



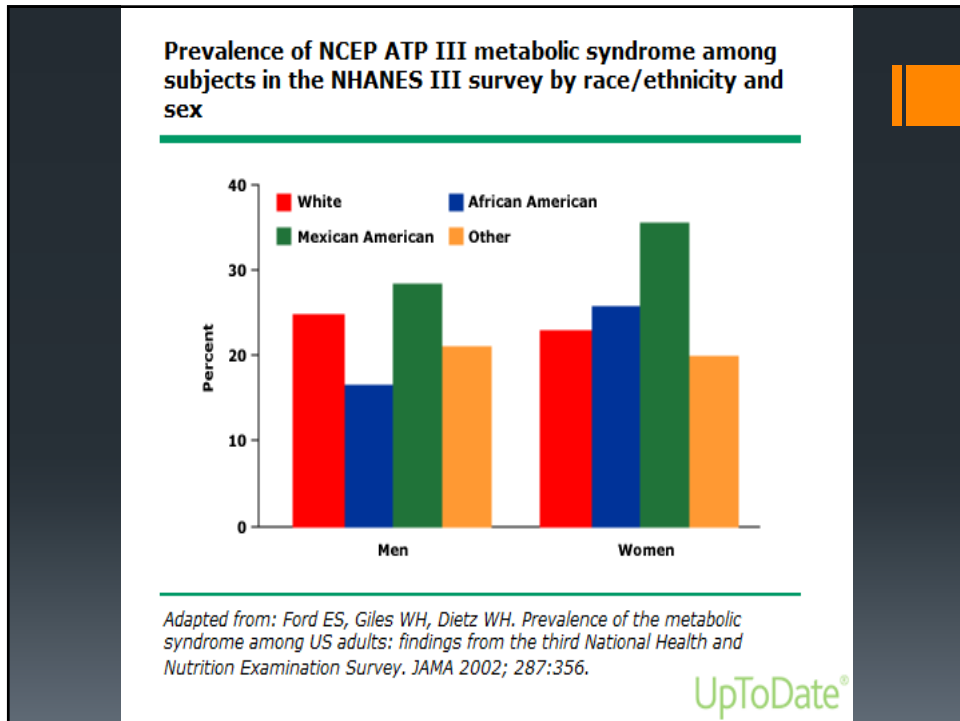
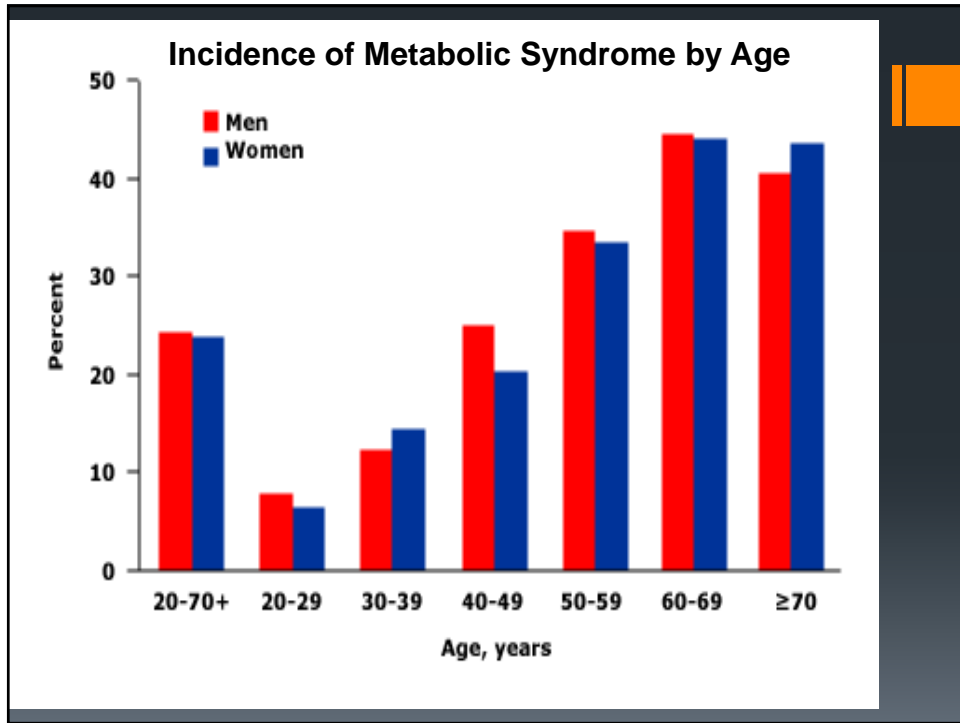
Metabolic Syndrome and Chronic Kidney Disease



