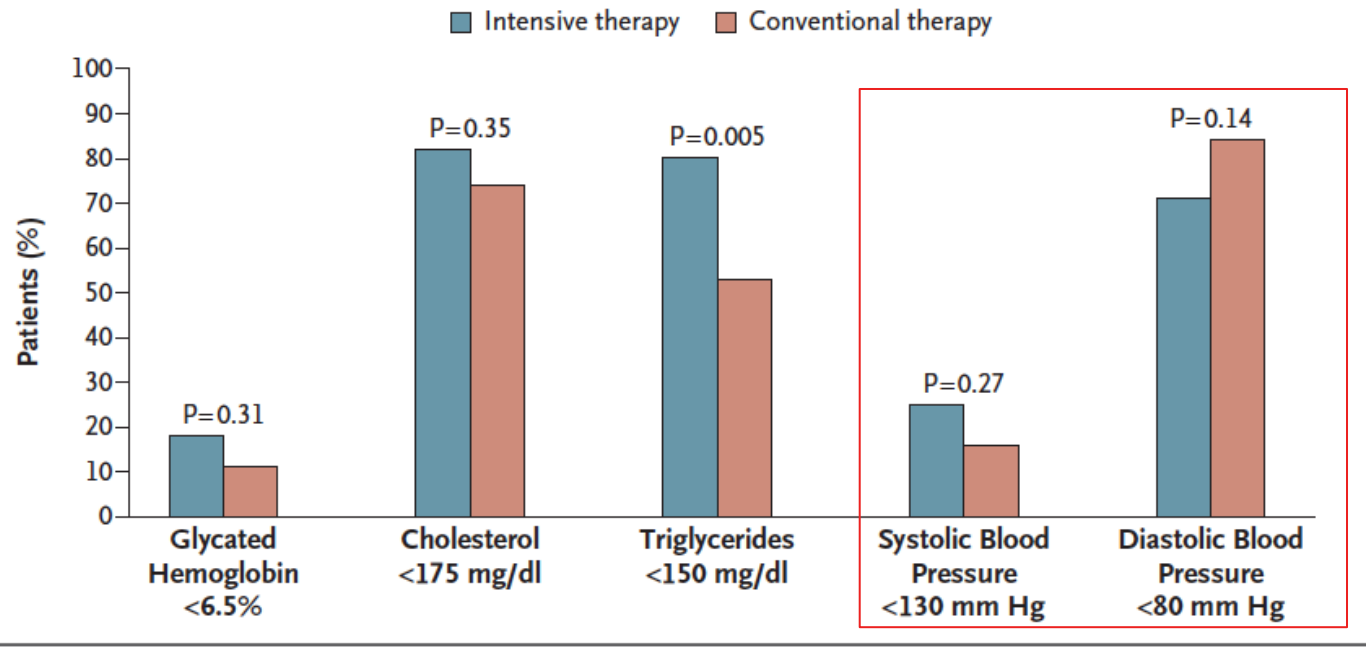
Note: At baseline, mean eGFR was normal with normal urine albumin excretion

Renal perspective of ACCORD study

N Engl J Med 2010;362:1575-85

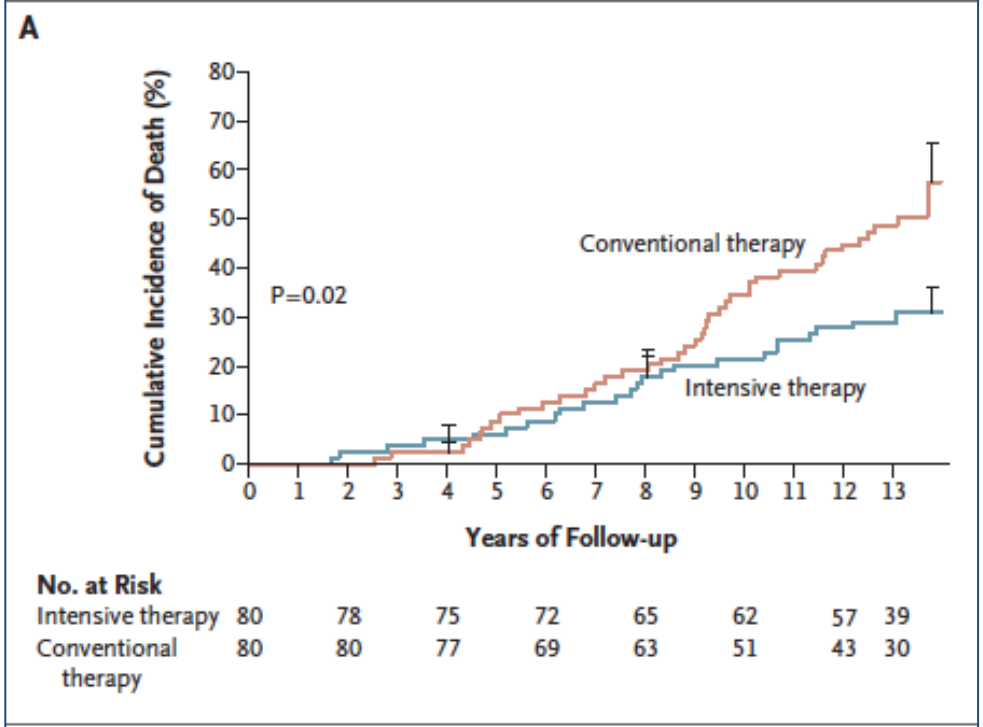
STENO-2 is multi intervention study

Target SBP of <130 mm Hg & a DBP <80 mm Hg



In the Steno-2 Study, they randomly assigned 160 patients with type 2 diabetes and persistent microalbuminuria to receive either intensive therapy or conventional therapy; the mean treatment period was 7.8 years. Patients were subsequently followed observationally for a mean of 5.5 years, until December 31, 2006

