Diabetic nephropathy

- **Diabetic nephropathy** is a clinical syndrome characterized by the following :

Persistent albuminuria (>300 mg/d or >200 µg/min) that is confirmed on at least 2 occasions 3-6 months apart

Progressive decline in the glomerular filtration rate (GFR)

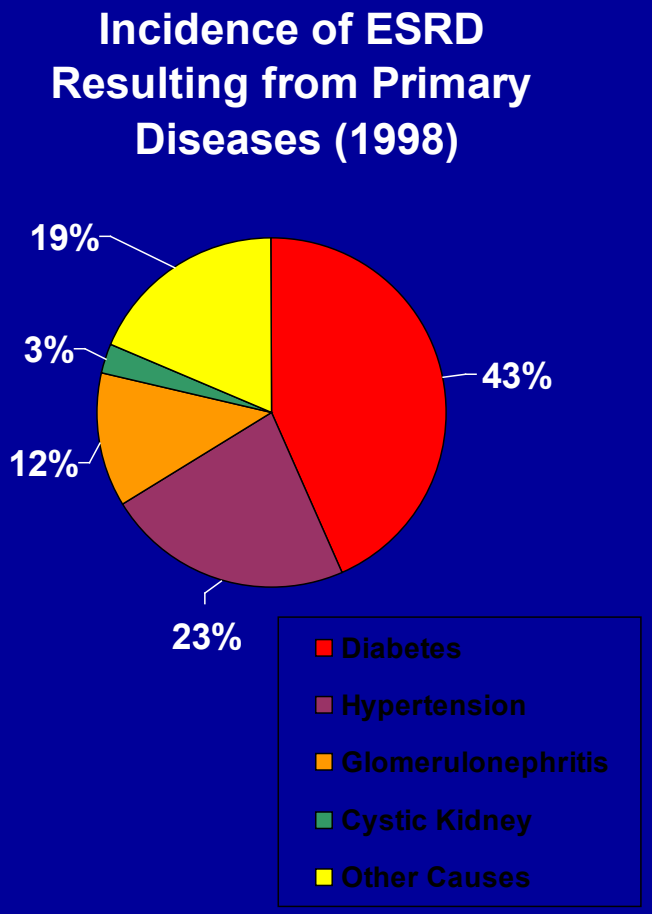
- Elevated arterial blood pressure

- Proteinuria was first recognized in diabetes mellitus in the late 18th century. In the 1930s, Kimmelstiel and Wilson described the classic lesions of nodular glomerulosclerosis in diabetes associated with proteinuria and hypertension.

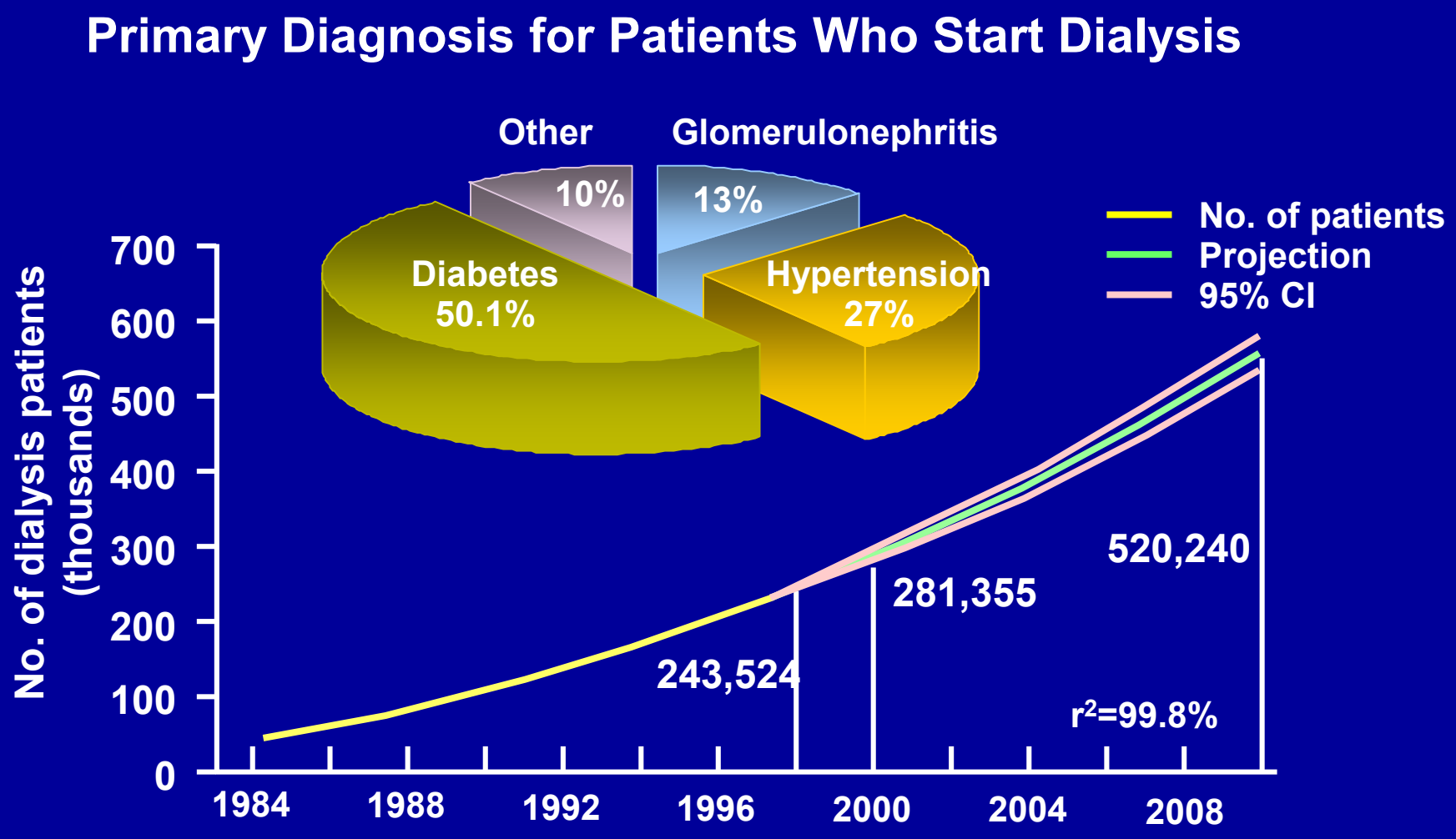
- By the 1950s, kidney disease was clearly recognized as a common complication of diabetes, with as many as 50% of patients with diabetes of more than 20 years having this complication.

Diabetic Nephropathy

- Over 40% of new cases of end-stage renal disease (ESRD) are attributed to diabetes.
- In 2001, 41.312 people with diabetes began treatment for end-stage renal disease.
- In 2001, it cost $22.8 billion in public and private funds to treat patients with kidney failure.



Diabetes: The Most Common Cause of ESRD



United States Renal Data System. Annual data report. 2000.

- Diabetic nephropathy is categorized into stages:
- microalbuminuria (UAE >20 µg/min and ≤199 µg/min)
- macroalbuminuria (UAE ≥200 µg/min).

- Hyperglycemia, increased blood pressure levels, and genetic predisposition are the main risk factors for the development of diabetic nephropathy.