Definition of Metabolic Syndrome

National Cholesterol Education Program (NCEP)
Adult Treatment Panel (ATP) III

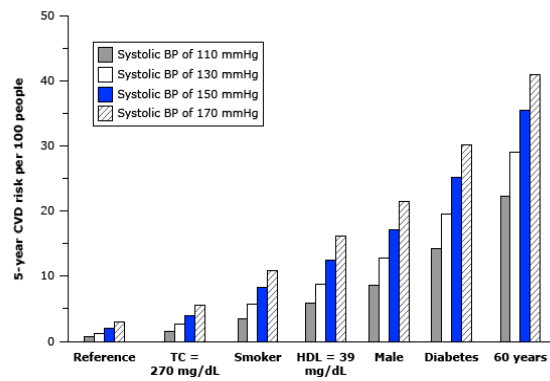
- Abdominal obesity, defined as a waist circumference in men >102 cm (40 in) and in women >88 cm (35 in)
- Serum triglycerides ≥ 150 mg/dL (1.7 mmol/L) or drug treatment for elevated triglycerides
- Serum high-density lipoprotein (HDL) cholesterol <40 mg/dl in men and < 50 mg/dl in women or drug treatment of low HDL cholesterol
- Blood pressure $\geq 130/85$ mmHg or drug treatment for elevated blood pressure
- Fasting plasma glucose (FPG) ≥ 100 mg/dL (5.6 mmol/L) or drug treatment for elevated blood glucose



Risk Factors for CVD

- Hypertension
- Cigarette smoking
- Diabetes mellitus
- Hyperlipidemia
- CKD
- Obesity
- Male sex

Additive effects of risk factors on cardiovascular disease at five years



Cumulative absolute risk of CVD at five years according to systolic blood pressure and specified levels of other risk factors. The reference category is a nondiabetic, nonsmoking 50-year-old woman with a serum TC of 154 mg/dL (4.0 mmol/L) and HDL-cholesterol of 62 mg/dL (1.6 mmol/L). The CVD risks are given for systolic blood pressure levels of 110, 130, 150, and 170 mmHg. In the other categories, the additional risk factors are added consecutively. As an example, the diabetes category is a 50-year-old diabetic man who is a smoker and has a TC of 270 mg/dL (7 mmol/L) and HDL-cholesterol of 39 mg/dL (1 mmol/L).

BP: blood pressure; CVD: cardiovascular disease; TC: total cholesterol.

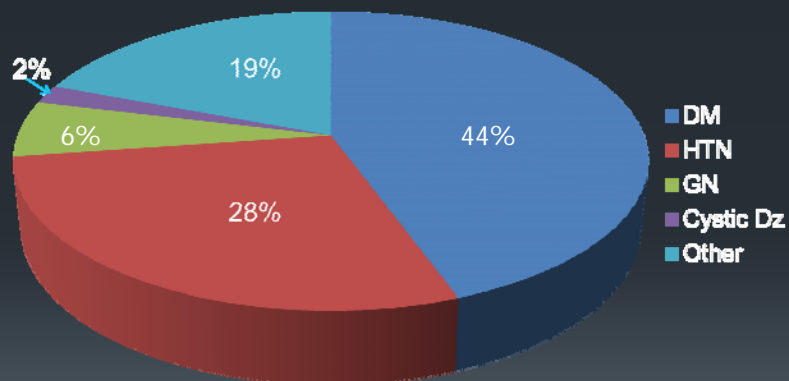
Adapted from: Jackson R, Lawes CM, Bennett DA, et al. *Lancet* 2005; 365:434.