N Engl J Med 2008;358:580-91



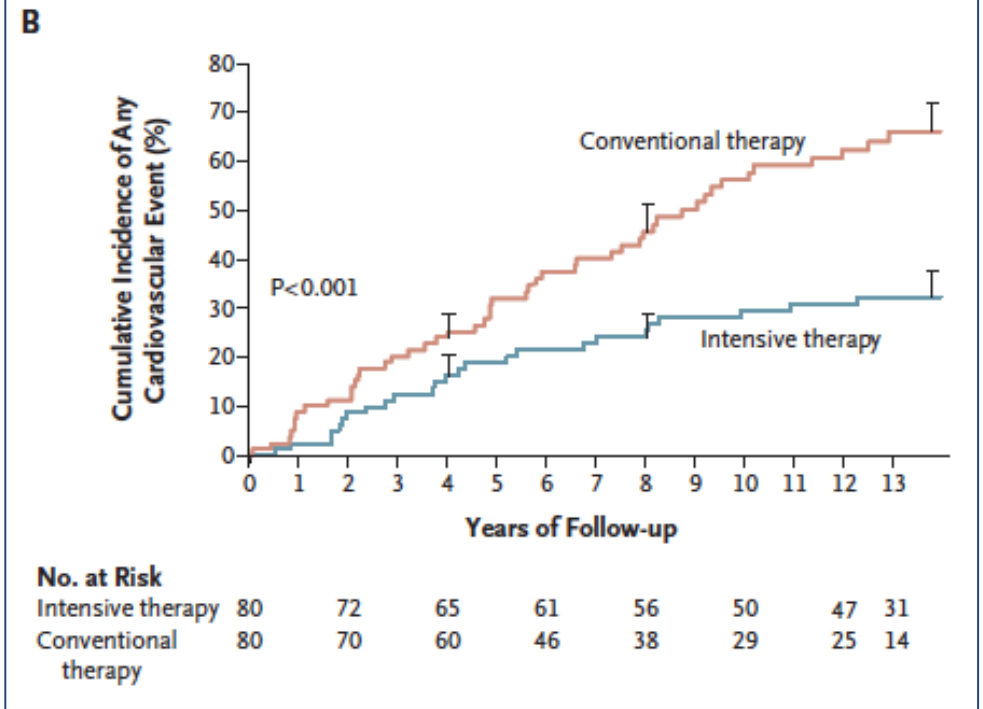
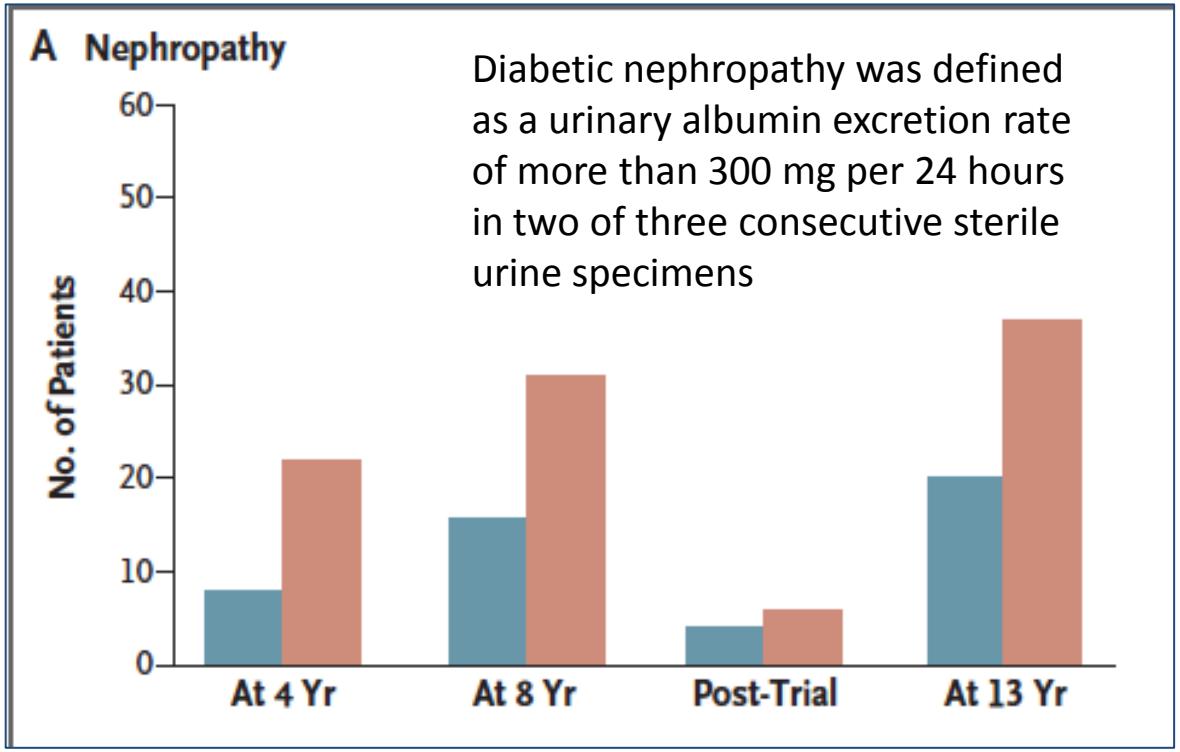


Figure 3. Kaplan–Meier Estimates of the Risk of Death from Any Cause and from Cardiovascular Causes and the Number of Cardiovascular Events, According to Treatment Group.

Panel A shows the cumulative incidence of the risk of death from any cause (the study's primary end point) during the 13.3-year study period. Panel B shows the cumulative incidence of a secondary composite end point of cardiovascular events, including death from cardiovascular causes, nonfatal stroke, nonfatal myocardial infarction, coronary-artery bypass grafting (CABG), percutaneous coronary intervention (PCI), revascularization for peripheral atherosclerotic artery disease, and amputation; Panel C shows the number of events for each component of the composite end point. In Panels A and B, the I bars represent standard errors.

N Engl J Med 2008;358:580-91

STENO-2 and renal outcome



During the entire observation period, diabetic nephropathy developed in 20 patients in the intensive-therapy group, as compared with 37 patients in the conventional-therapy group (relative risk, 0.44; 95% CI, 0.25 to 0.77; P = 0.004). One patient in the intensive-therapy group had progression to end-stage renal disease requiring dialysis, as compared with six patients in the conventional- therapy group (P = 0.04).