Elevated serum lipids, smoking habits, and the amount and origin of dietary protein also seem to play a role as risk factors.

Screening for microalbuminuria

-should be performed yearly, starting 5 years after diagnosis in type 1 diabetes or earlier in the presence of puberty or poor metabolic control.

In patients with type 2 diabetes, screening should be performed at diagnosis and yearly thereafter.

Patients with micro- and macroalbuminuria should undergo an evaluation regarding the presence of comorbid associations, especially retinopathy and macrovascular disease.

EPIDEMIOLOGY

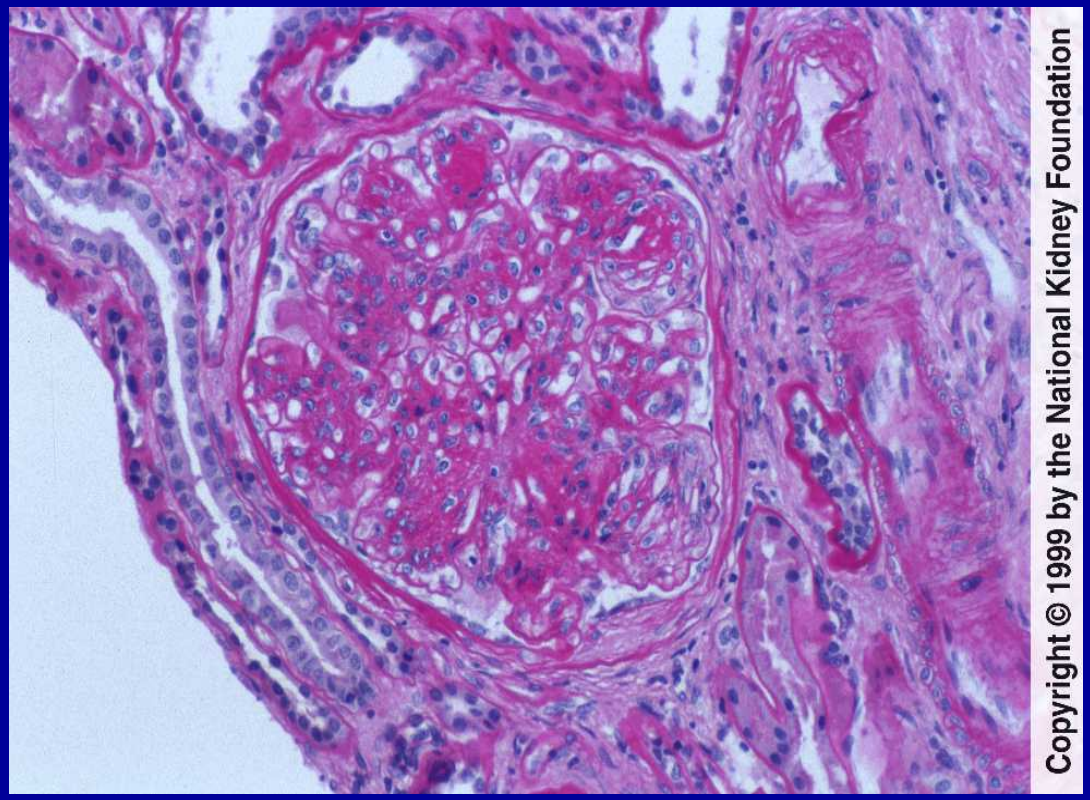
- Diabetic nephropathy is more prevalent among African Americans, Asians, and Native Americans than Caucasians .
- Among patients starting renal replacement therapy, the incidence of diabetic nephropathy doubled from the years 1991–2001 . Fortunately, the rate of increase has slowed down, probably because of the adoption in clinical practice of several measures that contribute to the early diagnosis and prevention of diabetic nephropathy, which thereby decreases the progression of established renal disease.

Pathophysiology of DKD

- Critical metabolic changes that alter kidney hemodynamics and promote inflammation and fibrosis in early diabetes include hyperaminoacidemia, a promoter of glomerular hyperfiltration and hyperperfusion, and hyperglycemia .
- In DM2, systemic hypertension and obesity also contribute to glomerular hyperfiltration *via* mechanisms, such as high transmitted systemic BP and glomerular enlargement . Glomerular hyperfiltration is a well characterized consequence of early diabetes.

- Mechanisms underlying glomerular hyperfiltration in diabetes are incompletely understood ; however, one plausible mechanism is increased proximal tubular reabsorption of glucose *via* sodium–glucose cotransporter 2, which decreases distal delivery of solutes, particularly sodium chloride, to the macula densa .
- The resulting decrease in tubuloglomerular feedback may dilate the afferent arteriole to increase glomerular perfusion, while concurrently, high local production of angiotensin II at the efferent arteriole produces
- vasoconstriction. The overall effect is high intraglomerular pressure and glomerular hyperfiltration

DN-PATHOLOGY



- GBM THICKENING
- MESANGIAL SCLEROIS
  - DIFFUSE
  -NODULAR (Kimmelstiel-Wilson)
- FIBRIN CAP/CAPSULAR DROP
- ARTERIOLAR HYALINOSIS
- INTERSTITIAL FIBROSIS
- ISCHEAMIC CHANGES
- PYELONEPHRITIC CHANGES.

Diabetic Nephropathy

- Most common cause of nephrotic syndrome in adults.
- Leading cause of ESRD in USA
- 30% of patients with Type I and 20% of patients with Type II DM develop diabetic nephropathy.
- Initially microalbuminuria followed by heavy proteinuria and decline in renal function.
- Diagnosis usually made on clinical grounds and biopsy not needed.

Generally, diabetic nephropathy is considered after a routine urinalysis and screening for microalbuminuria in the setting of diabetes. Patients may have physical findings associated with long-standing diabetes mellitus.

- Good evidence suggests that early treatment delays or prevents the onset of diabetic nephropathy or diabetic kidney disease. This has consistently been shown in both type 1 and type 2 diabetes mellitus.

Take Message 1

- Diabetic nephropathy is progressive kidney disease
- Most common cause of ESRD
- Lowering blood pressure with RAAS blockade is critical
- Combinations of ACEi + ARB
- Prevent cardiovascular morbidity and mortality

