The Heart and the Kidney

Jeff Kaufhold, MD, FACP

Jan 2016

Summary

- Case
- Why this matters
- Normal Physiology
- Abnormal Physiology
- ARF and CKD staging
- Renal Syndromes related to the heart
- Cardiorenal Syndrome
- Contrast induced acute Kidney Injury
- Treatment considerations in CRS

Objectives

- 1. Normal physiology of heart and kidney
- --- 25% of cardiac output goes to the kidneys
- --- Renin angiotensin - aldosterone cascade regulates blood pressure, and can become pathologic

- 2. Heart disease can cause acute renal failure by several mechanisms:
- Contrast injury, cholesterol emboli as a consequence of cardiac cath
- Impaired output from arrhythmia or MI
- medication effects from ACE or diuretics
- 3. Kidney disease has significant negative effects on the heart.

Case

- 56 yo man with CHF admitted with 2 week hx of worsening symptoms. Has DM-2, on metformin, Lisinopril, lasix metolazone and digoxin
- BP 88/60, P 95 R 20. JVD and S3 present. Edema to mid thigh
- He is a bit confused, and hands are cold/ clammy.
- Creatinine 3.1 up from 1.1. sodium 133
- CXR shows CHF

case

- In addition to IV diuretics, which of the following is most appropriate management?
- A. Dobutamine
- B. IABP
- C. Milrinone
- D. Right heart cath

Case:

- Correct answer:
  - A - add dobutamine.
  - This will improve CO
  - Milrinone is excreted by the kidneys and will vasodilate – lowering BP
  - IABP would be consideration if he does not respond rapidly to dobutamine
  - Swan can be helpful to guide therapy, especially if he does not respond as expected.

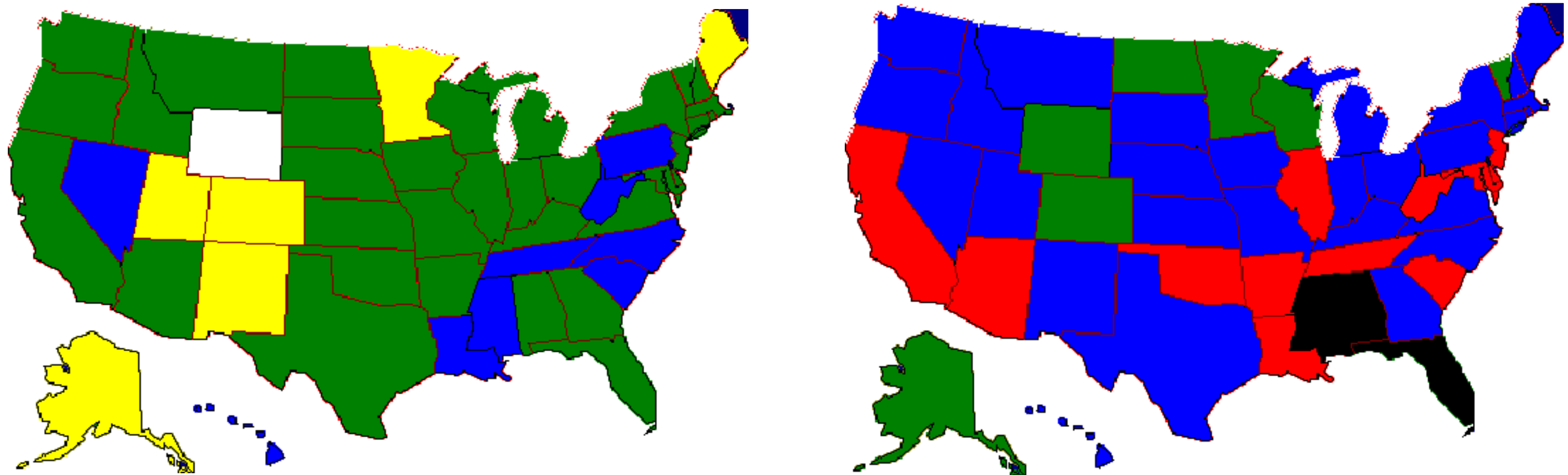
Burden of Atherosclerotic Vascular Disease: CAD, CVD, PVD

- Prevalence–25 million in United States
- Annual rates
  - Myocardial infarction–1.2 million
  - Strokes–700,000
  - CVD mortality–931,000 (a death every 30 seconds)
  - Cardiac catheterization–1.4 million
  - Percutaneous revascularization–1.1 million
  - Surgical revascularization–571,000
- Annual cost = $250 billion

American Heart Association. *2004 Heart and Stroke Statistical Update*. At: http://www.americanheart.org.