N Engl J Med 2008;358:580-91

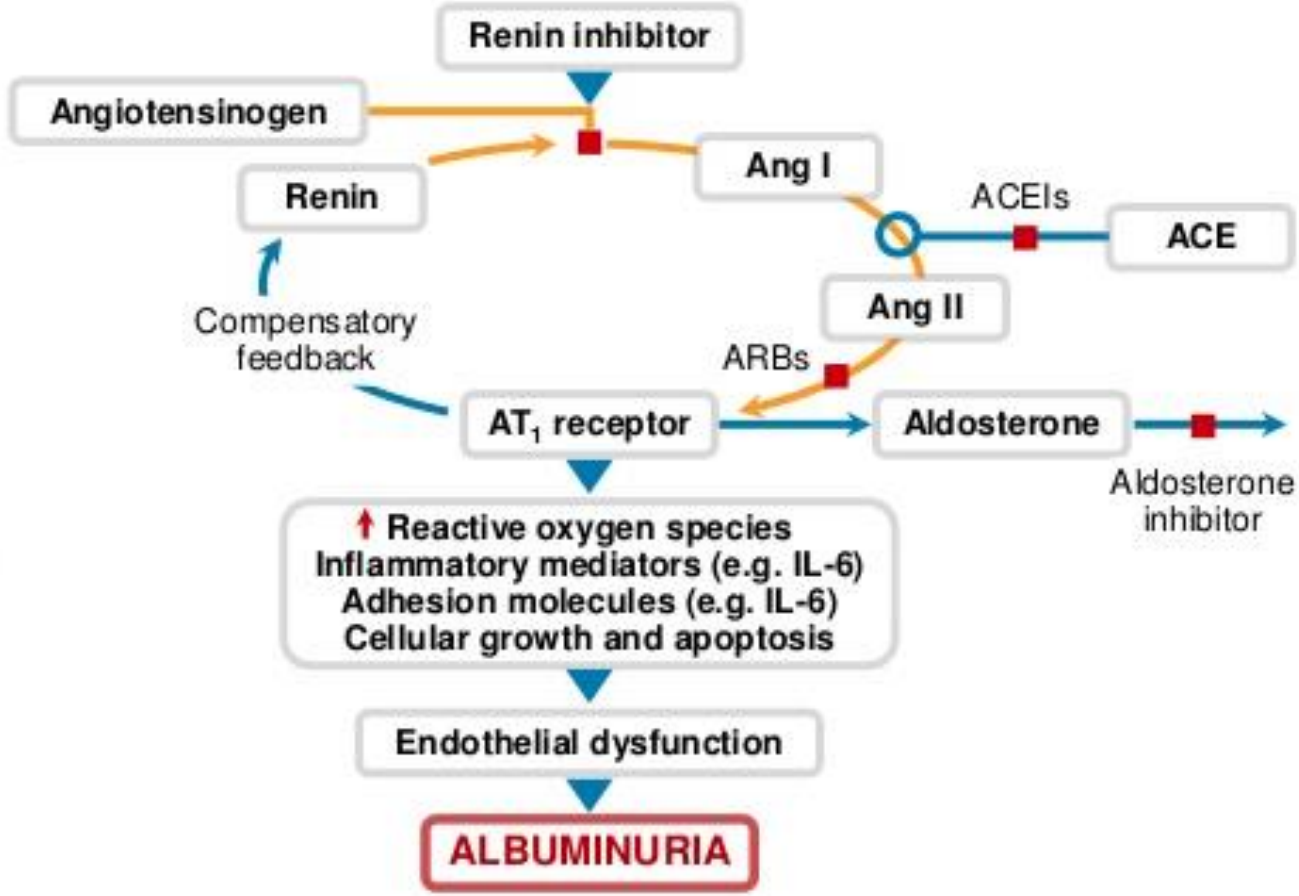
In a nutshell

Maintain appropriate BP target for patients with DM CKD depending on the presence or absence of excess albuminuria

What is best class of anti-HPT for DM nephropathy?

- ACE inhibitor (ACEI)
- Angiotensin receptor blocker (ARB)

The RAAS and possible interventions



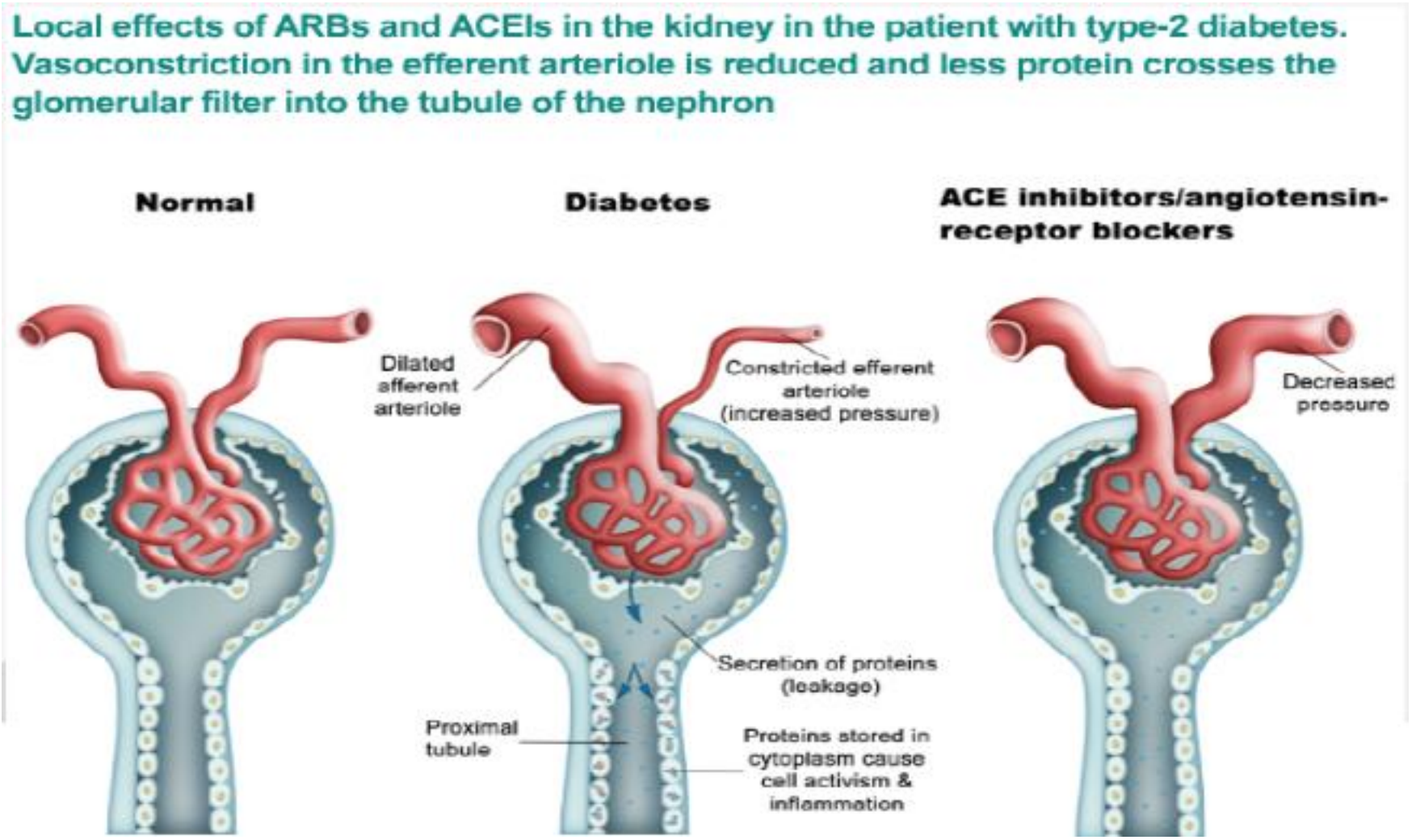
Ang = angiotensin; AT_1 = angiotensin II type 1; ACEI = ACE inhibitor; ARB = AT receptor blocker; IL-6 = interleukin 6; ICAN-1 = intercellular adhesion molecule.

How does RAS blockade with ACEI or ARB protect the kidneys?

The theory of hyperfiltration injury

WHY ACEI OR ARB?