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Risk Factors for CKD Associated with Metabolic Syndrome

- Diabetes mellitus
- Hypertension
- Cardiovascular disease
- Obesity
- Hyperlipidemia

Causes of CKD



Incidence of CKD in Patients with Metabolic Syndrome

- Risk of CKD 2.6 times higher with metabolic syndrome
- Risk of albuminuria 1.9 times higher
- 10% of patients with metabolic syndrome developed CKD
- 6% of patients without metabolic syndrome developed CKD
- Risk increases with number of components of metabolic syndrome

Therapeutic goals for management of metabolic syndrome

	Goals
Lifestyle risk factors	
Abdominal obesity	Year 1: reduce body weight 7 to 10 percent Continue weight loss thereafter with ultimate goal BMI <25 kg/m ²
Physical inactivity	At least 30 min (and preferably ≥60 min) continuous or intermittent moderate intensity exercise 5X/wk, but preferably daily
Atherogenic diet	Reduced intake saturated fat, trans fat, cholesterol
Metabolic risk factors	
Dyslipidemia	
Primary target elevated LDL-C	High risk*: <100 mg/dL (2.6 mmol/L); optional <70 mg/dL Moderate risk: <130 mg/dL (3.4 mmol/L) Lower risk: <160 mg/dL (4.9 mmol/L)
Secondary target elevated non-HDL-C	High risk*: <130 mg/dL (3.4 mmol/L); optional <100 mg/dL (2.6 mmol/L) very high risk Moderate risk: <160 mg/dL (4.1 mmol/L) Lower risk: <190 mg/dL (4.9 mmol/L)
Tertiary target reduced HDL-C	Raise to extent possible w/weight reduction and exercise
Elevated bp	Reduce to at least <140/90 (<130/80 if diabetic)
Elevated glucose	For IFG, encourage weight reduction and exercise For type 2 DM, target A1C <7 percent
Prothrombotic state	Low dose aspirin for high risk patients
Proinflammatory state	Lifestyle therapies; no specific interventions

DM: diabetes mellitus; IFG: impaired fasting glucose; bp: blood pressure.

* High risk: diabetes, known coronary artery disease.

Data from: Grundy S, Cleeman J, Daniels S, et al. Diagnosis and management of the metabolic syndrome. An American Heart Association/National Heart, Lung, and Blood Institute scientific statement. *Circulation* 2005; 112:2735.

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Hypertension in CKD

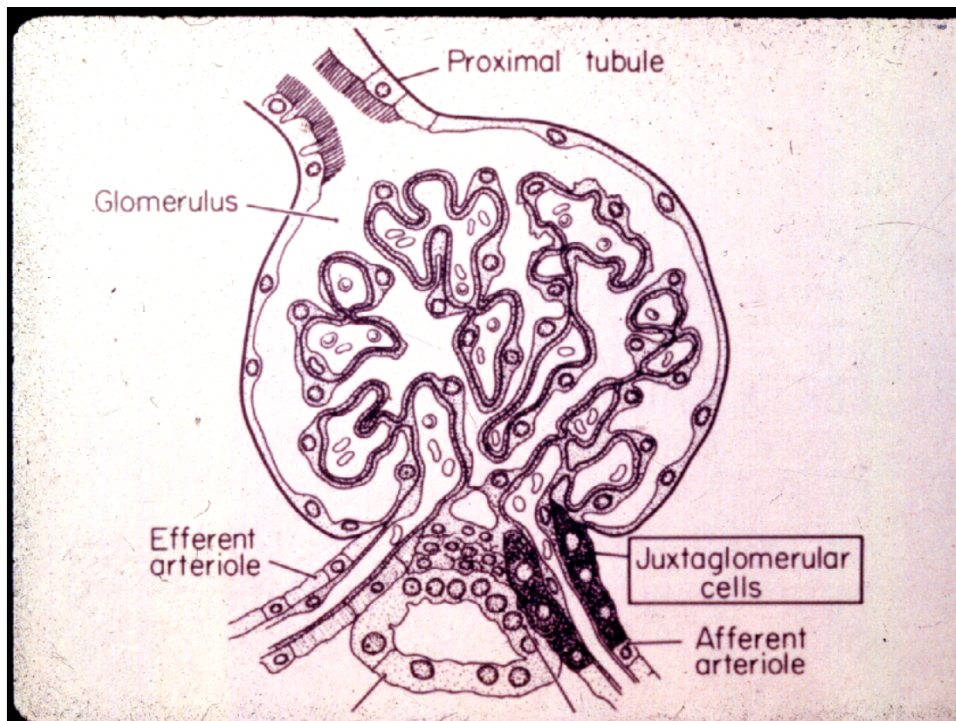
- ⊙ Both cause and result of CKD
- ⊙ **Most important factor in progression to ESRD**
- ⊙ Usually volume related in CKD patients – 80%
 - Sodium restriction essential
 - Fluid restriction not beneficial
- ⊙ Drugs:
 - Diuretic (loop or metolazone if GFR <30)
 - ACE inhibitor or ARB
 - Calcium channel blocker
- ⊙ **Always** treat