Prevalence of Diabetes Among US Adults

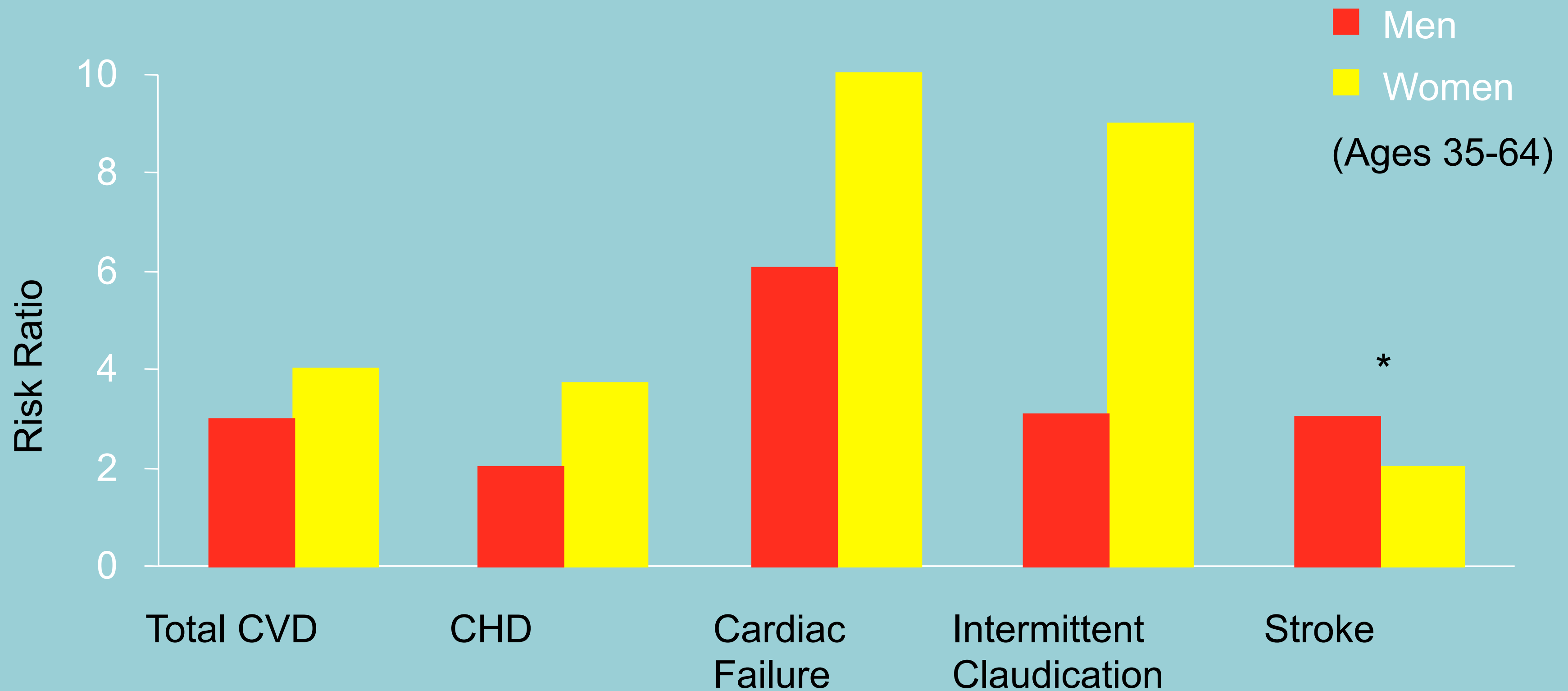
1991 2001



No Data <4% 4%-6% 7%-8% 9%-10% >10%

Mokdad AH et al. *JAMA*. 2003;289:76-80.