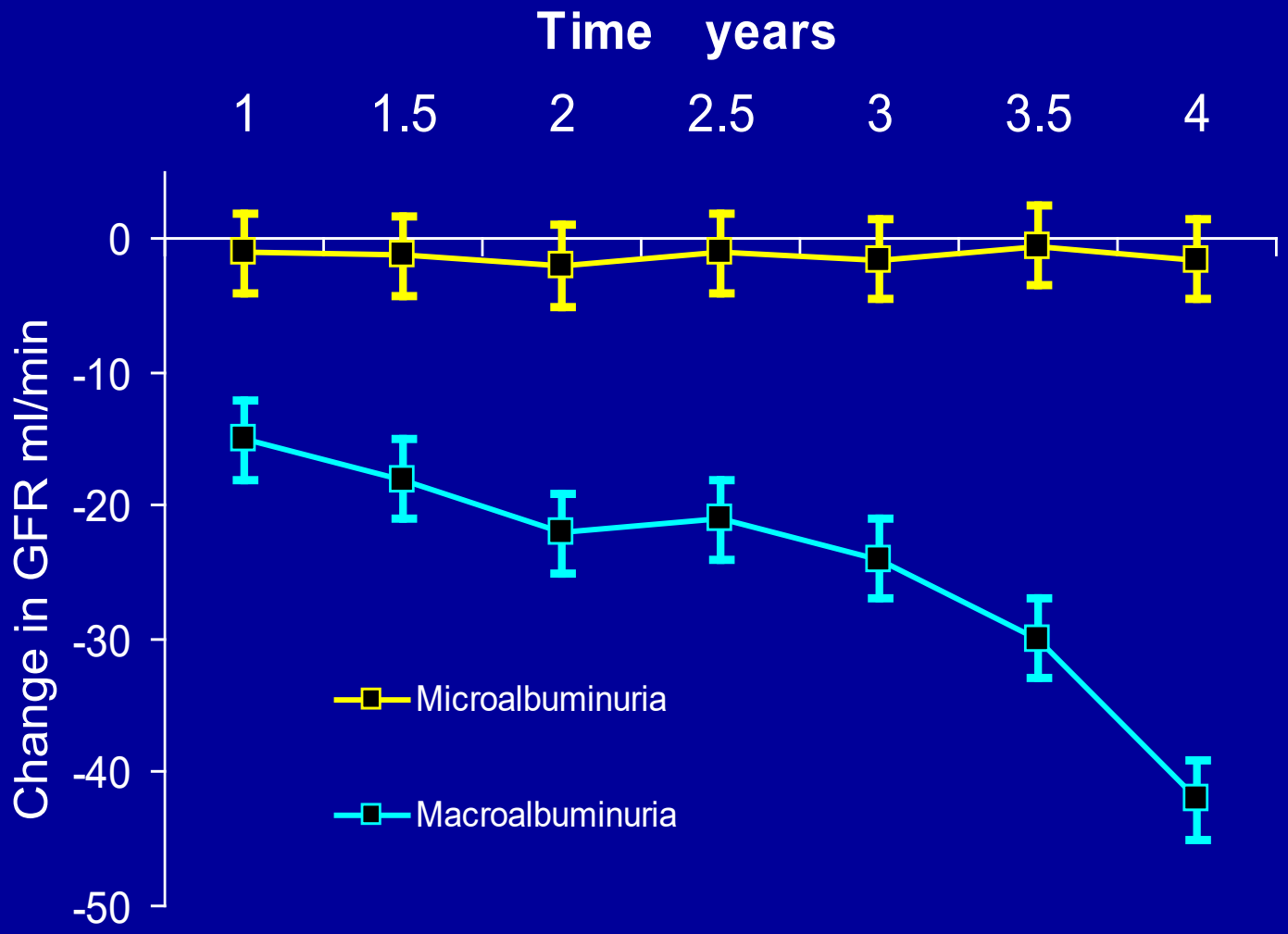
DIAGNOSIS OF DIABETIC NEPHROPAHTY

- MICROALBUMINURIA

  -urine albumin>30mg/d & <300 mg/d
- OVERT NEPHROPATHY
  - Proteinuria>300mg/day.
  - Establish retinopathy.
  - Absence of features sugg. of Non-Diabetic renal disease.

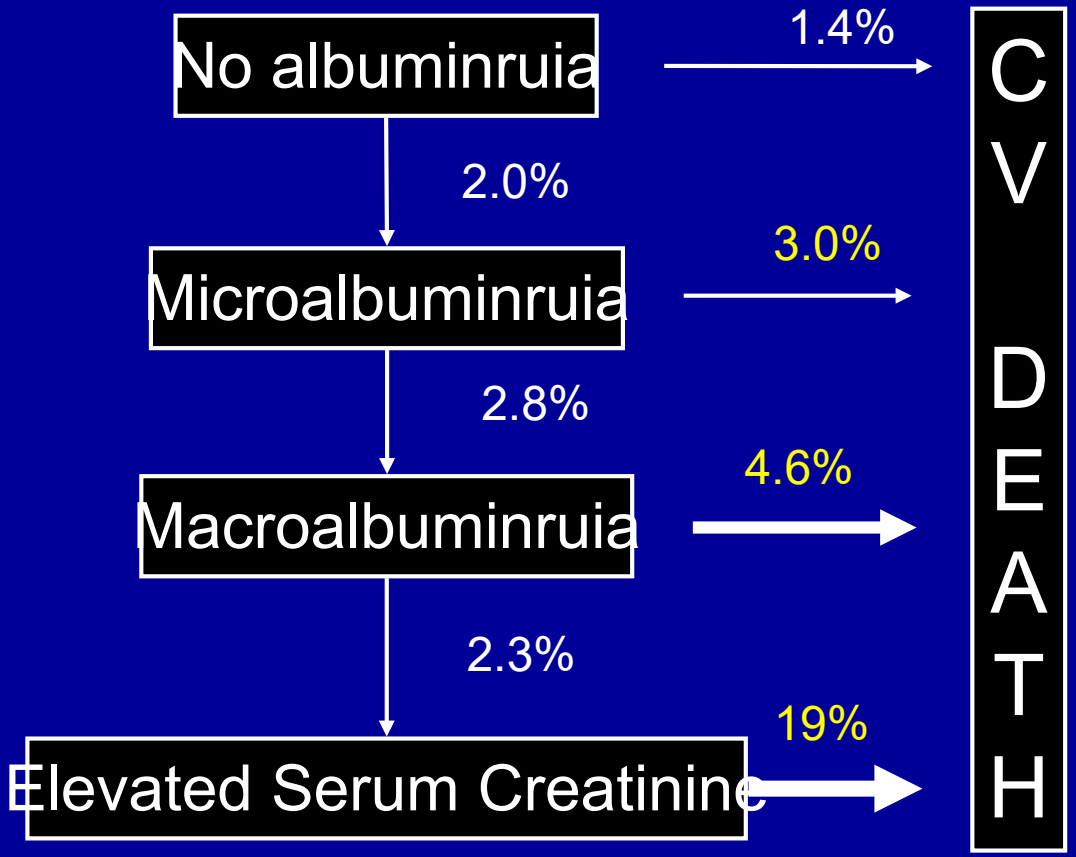
- Recently, attention has been called to atypical presentations of diabetic nephropathy with dissociation of proteinuria from reduced kidney function.
- Also noted is that microalbuminuria is not always predictive of diabetic nephropathy.
- A majority of the cases of diabetic nephropathy presents with proteinuria, which progressively gets worse as the disease progresses, and is almost uniformly associated with hypertension.

Development of Macroalbuminuria Heralds Rapid Decline in Glomerular Filtration in Type II Diabetes



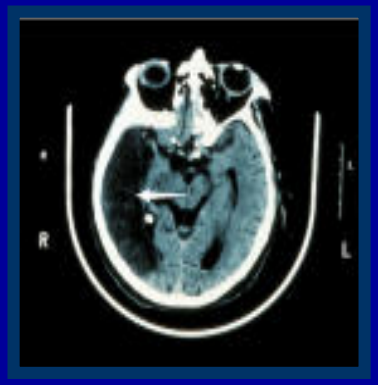
Diabetics with Macroalbuminuria are More Likely to Die than Develop ESRD

The United Kingdom Prospective Diabetes Study (approx. 5000 Type 2 Diabetics)
Newly diagnosed, predominantly white, medically treated

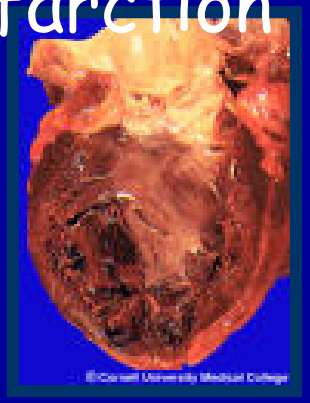


What are Diabetics with Nephropathy Dying From?