Reducing intra-glomerular pressure



Treating DM nephropathy

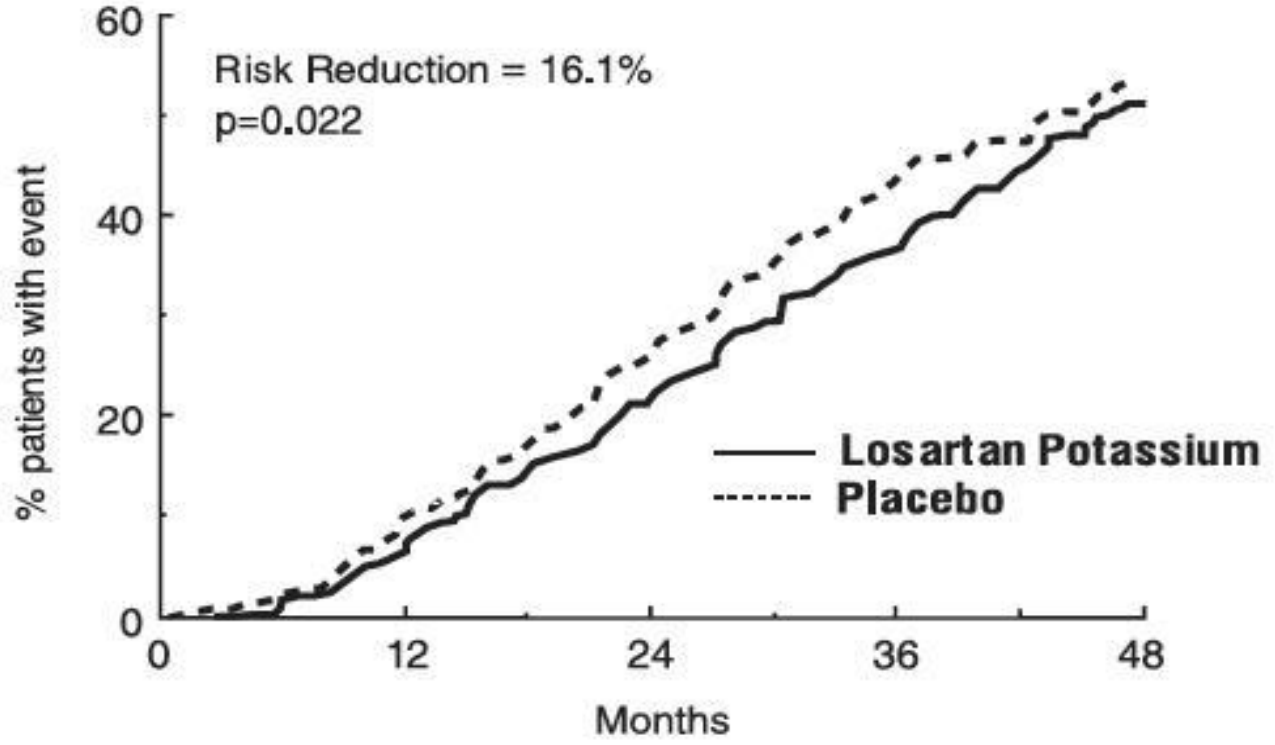
Late stage DM nephropathy

(CKD stage 3-4)

RENAAL: The basis for Losartan use in DM type II CKD

The Reduction of Endpoints in NIDDM with the Angiotensin II Receptor Antagonist Losartan (RENAAL) study of DM CKD stage 3-4 with UACR > 300mg/g (overt)

N Engl J Med. 2001; 345:861-9

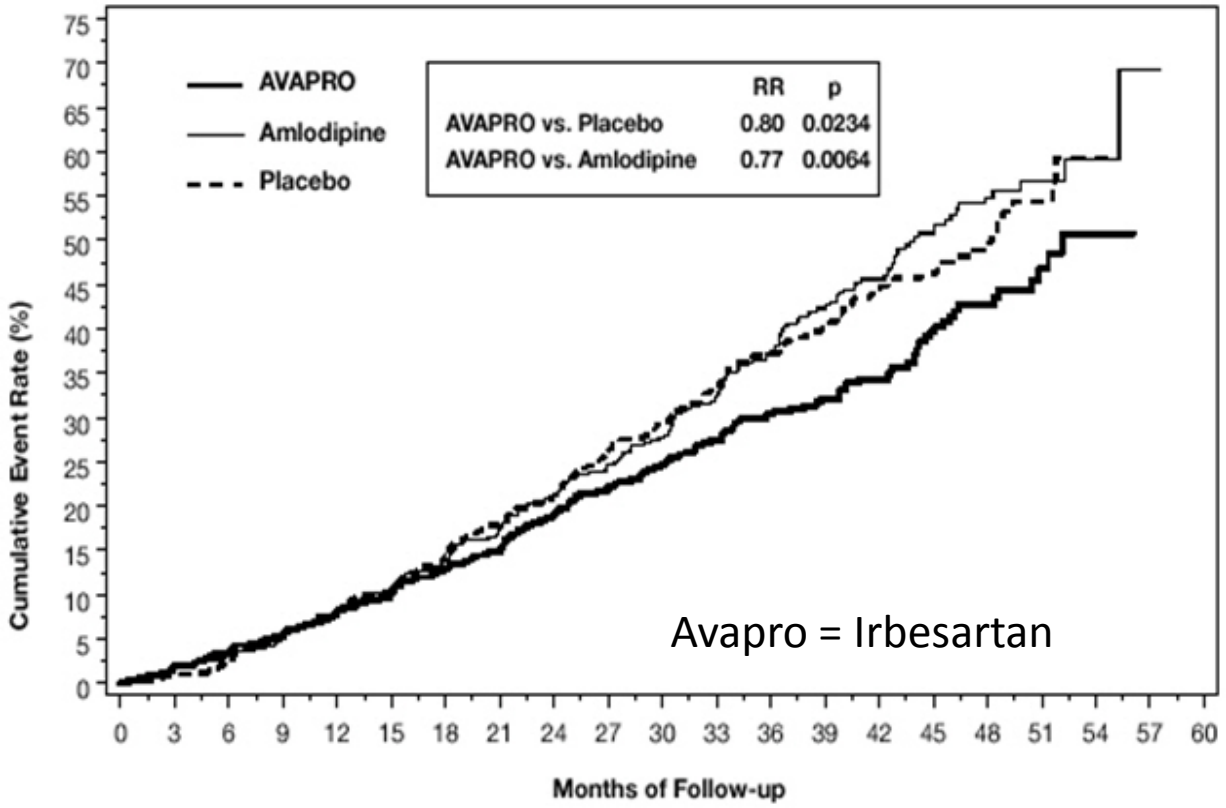


Results: Primary composite end points of doubling of serum creatinine, need for dialysis or death

IDNT: The basis for Irbesartan use in DM type II CKD

The Irbesartan Diabetic Nephropathy Trial (IDNT) of DM type II CKD stage 3-4 with proteinuria of 900mg/day