Blood pressure goals

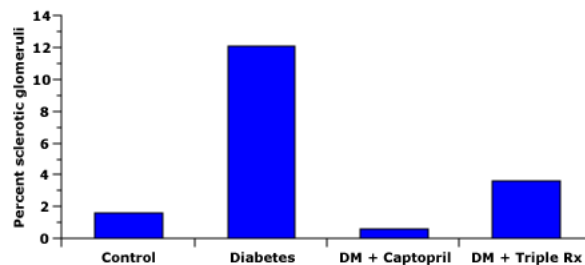
- CKD with proteinuria < 500 mg/day – < 140/90
- CKD with proteinuria > 1000 mg/day – < 130/80
- Diastolic should ideally remain > 70 in patients with CAD
- Diffuse atherosclerotic disease reduces blood flow to all organs. Need to be practical about BP control

Effects of Angiotensin II

- General vasoconstriction
- Increase aldosterone production
- Enhanced vasoconstriction of efferent arterial greater than afferent arterial
- Net effect is increased BP ($MAP = SVR \times CO$)
 - Increased systemic vascular resistance
 - Increased intravascular volume
- ACE inhibitor decreases AG-II by preventing conversion of AG-I to AG-II
- ARB prevents effect of A-II by blocking receptor
- Decreasing AG-II decreases proteinuria



ACE inhibitor is more effective than triple therapy in protecting against experimental diabetic nephropathy

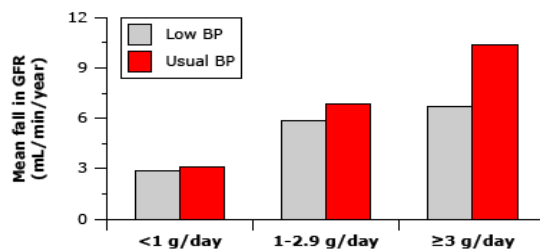


Efficacy of antihypertensive therapy in diabetic rats in reducing the number of sclerotic glomeruli at 70 weeks. Triple therapy with hydrochlorothiazide, hydralazine, and reserpine was partially protective, but captopril was completely protective, with the degree of glomerulosclerosis being less than that in control (normal) rats (left column). Captopril also normalized the intraglomerular pressure (46 mmHg) versus 64 mmHg in untreated diabetic animals and 56 mmHg with triple therapy.

Data from Anderson S, Rennke HG, Garcia DL, et al. *Kidney Int* 1989; 36:526.

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Aggressive BP control preserves renal function in proteinuric patients

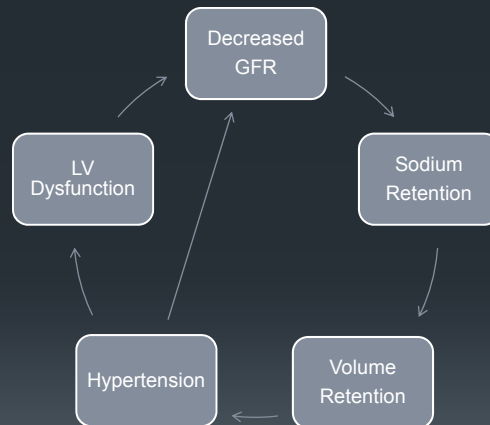


Mean fall in glomerular filtration rate (GFR) according to the degree of proteinuria in patients treated with usual blood pressure control (mean BP about 130/80 mmHg) or with more aggressive antihypertensive therapy in which the mean BP was 4.7 mmHg lower over a three-year period. The rate of fall in GFR varied directly with protein excretion, and the benefit of aggressive BP control was absent in the 420 patients excreting less than 1 g/day, modest in the 104 patients excreting between 1 and 3 g/day, and substantial (3.5 mL/min per year slower) and statistically significant in the 54 patients excreting at least 3 g/day.

Data from: Klahr S, Levey AS, Beck GJ, et al. *N Engl J Med* 1994; 330:877.