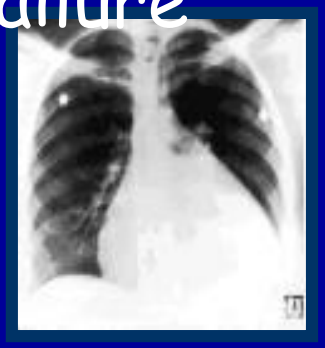
Stroke



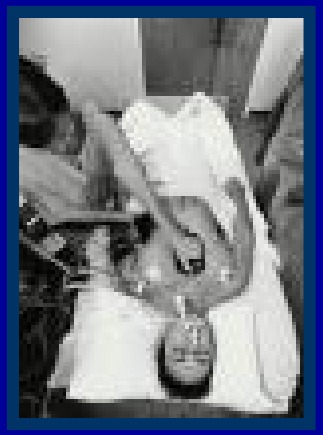
Myocardial Infarction



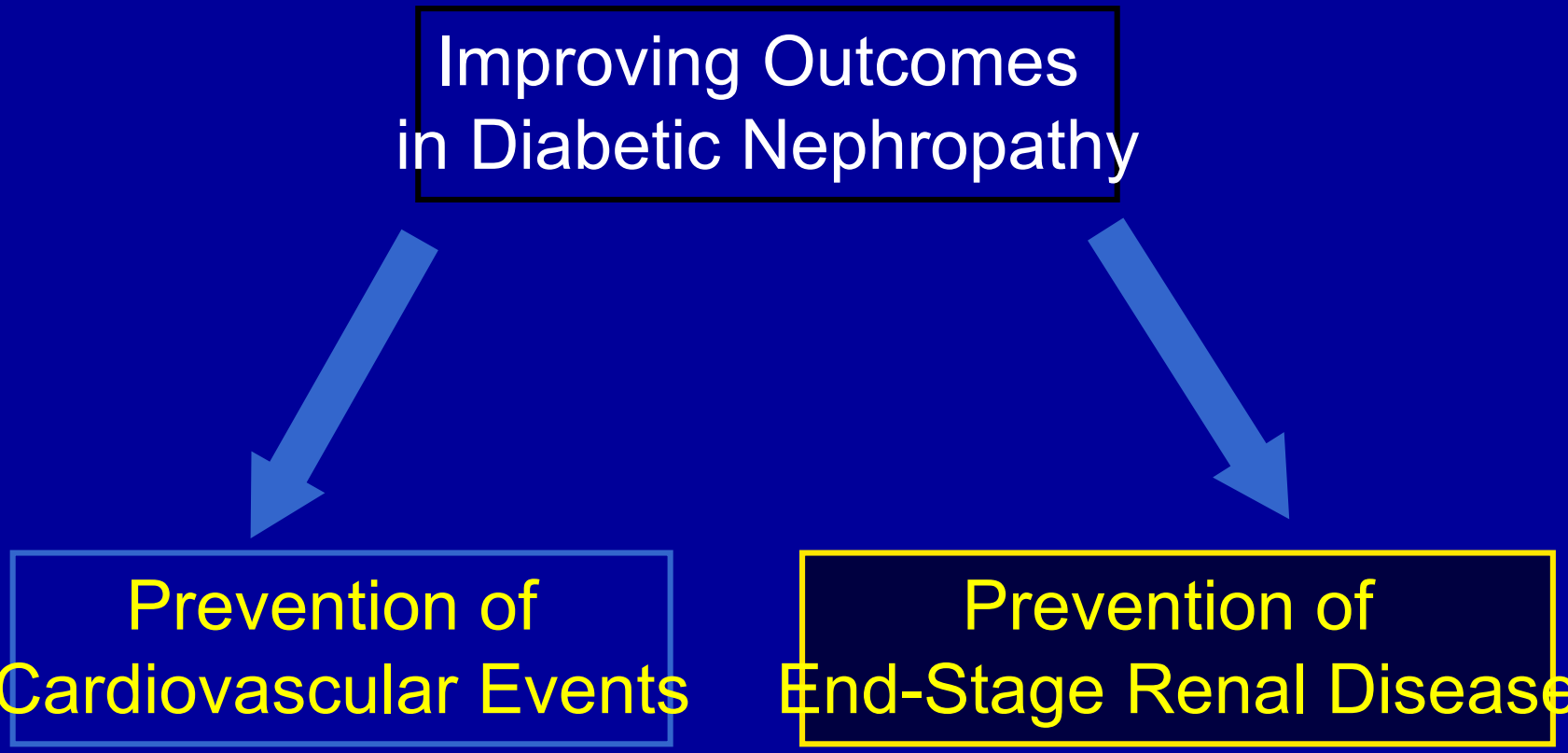
Heart Failure



Sudden Death



Diabetic Nephropathy



Diabetic Nephropathy: Take Message 2

- Leading cause of end-stage kidney disease
- Characterized by hypertension, proteinuria and progressive loss of kidney function
- Cardiovascular complications excessive an increase with worsening kidney function
- More likely to die than progress to end-stage

Definition of Abnormal Albuminuria in Diabetes Mellitus

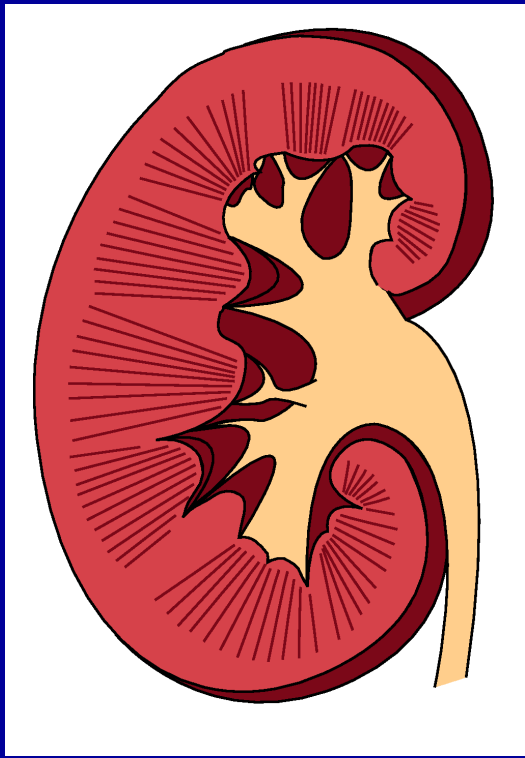
	Microalbuminuria	Macroalbuminuria (Nephropathy)
Detected by dipstick	No	Yes
Urine Albumin	30 - 299 mg Alb / g	≥ 300 mg Alb / g
Renal Risk	Marker of future nephropathy in some	Marker progressive renal disease
Cardiovascular Risk	Increased	Increased

Five Stages of Kidney Disease

Stage 1: Hyperfiltration, or an increase in glomerular filtration rate (GFR) occurs. Kidneys increase in size.