N Engl J Med. 2001; 345:851-60

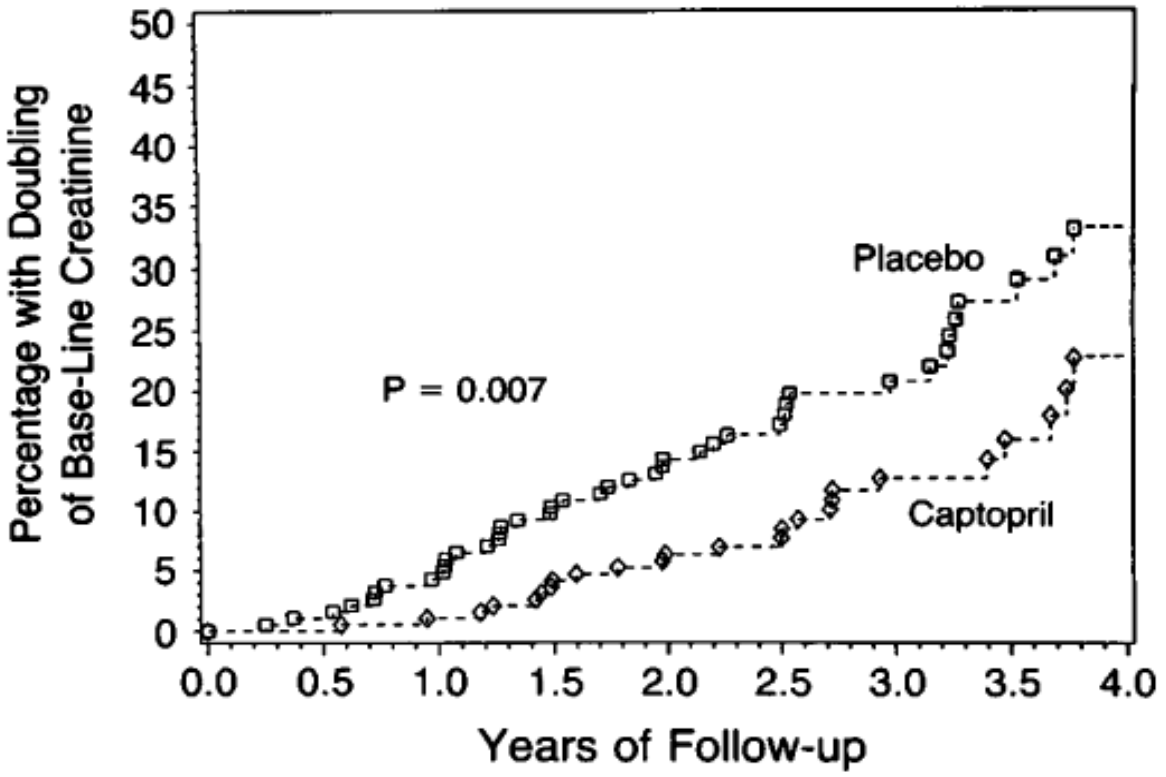


Results: Primary composite end points of doubling of serum creatinine, need for dialysis or death

CSG: The basis for ACEI use in DM (type I) CKD

Collaborative Study Group: use of ACEI in DM type I with proteinuria > 500mg/day and CKD stage 2-3

N Engl J Med. 1993 Nov 11;329(20):1456-62



Results: Primary outcome is doubling of serum creatinine to at least 2mg/dl

In a nutshell

Overt DM nephropathy (CKD 3-4 with overt proteinuria) should be treated with ARB or ACEI – using optimal dose as tolerated

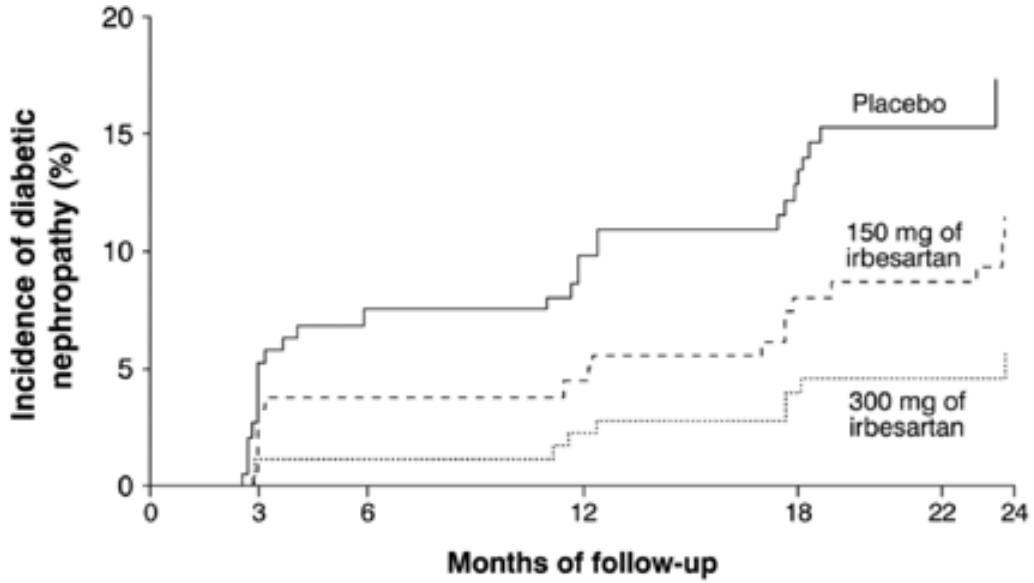
Treating DM nephropathy

Early stage DM nephropathy
(CKD stage 1-2)