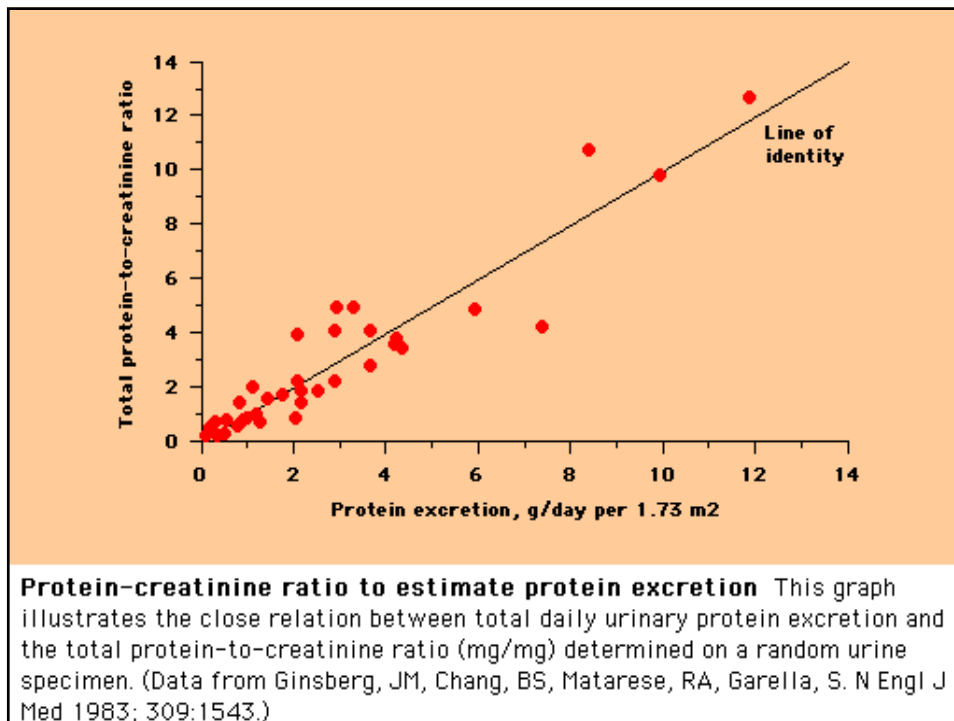
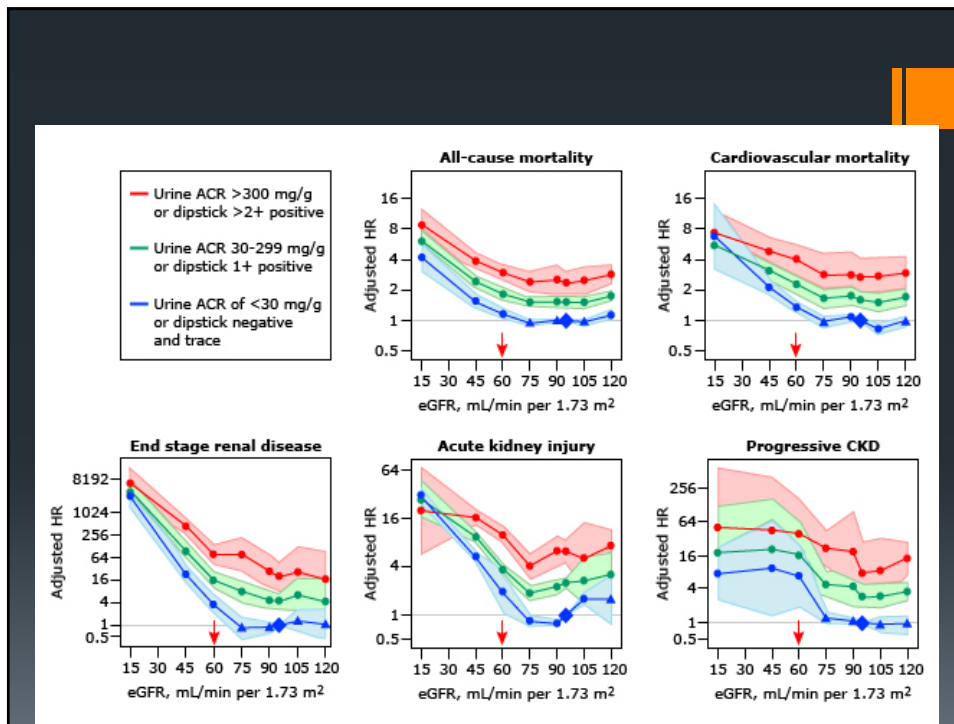
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The Cycle of *No* Life