Stage 2: Glomeruli begin to show damage and microalbuminurea occurs.

Stage 3: Albumin excretion rate (AER) exceeds 200 micrograms/minute, and blood levels of creatinine and urea-nitrogen rise. Blood pressure may rise during this stage.

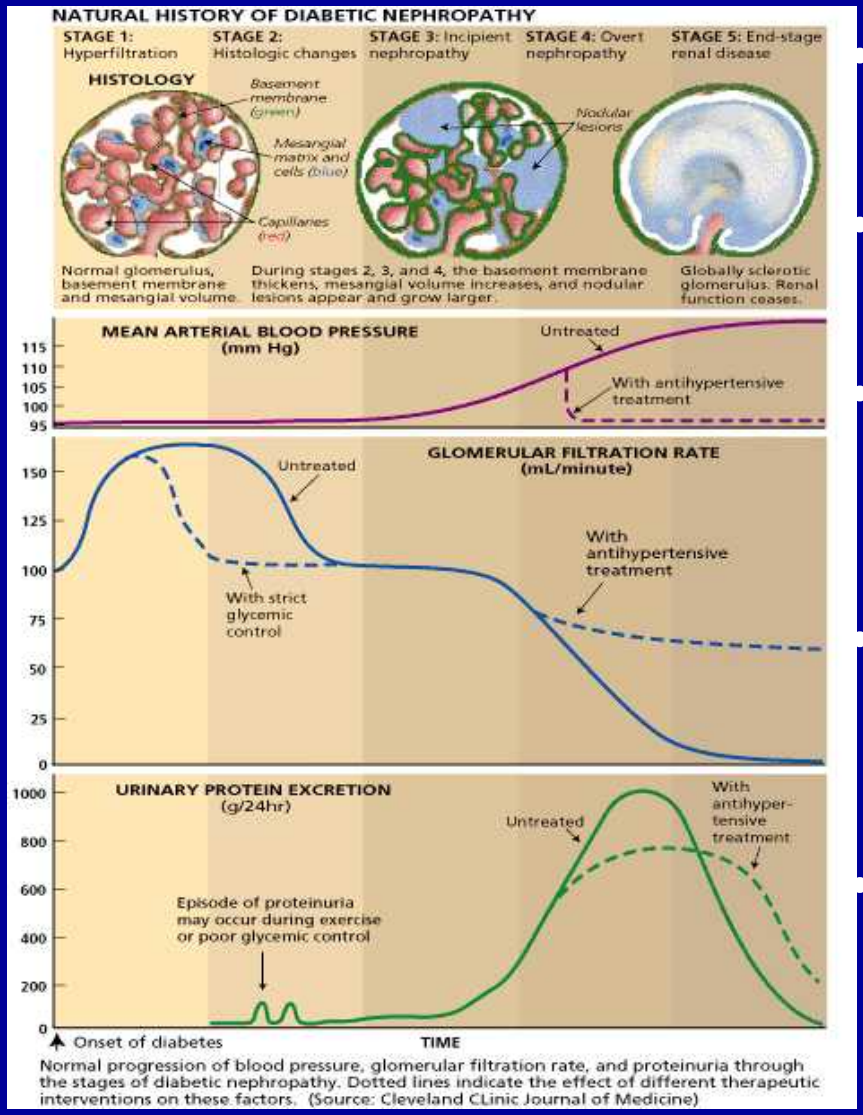


Five Stages of Kidney Disease (con't.)

Stage 4: GFR decreases to less than 75 ml/min, large amounts of protein pass into the urine, and high blood pressure almost always occurs. Levels of creatinine and urea-nitrogen in the blood rise further.

Stage 5: Kidney failure, or end stage renal disease (ESRD). GFR is less than 10 ml/min. The average length of time to progress from Stage 1 to Stage 4 kidney disease is 17 years for a person with type 1 diabetes. The average length of time to progress to Stage 5, kidney failure, is 23 years.

STAGES OF DN



Normal progression of blood pressure, glomerular filtration rate, and proteinuria through the stages of diabetic nephropathy. Dotted lines indicate the effect of different therapeutic interventions on these factors. (Source: Cleveland CLinic Journal of Medicine)

- **STAGE-1 HYPERFILTRATION**
- **STAGE-2 SILENT STAGE**
- **STAGE-3 INCIPIENT NEPHROPATHY**
- **STAGE-4 OVERT NEPHROPATHY**
- **STAGE-5 CHRONIC RENAL FAILURE**

DIABETIC NEPHROPATHY

- Stage 1& 2(GFR): lasts about 5 to15 years
- Stage 3 (microalbuminuria or 30 – 300 mg albumin/day): lasts 1 -5 years and strongly predicts diabetic nephropathy and increases cardiovascular mortality.
- Stage 4 (overt proteinuria): detected by dip stick and risk for worsening of HTN & decline in renal function
- Stage 5(renal failure): ESRD 7-10 yrs after onset of overt proteinuria