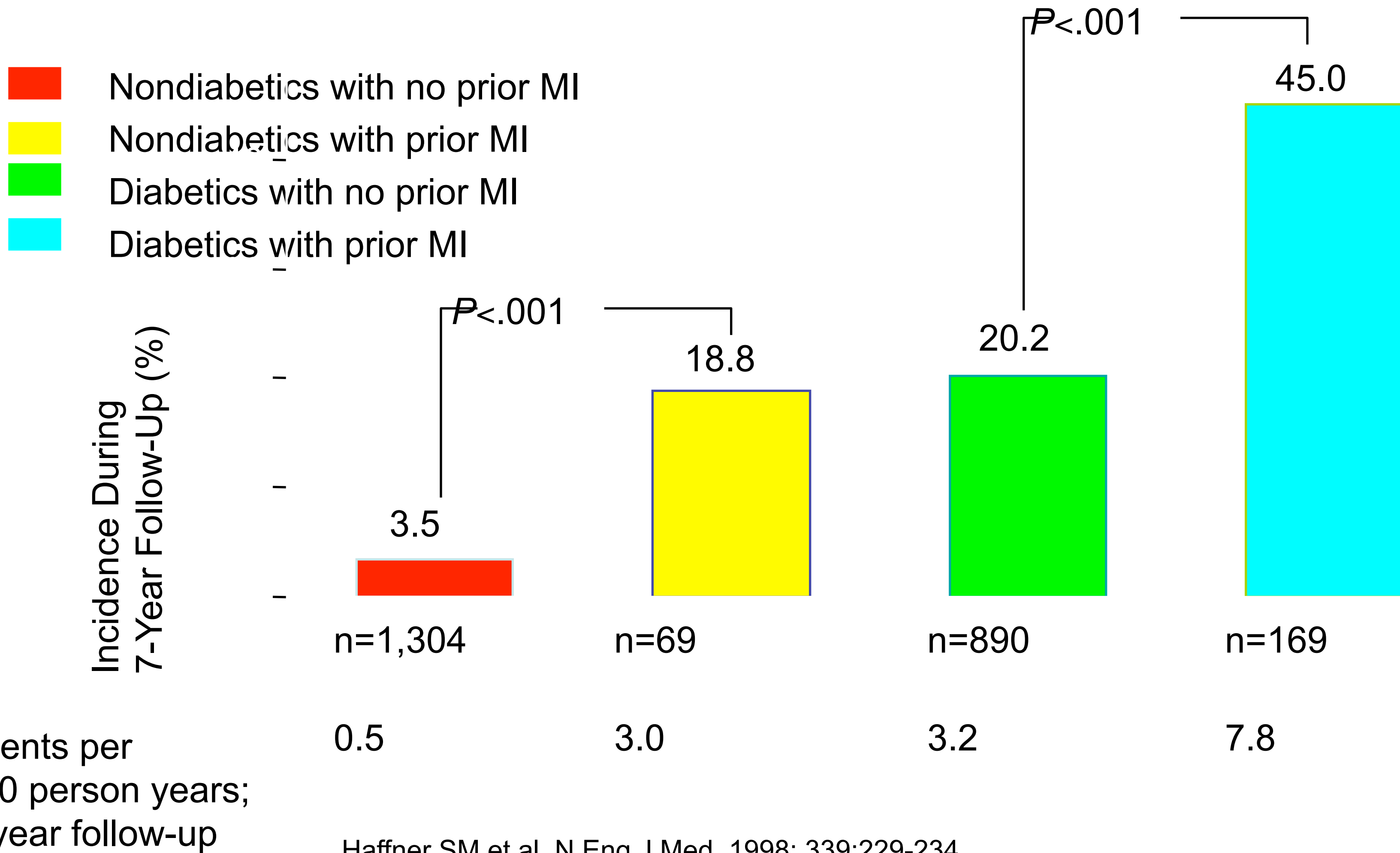
Framingham Heart Study 30-Year Follow-Up of CVD Events in Patients With Diabetes



P<.001 for all values except **P*<.05.