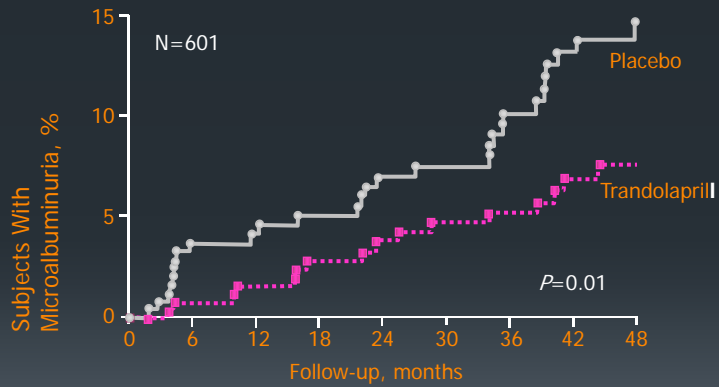


Protein in the Urine

- Proteinuria = >200 mg/day
- Microalbuminuria (now moderate albuminuria)
30 – 300 mg/day
- Macroalbuminuria (now severe albuminuria)
>300 mg/day
- Dipstick records albumin levels only above
300 mg/day
- ACE inhibitors and ARBs drugs of choice
- Decreasing proteinuria decreases rate of
progression of CKD



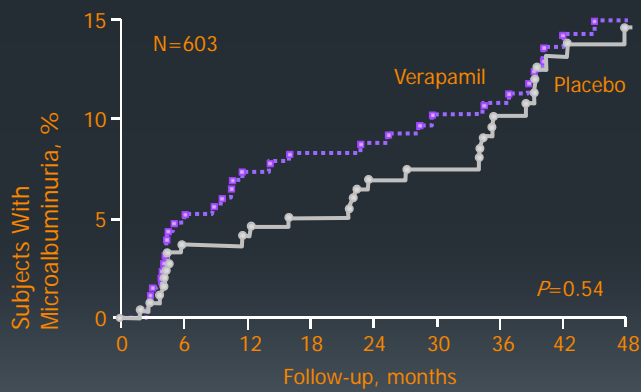
RAAS Blockade Delayed the Onset of Microalbuminuria by a Factor of 2.1 vs Placebo in Type 2 Diabetes



Bergamo Nephrologic Diabetes Complications Trial (BENEDICT)

Ruggenenti P et al. *N Engl J Med.* 2004;351:1941-1951.

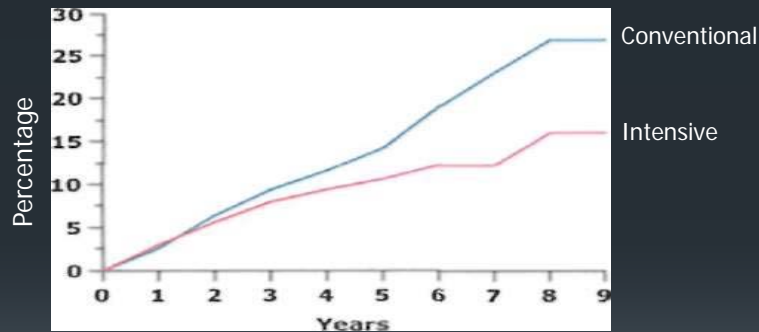
Verapamil Does Not Delay the Onset of Microalbuminuria in Type 2 Diabetes



Bergamo Nephrologic Diabetes Complications Trial (BENEDICT)

Ruggenenti P et al. *N Engl J Med.* 2004;351:1941-1951.