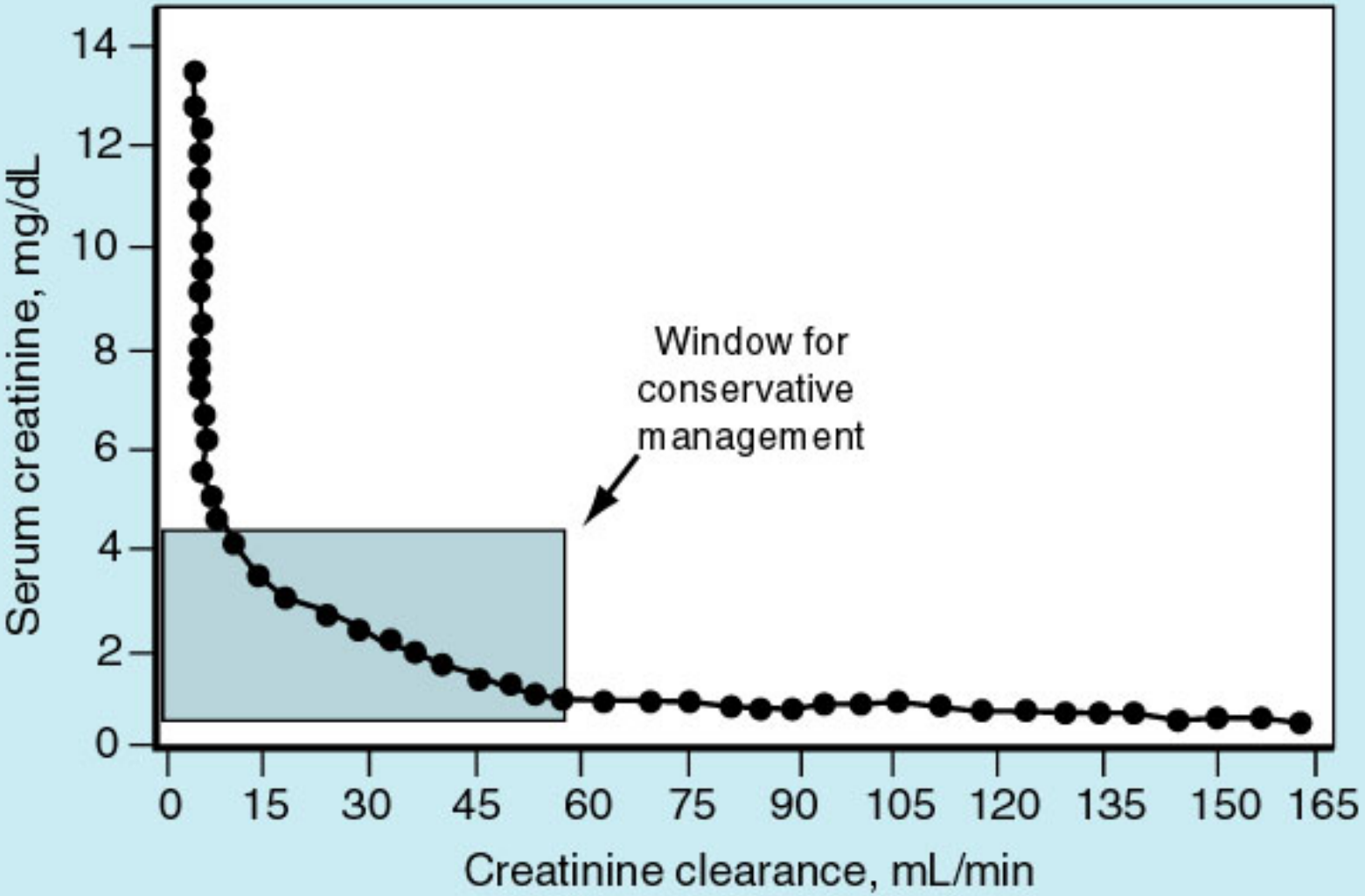
DIABETIC NEPHROPATHY

TYPE 2

- ONSET NOT KNOWN. MAY PRESENT IN ANY STAGE.
- HTN MAY PRECEDE DN.
- 60% OF DN HAVE RETINOPATHY.
- NON-DIABETIC RENAL DISEASE HIGH.

TYPE 1

- ONSET WELL KNOWN. PROGRESS STAGE BY STAGE.
- HTN ALWAYS AFTER STAGE-3.
- >90% OF DN HAVE RETINOPATHY.
- NON-DIABETIC RENAL DISEASE LOW.


Serum creatinine, mg/dL
14
12
10
8
6
4
2
0
Window for
conservative
management
0
15
30
45
60
75
90
105
120
135
150
165
Creatinine clearance, mL/min

PREVENTION OF DIABETIC NEPHROPATHY

- Identification of high risk patients.
- Role of treatment of HTN
- Role of glycemic control.
- Role of acei therapy.
- Treatment of hyperlipidemia
- Ident. Of non-diabetic renal disease & specific treatment

Differential diagnosis

- Differential diagnosis is usually based on the history, physical examination, laboratory evaluation, and imaging of the kidneys. Renal biopsy is only recommended in special situations. The diagnosis of diabetic nephropathy is easily established in long-term type 1 diabetic patients (>10 years diabetes duration), especially if retinopathy is also present. Typical diabetic nephropathy is also likely to be present in proteinuric type 2 diabetic patients with retinopathy.

- The presence of symptoms during urination suggests urinary tract disorders such as obstruction, infection, or stones. Skin rash or arthritis may indicate systemic lupus erythematosus or cryoglobulinemia. Presence of risk factors for parenterally transmitted disease may raise the suspicion of kidney disease associated with HIV, hepatitis C, or hepatitis B.
- History of proteinuria and/or hypertension during childhood or pregnancy may suggest other glomerulonephritis. Also, family history of kidney disease may indicate the presence of polycystic kidney disease or other genetic diseases .

Monitoring of renal function

- GFR is the best parameter of overall kidney function and should be measured or estimated in micro- and macroalbuminuric diabetic patients. In microalbuminuric patients, GFR may remain stable, but a subset of patients has shown a rapid decline in GFR levels .
- In type 1 macroalbuminuric patients, GFR declines about 1.2 ml · min^{-1} · $month^{-1}$ without therapeutic interventions .
- In patients with type 2 diabetes, GFR decline is more variable. One study reported a mean decline of ~0.5 ml · min^{-1} · $month^{-1}$, although in some patients GFR may remain stable for long periods . Patients with a more rapid GFR decline usually have more advanced diabetic glomerulopathy and worse metabolic control.

Comorbid associations

- It is particularly important to investigate retinopathy. Ideally, this should be done by an experienced ophthalmologist, since retinopathy is frequent in the presence of diabetic nephropathy and is a clue for its diagnosis. Prospective studies in type 2 diabetic patients showed that diabetic retinopathy was a predictor of later development of diabetic nephropathy . Retinopathy is probably a risk marker and not a risk factor in itself, since these microvascular complications (diabetic nephropathy and diabetic retinopathy) share common determinants, such as poor glycemic, blood pressure, and lipid control. Other complications of diabetes, such as peripheral and autonomic neuropathy, should also be evaluated, since they are seen more frequently in patients with diabetic nephropathy and are associated with increased morbidity and mortality.

Comorbid associations

- Patients with diabetic nephropathy, due to their high cardiovascular risk, should be routinely evaluated for the presence of coronary heart disease, independently of the presence of cardiac symptoms. Other atherosclerotic complications, such as carotid disease, peripheral artery disease, and atherosclerotic renal-artery stenosis should also be assessed.
- Radiocontrast agents used in angiography may cause acute renal failure in up to 35% of diabetic patients, especially in those with decreased renal function . This can be prevented by prior hydration and administration of an iso-osmolar contrast media . Acetylcysteine, a free-radical scavenger, has also been shown to be renoprotective in some studies , but this was not confirmed in a recent study

Prevention: normoalbuminuric patients

- The basis for the prevention of diabetic nephropathy is the treatment of its known risk factors: hypertension, hyperglycemia, smoking, and dyslipidemia. These are also risk factors for cardiovascular disease and should be vigorously treated.

What is the Proper Therapy of Kidney Disease in patients with Diabetes?

Diet intervention

- Replacing red meat with chicken in the usual diet reduced UAE by 46% and reduced total cholesterol, LDL cholesterol, and apolipoprotein B in microalbuminuric patients with type 2 diabetes in a 4-week study .
- This was probably related to the lower amount of saturated fat and the higher proportion of polyunsaturated fatty acids found in chicken meat than in red meat.
- The beneficial effect of polyunsaturated fatty acids on endothelial function could also reduce UAE. A normal protein diet with chicken as the only source of meat may represent an additive strategy for the treatment of microalbuminuric type 2 diabetic patients.

Treatment of Diabetic Nephropathy

- Hypertension Control - Goal: lower blood pressure to <130/80 mmHg
  - Antihypertensive agents
    - Angiotensin-converting enzyme (ACE) inhibitors
      - **captopril, enalapril, lisinopril, benazepril, fosinopril, ramipril, quinapril, perindopril, trandolapril, moexipril**
    - Angiotensin receptor blocker (ARB) therapy
      - **candesartan cilexetil, irbesartan, losartan potassium, telmisartan, valsartan, esprosartan**
    - Beta-blockers

Treatment of Diabetic Nephropathy

- Glycemic Control
  - Preprandial plasma glucose 90-130 mg/dl
  - HBA1C <7.0%
  - Peak postprandial plasma glucose <180 mg/dl
  - Self-monitoring of blood glucose (SMBG)
  - Medical Nutrition Therapy
- Restrict dietary protein to RDA of 0.8 g/kg body weight per day

How I do get My Patient's BP to the Goal of <130 / < 80 mmHg?