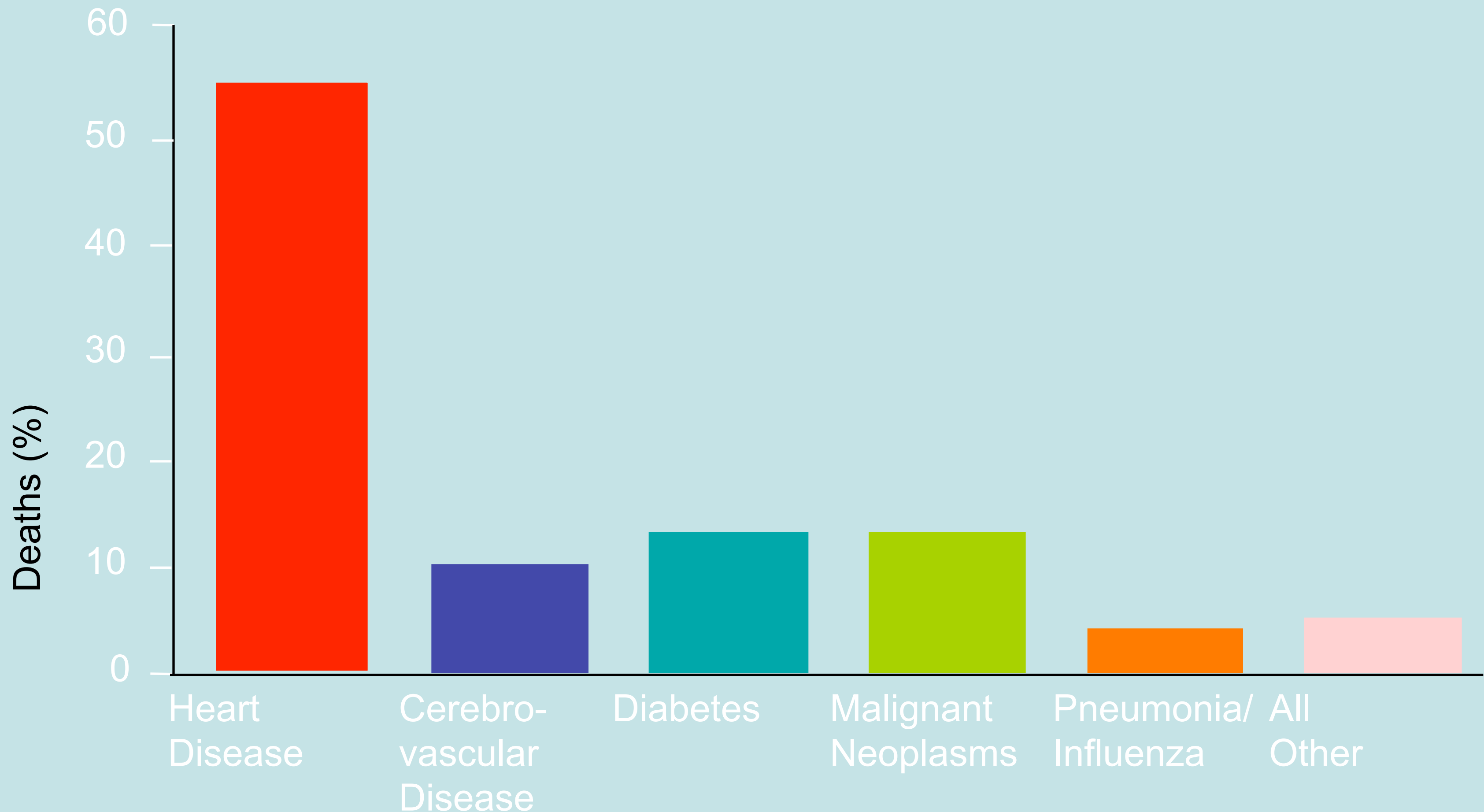
Wilson PWF, Kannel WB. In: Ruderman N et al, eds. *Hyperglycemia, Diabetes and Vascular Disease*. 1992.