IRMA 2: The basis for Irbesartan use in early DM type II CKD

Irbesartan study in DM with Microalbuminuria

N Engl J Med. 2001; 345:870-8



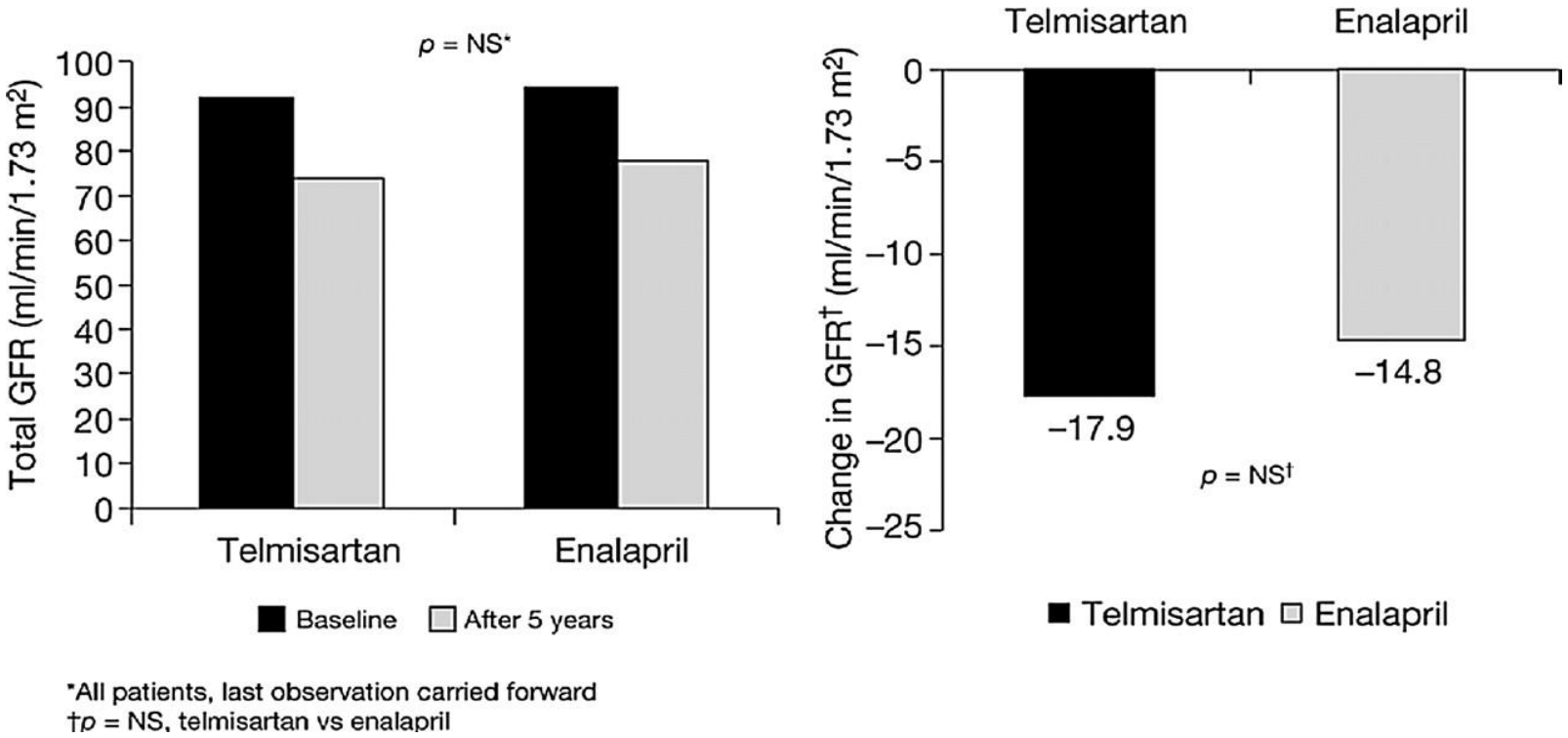
No. at risk							
Placebo	201	201	164	154	139	129	36
150 mg of irbesartan	195	195	167	161	148	142	45
300 mg of irbesartan	194	194	180	172	159	150	49

Outcome: prevention of development to over proteinuria

DETAIL: The basis for the use of ACEI vs ARB in early DM type II CKD

Diabetics Exposed to Telmisartan & Enalapril study of DM type II CKD 1-2 with mostly microalbuminuria (80%)

N Engl J Med 2004;351:1952-61

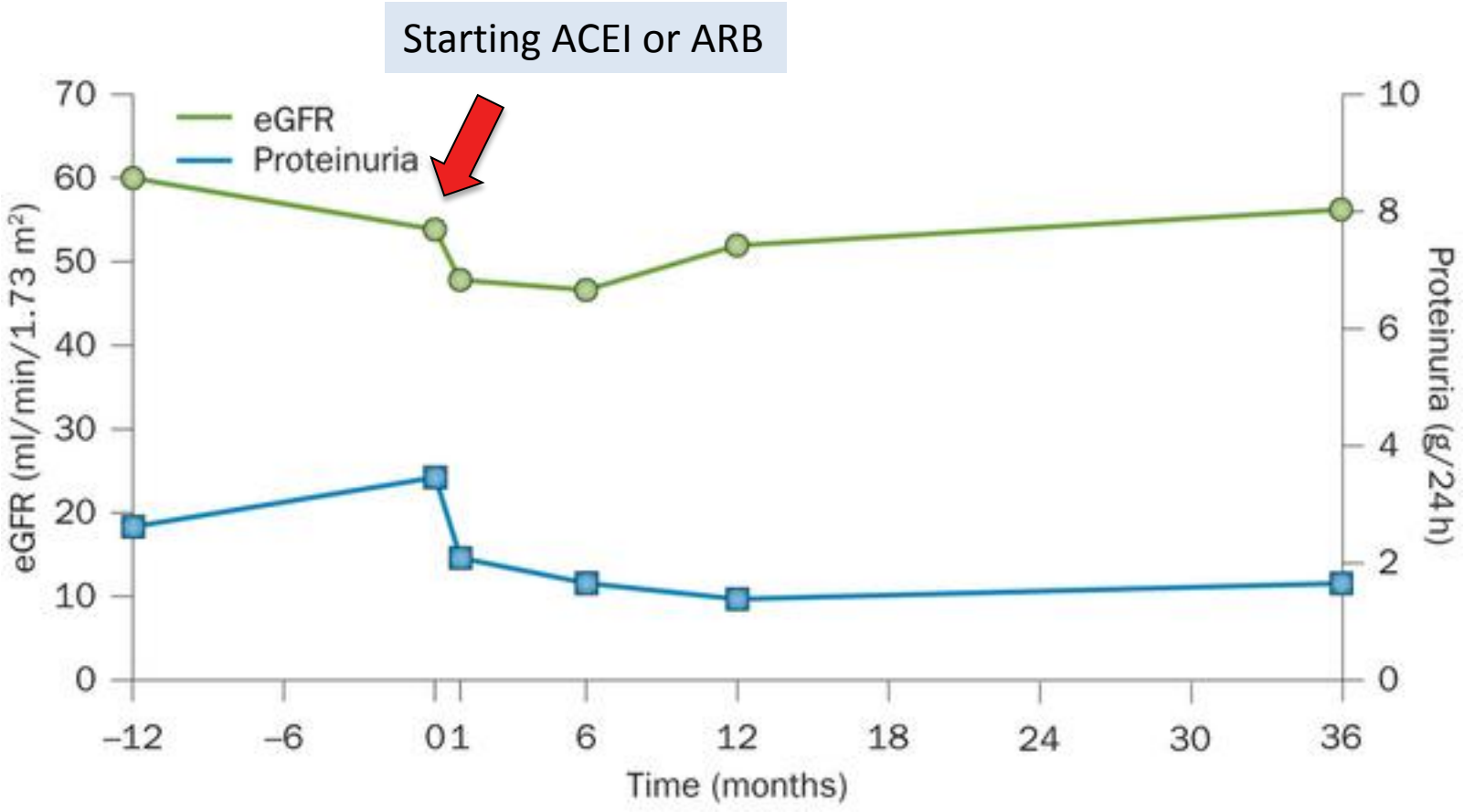


*All patients, last observation carried forward
†p = NS, telmisartan vs enalapril

In a nutshell

Early DM nephropathy (CKD 1-2 with microalbuminuria) should be treated with ARB or ACEI

Improvement in proteinuria but also a temporary decline in GFR



Nature Reviews Nephrology **10**, 77–87 (2014)