- ACE Inhibitor / AII Receptor Antagonist (maximum dose)
- Low (2 gram) Sodium Diet
- Diuretic
  - eGFR $\geq$ 50 ml/min, thiazide
  - eGFR < 50 ml/min, loop diuretic
- Long-Acting CCB or β-blocker
- Long-acting α-blocker vs clonidine
- Minoxidil

Multiple Risk Factor Intervention Improves Outcomes in Type 2 diabetics with Microalbuminuria

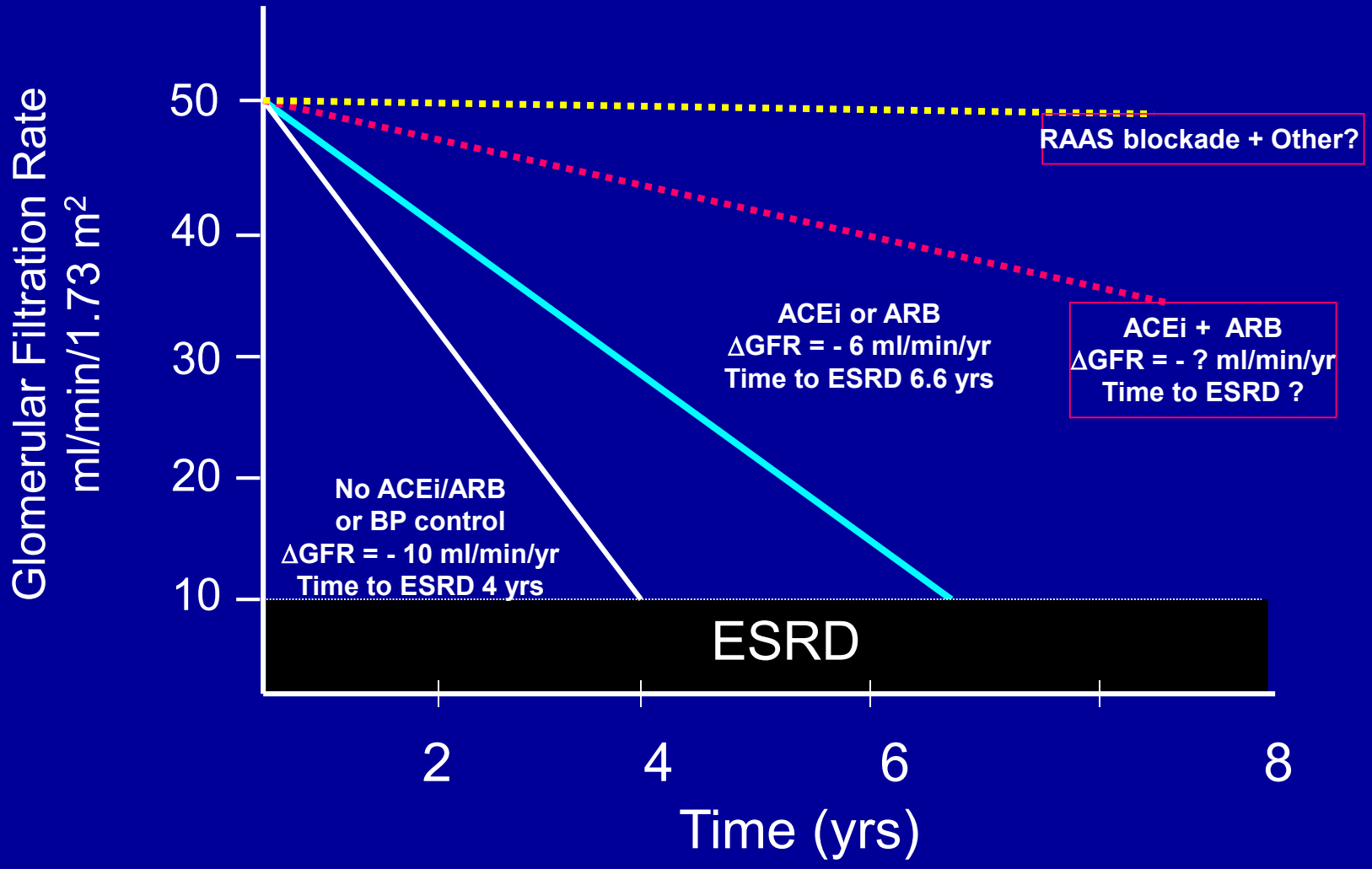
- Randomized, open-label, target driven, long-term intensified intervention trial aimed at multiple risk factors in patients with type 2 diabetes and microalbuminuria
  - BP < 130/80, (all treated with an ACEi or ARB)
  - A1c < 6.5%
  - Total Cholesterol < 175 mg/dl
  - Total Triglyceride 150 mg/dl
  - Aspirin 80 mg daily
  - Exercise program
  - Smoking Cessation

Diabetic Nephropathy: Take Home Message 2

- Lower blood pressure < 130 / 80 mmHg
- Reducing Proteinuria
- Inhibition of Renin-Angiotensin System
- Multiple risk factor intervention
  - Glycemia
  - Dyslipidemia
  - Physical activity
  - Aspirin
  - Smoking cessation

Is Combination Therapy With An ACE Inhibitor And An ARB Safe And Effective For Patients With Diabetic Renal Disease?

ACEi- or ARB-Based Regimens for Diabetic Nephropathy Do Not Go Far Enough!