Intensive vs. Conventional Control of Type I DM



Incidence of microalbuminuria over 9 years ($p < 0.04$)

Treatment of Type 2 DM in CKD

- Preferred sulfonylurea is glipizide (Glucotrol)
 - Shorter half life
 - 2.5 – 10 mg daily
 - Should probably avoid sulfonylureas if GFR <45
- Rapaglinide (Prandin) may be used instead of glipizide
 - Start with 0.5 mg 30 minutes before meals
 - Max 16 mg per day
- Metformin use with caution in CKD
 - Do not use if GFR <30 ml/min
 - May use if GFR >45 ml/min
 - GFR 30 – 44 ml/min not defined, but probably okay
 - 500 mg bid to 1000 mg bid
- Sitagliptin (Januvia)
 - GFR 30 – 49 ml/min 50 mg per day
 - GFR <30 ml/min 25 mg/day
- Sodium-glucose co-transporter 2 (SGLT2)
 - Avoid use GFR 30 – 45
 - Contraindicated if GFR <30
- Insulin usually required



Obesity and CKD

- May simply be due to increased incidence of
 - Diabetes mellitus
 - Hypertension
 - Hyperlipidemia
- Very obese can develop focal segmental sclerosis



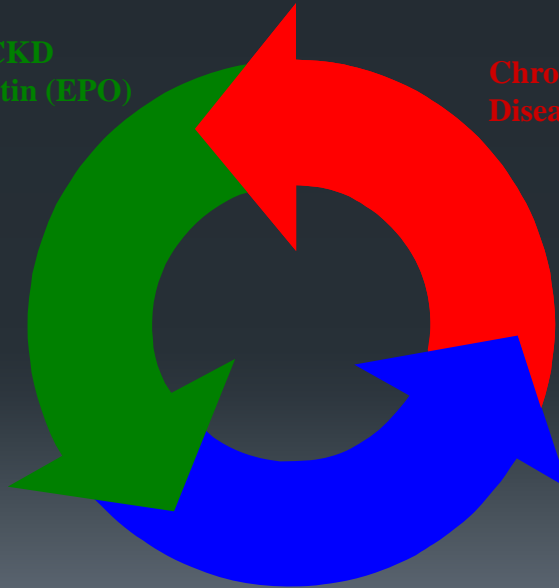
Hyperlipidemia and CKD

- Increased rate of renal deterioration seen experimentally only
- Increase incidence of CVD may be mechanism
- Hyperlipidemia should be treated in most regardless of concomitant CKD

The Critical Links

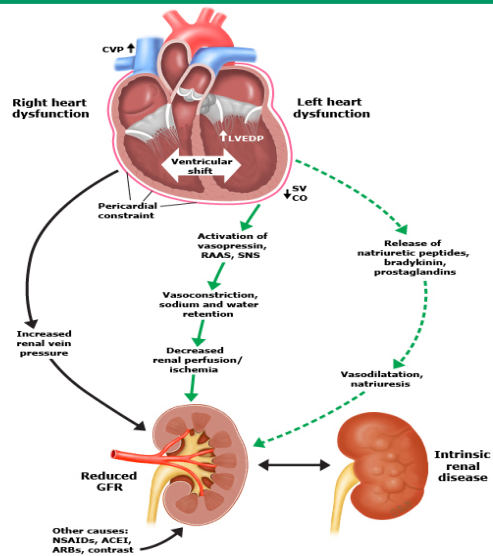
Anemia of CKD
Erythropoietin (EPO)
Deficiency

Chronic Kidney
Disease (CKD)



Cardiovascular Disease (CVD)

Pathophysiology of cardiorenal syndrome



ACEI: angiotensin converting enzyme inhibitor; ARBs: angiotensin II receptor blockers; CO: cardiac output; CVP: central venous pressure; LVEDP: left ventricular end-diastolic pressure; ETS: endothelins; NO: nitric oxide; NP: natriuretic peptides; NSAIDs: nonsteroidal antiinflammatory drugs; RAAS: Renal angiotensin aldosterone system; SNS: sympathetic nervous system; SV: stroke volume; GFR: glomerular filtration rate.

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Types of Cardiorenal Syndrome



- Type 1 (acute) – Acute HF results in acute kidney injury
- Type 2 – Chronic cardiac dysfunction (eg, chronic HF) causes progressive chronic kidney disease
- Type 3 – Abrupt and primary worsening of kidney function acute cardiac dysfunction which may be manifested as heart failure
- Type 4 – Primary CKD contributes to cardiac dysfunction, which may be manifested as coronary artery disease, heart failure or arrhythmia
- Type 5 (secondary) – Acute or chronic systemic disorders (eg, sepsis or diabetes mellitus) that cause both cardiac and renal disease