Incidence of Fatal or Nonfatal MI in Patients With and Without Diabetes



Haffner SM et al. N Eng J Med. 1998; 339:229-234

Approximate Distribution of Causes of Death in Persons With Diabetes, Based on US Studies



Based on four cohort studies conducted 1971-1988.

Geiss LS et al. *Diabetes in America*. Bethesda, Md: National Institutes of Health; 1995:233-257.

Normal Physiology

- 25% of cardiac output goes to the kidneys
- Renin/Angiotensin/Aldosterone cascade regulates blood pressure, and can become pathologic
- Brain and atrial Natriuretic peptides, along with Aldosterone, regulate volume.

Abnormal Physiology

- Dysregulation of Renin/AT/Aldosterone cascade can lead to vascular and myocardial injury,
- Malignant Hypertension,
- Flash Pulmonary Edema.
- Alterations in Effective arterial blood volume (EABV) lead to upregulation of angiotensin and aldosterone, ADH

New Terminology
ARF - RIFLE criteria

- **Risk** low uop for 6 hours, creat up 1.5 to 2 times baseline
- **Injury** creat up 2 to 3 times baseline, low uop for 12 hours
- **Failure** Creat up > 3 times baseline or over 4, anuria
- **Loss of Function** Dialysis requiring for > 4 weeks
- **ESRD** Dialysis requiring for > 3 months

CKD prevalence in world Populations

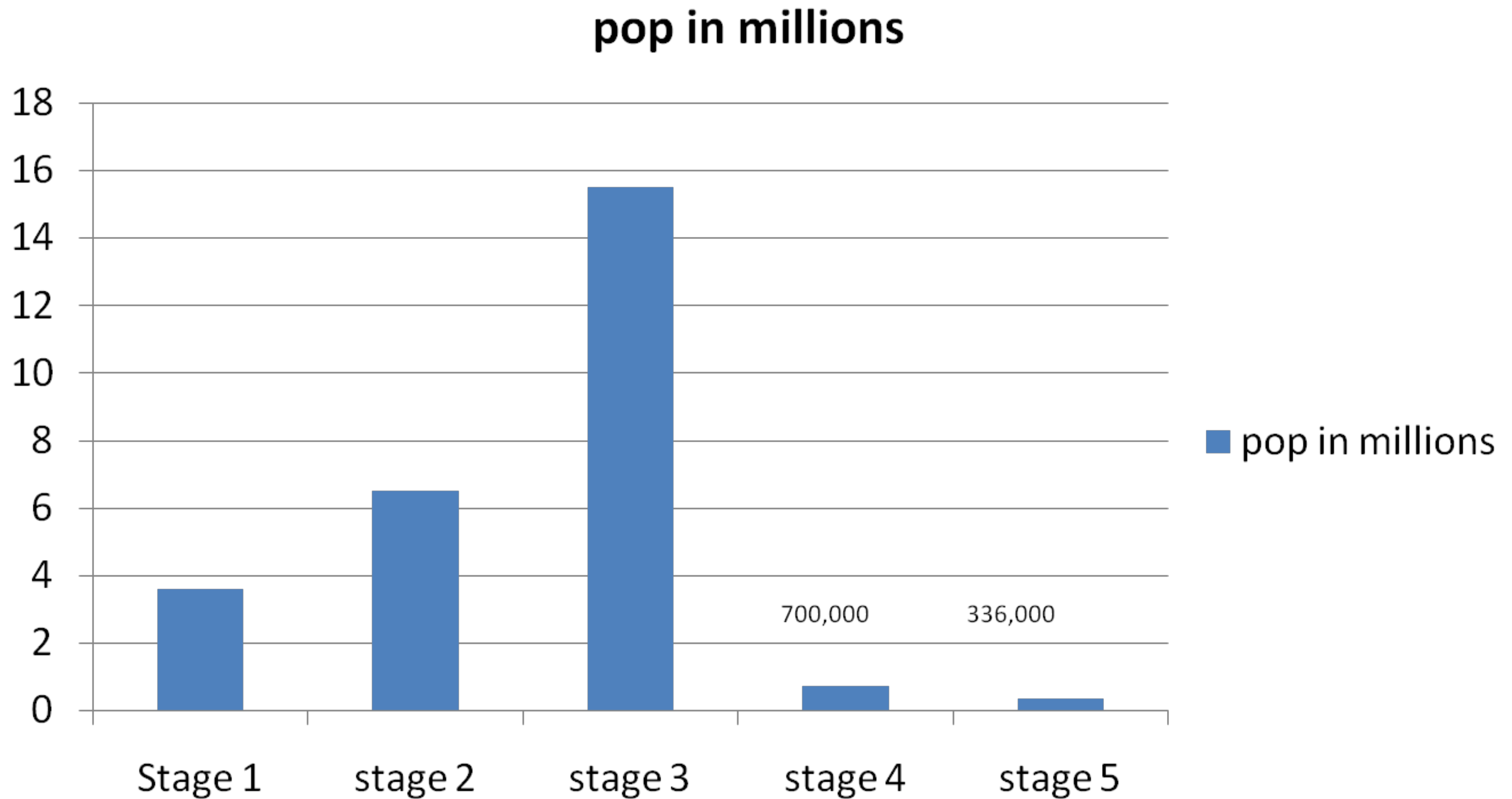
Country	Population	CKD est.
– China	1.298.847.624	35.336.295
– India	1.065.070.607	28.976.185
– Indonesia	238.452.952	6.487.322
– Pakistan	159.196.336	4.331.076
– Philipines	86.241.697	2.346.281
– Vietnam	82.662.800	2.248.914