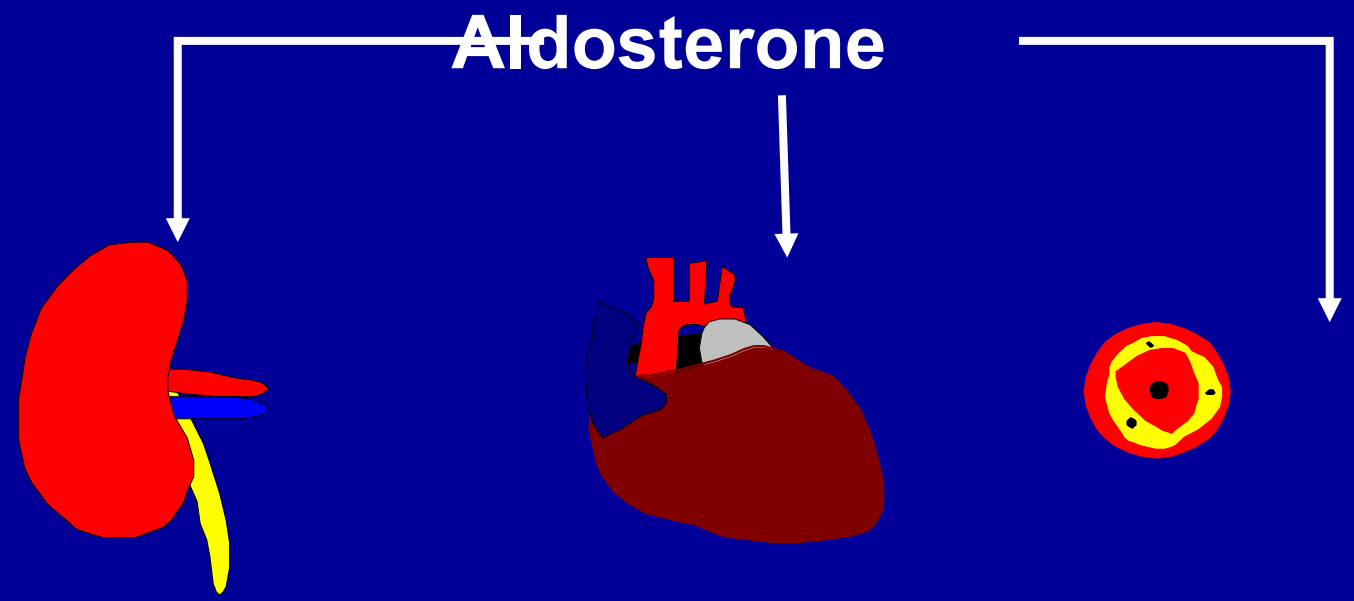


Diabetic Nephropathy: Take Home Message 4

- Small short-term studies suggest combinations of ACEi and ARB reduce proteinuria synergistically
  - Greater reductions in proteinuria with or without additional lowering in blood pressure
  - Hyperkalemia and Increased creatinine not well documented
- Safety and Efficacy of combination ACEi and ARB in diabetic with nephropathy not well established

Is There a Role for Spironolactone (or Eplerenone) in Combination with Other Drugs in Patients with Diabetic Nephropathy?

Adverse Renal and Cardiovascular Effects of Aldosterone



Glomerulosclerosis
Interstitial Fibrosis
Proteinuria

Renal Failure

Ventricular Hypertrophy
Cardiac Fibrosis
Contractile Dysfunction

Heart Failure

Endothelial dysfunction
Inflammation
Oxidative Stress

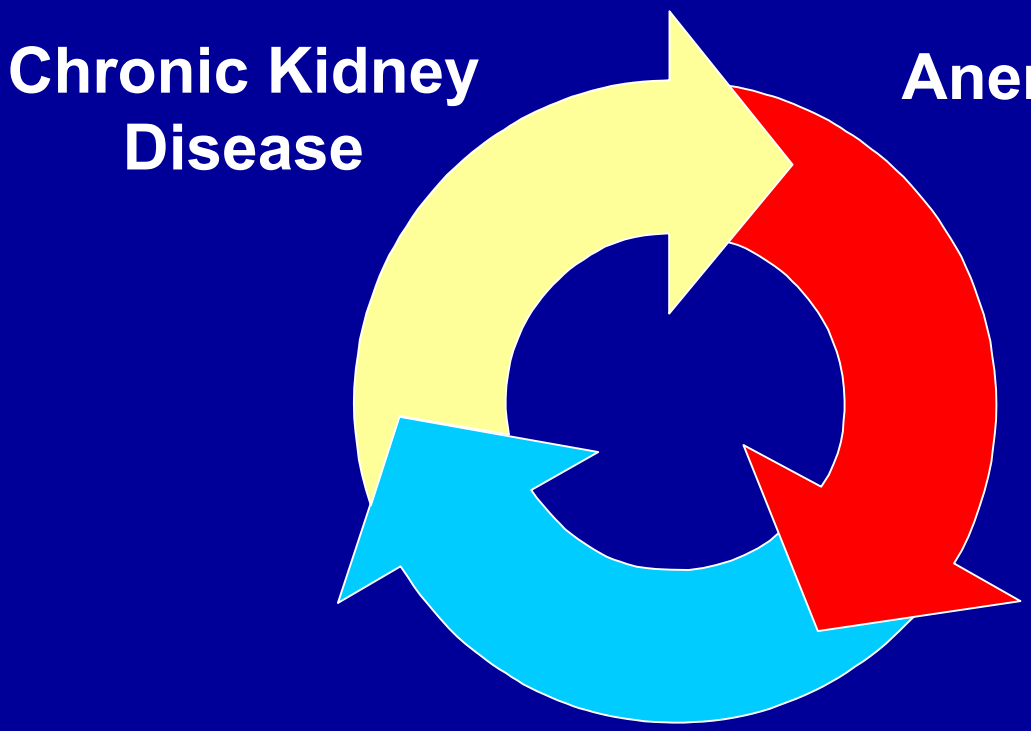
Study Hypothesis

Blockade of the renin-angiotensin system beyond ACE inhibition decreases proteinuria and slows progression of renal disease in diabetics with overt nephropathy by suppressing aldosterone synthesis or blocking the aldosterone receptor.

Diabetic Nephropathy: Take Home Message 5

- Role for spironolactone or eplerenone in diabetics with nephropathy not established
- Small, short-term studies suggest adding on is efficacious for lowering proteinuria
- Not clear if combinations are safe in larger population
- No long-term trials with cardiovascular or renal endpoints

Hypothesis: Anemia is an Important CV Risk Factor in Chronic Kidney Disease



How Should I Manage My Patient With Diabetic Nephropathy Today?

Monitoring in patients with DM

- Smoking cessation → every visit
- BP control → every visit
- Dilated eye exam → annually
- Foot examination → annually
- Serum lipid profile → annually
- HbA1c → every 3 to 6 month
- Microalbuminuria → annually
- Serum Cr → As indicated.
- ECG → annually
  - Pneumovax vaccination → one time

Influanza vaccination → annually

Diabetic Nephropathy: What about proteinuria?

- **Lower BP to goal with max dose ACEi or ARB**
- **Consider Adding: ACEi to ARB, mineralocorticoid receptor antagonist to ACEi or ARB**

Treatment of End-Stage Renal Disease (ESRD)

There are three primary treatment options for individuals who experience ESRD:

1. Hemodialysis
2. Peritoneal Dialysis
3. Kidney Transplantation

How Can You Prevent Diabetic Kidney Disease?

- Maintain blood pressure <130/80 mm/Hg
- Maintain preprandial plasma glucose 90-130 mg/dl
- Maintain postprandial plasma glucose <180 mg/dl
- Maintain A1C <7.0%

ACUTE RENAL FAILURE IN DIABETES

- **DRUG TOXICITY**
  - NSAID, ACEI, RADIOCONRAST, Etc;
- **DIURETIC EXCESS**
- **PYELONEPHRITIS**
  - PAP. NECROSIS, FUNGUS BALLS.
- **SEPTICEMIA.**
- **PIGN.**
- **DKA**
- **OTHERS**

NON-DIABETIC RENAL DISEASE

- **Retinopathy absent.**
- **RBC casts in urine.**
- **Renal insufficiency without proteinuria**

- **Low complement level**
- **Acute renal failure**
- **Overt proteinuria at the first years of diabetes**

URINARY TRACT INFECTION IN DIABETES

- Incidence only slightly increased in diabetics.
- Diabetic cystopathy → increased uti
- Tend to be more severe
- Special forms of uti
  - Papillary necrosis
  - Emphysematous pyelonephritis/cystits
  - Xanthogranulamatous pyelonephritis
  - Fungal UTI

Thank you for attention!!! •