Practical Tips: Potassium (K+) and Creatinine

Check serum K^+ and Cr

- Baseline
- Within 1-2 weeks of initiation or titration
- During acute illness

If K^+ becomes elevated or Cr >30% increase

Review therapy

Recheck serum K^+ and Cr

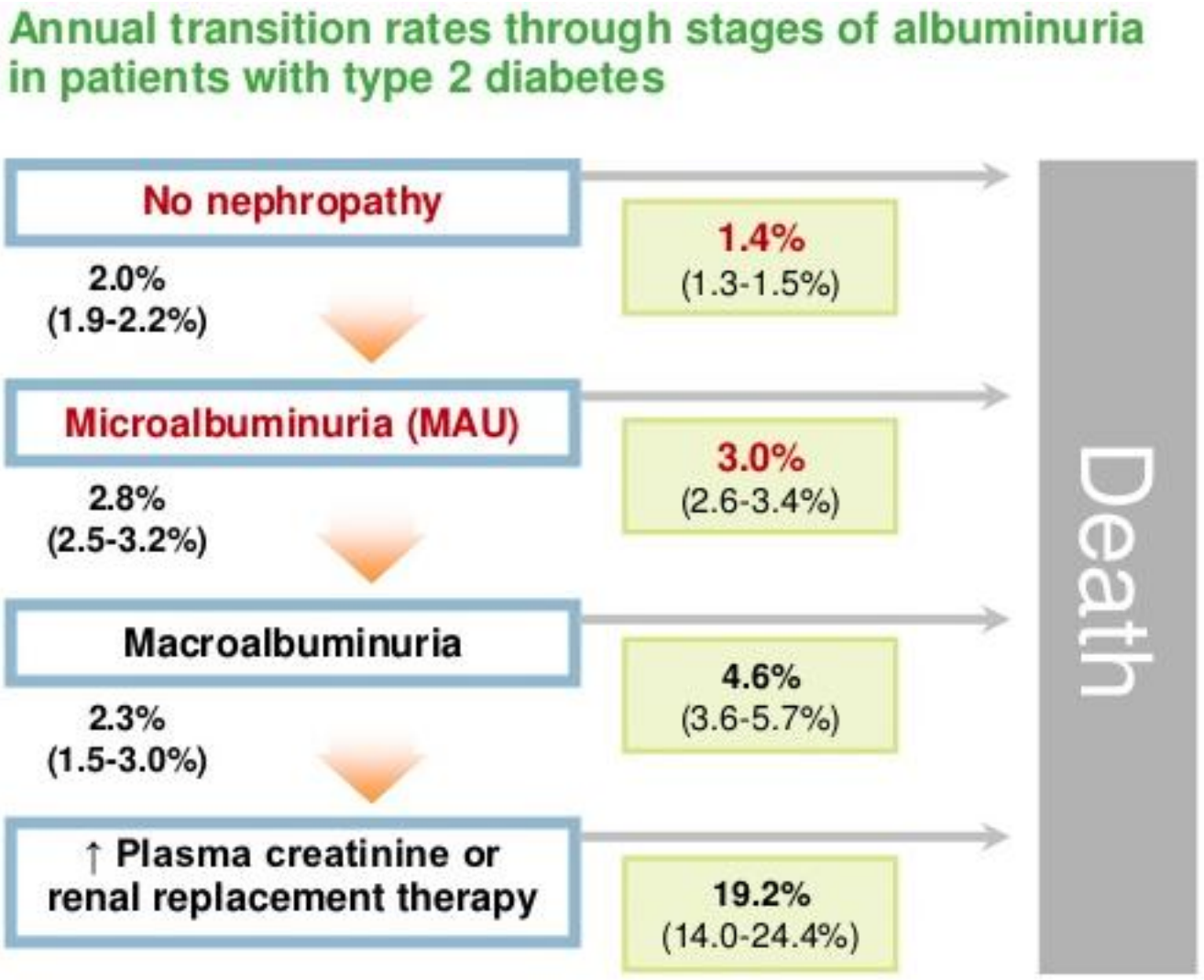
Practical Tips: Potassium (K+) and Creatinine

- Mild to moderate stable hyperkalemia
  - Counsel on a low potassium diet
  - If persistent, consider adding non-potassium sparing diuretics and/or oral sodium bicarbonate (in those with metabolic acidosis)
  - Consider temporarily holding or discontinuing ACEi, ARB or Direct Renin Inhibitor (DRI)
- Severe hyperkalemia
  - Hold or discontinue ACEi, ARB or DRI
  - Emergency management strategies

Caution!!

Combination of agents that block the renin-angiotensin-aldosterone system (ACE-inhibitor, ARB, DRI) should **not** be routinely used in the management of diabetes and CKD [Grade A, Level 1].

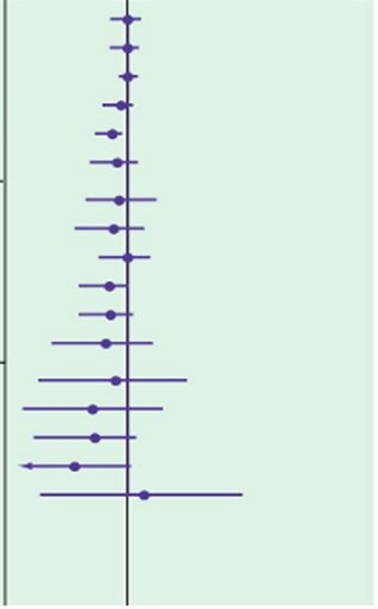
Can we prevent onset of nephropathy? Primary prevention



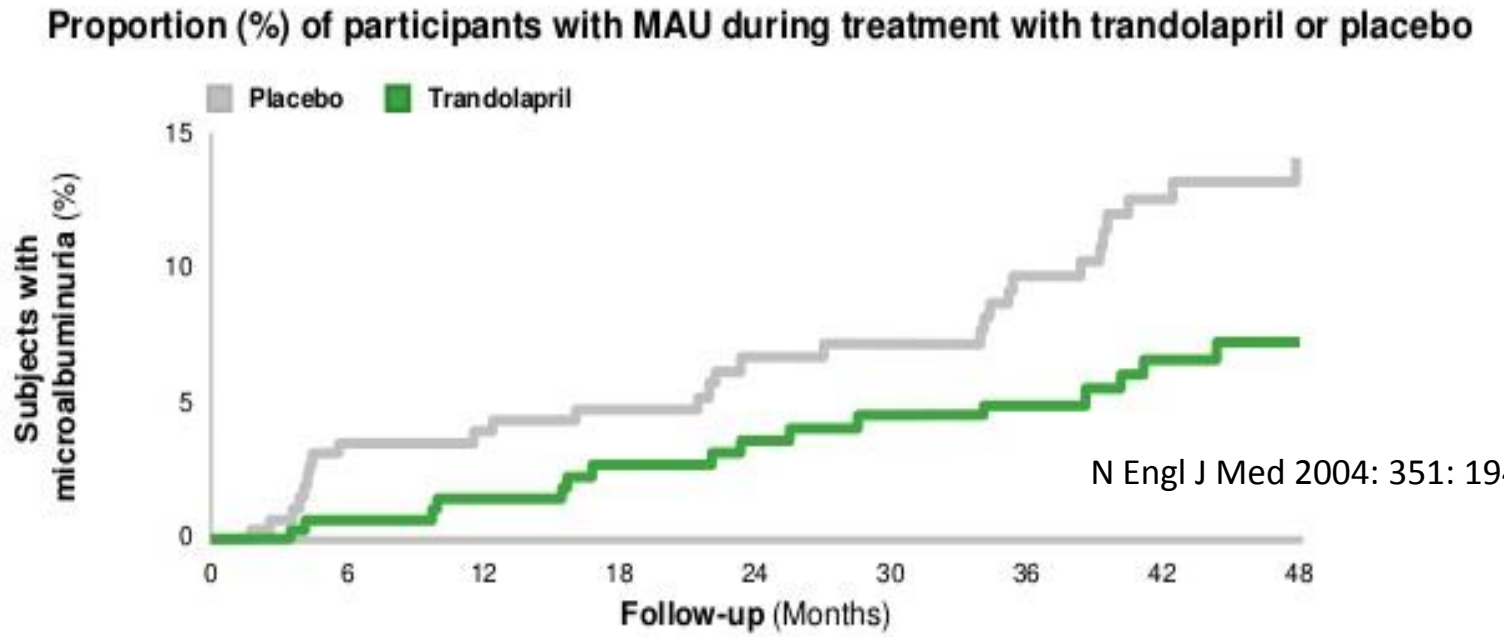
UKPDS – intensive control in type II DM and primary prevention

Intensive glycemic control in type 2 diabetes

Parameter	Therapy (years)	Risk reduction	*p* value
Microalbuminuria	0	0.89	0.24
	3	0.83	0.043
	6	0.88	0.13
	9	0.76	0.00062
	12	0.67	0.000054
	15	0.70	0.033
Proteinuria	0	0.79	0.37
	3	0.68	0.12
	6	0.90	0.61
	9	0.67	0.026
	12	0.66	0.036
	15	0.58	0.12
Twofold increase in plasma creatinine	0–3	0.67	0.37
	0–6	0.42	0.12
	0–9	0.40	0.61
	0–12	0.26	0.026
	0–15	1.25	0.036



Primary prevention in DM type II using ACEI

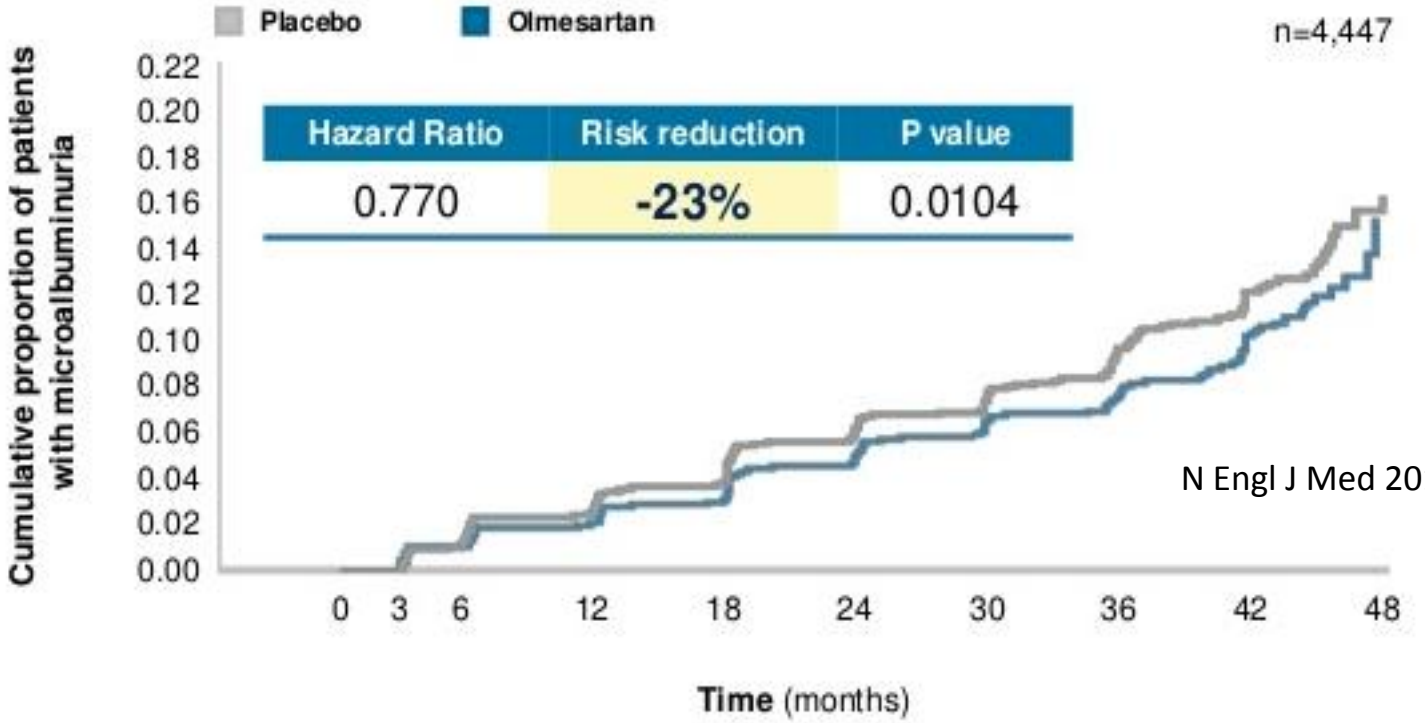


N Engl J Med 2004: 351: 1941-51

MAU = microalbuminuria; T2D = type 2 diabetes; HT = hypertension; BP = blood pressure; RAAS = renin-angiotensin-aldosterone system
*Defined as UACR ≥20g/min in at least 2 of 3 consecutive overnight urine collections and confirmed after approx. 2 months in at least 3 consecutive overnight urine collections; †Significant difference (p=0.01) vs. placebo after adjusting for pre-specified covariates.

Treatment with an ACE inhibitor reduces the incidence of MAU in individuals with T2D and hypertension

Primary prevention in DM type II using ARB



N Engl J Med 2011;364:907-17

Subjects: type 2 diabetes (T2D) and ≥1 additional CV risk factor (e.g. dyslipidaemia, hypertension, obesity, smoking).

94% of participants had blood pressure below 130/80 mmHg or were receiving antihypertensive treatment with a non-RAAS medication

ARB therapy significantly delays the onset of MAU – by 23% compared with placebo in individuals with T2D

(After correction for diastolic and systolic blood pressure, the risk reduction with olmesartan dropped to 18% and 17%, respectively, losing statistical significance)

In a nutshell

Primary prevention is possible with intensive glycemic control. It is also possible with the use of ACEI or ARB but only for those with HPT and need for anti-HPT

Questions?

THANK YOU