- Assumes 2.72 % incidence

CKD Stages

- Stage 1. Normal function with known dz
- Stage 2. GFR 60-80
- Stage 3. GFR 30-60
- Stage 4. GFR 15-30.
- Stage 5. GFR less than 15.
- Stage 6. ESRD on dialysis.

US Population with CKD



Coresh, Selvin, Stevens. Prevalence of CKD in the US. JAMA.2007;298(17)2038.

Impact of renal disease on the heart

- Why do patients with acute renal failure die?
- A. Hyperkalemia/ arrhythmia?
- B. GI Bleeding?
- C. Sepsis?
- D. Fluid overload/ hypoxia?
- E. Heart attack/ stroke?

Impact of renal disease on the heart

- Why do patients with acute renal failure die?
  - #1 Sepsis
  - # 2 Cardiovascular disease
    - (MI, stroke, CHF)
  - # 3 GI bleeding

Impact of renal disease on the heart

- Why do patients with Chronic renal failure die?
  - # 1   Cardiovascular disease
  - (MI, stroke, CHF)
  - Sepsis
  - GI bleeding

Cardiorenal Syndrome (CRS)

Syndrome in which a fairly normal kidney is dysfunctional because of a diseased heart, with the assumption that in the presence of a healthy heart, the kidney would function normally.

CRS type 1
Acute CRS
Acute heart injury leads to AKI

- Acute Renal Failure due to cardiogenic shock or reduced cardiac output.
- Decreased response to Diuretics
- Independent marker for initial and 1 year mortality in the face of CHF or MI.
- Another marker for increased mortality risk in CHF/ CRS is hyponatremia.

Renal Syndromes related to Heart Disease

- ARF
  - Due to contrast, cholesterol emboli
  - Reduced Cardiac Output from MI, arrhythmia
  - Med effects (ACE/ARB/Tekturna)
  - Overdiuresis from diuretics
  - Effects of NSAID's on the heart and kidneys-→

NSAID and the heart

- In a meta-analysis of 138 randomized trials, COX-2 inhibitors were associated with a significant increase in the risk for

    myocardial infarction (MI) (risk ratio [RR], 1.86; 95%

    confidence interval [CI], 1.33-2.59; *P* =.0003)

  – and vascular events (RR, 1.42; 95% CI, 1.13-1.78; *P* = .003) compared with placebo.
- Animal studies suggest that the adverse cardiovascular effects observed with COX-2 inhibitors are due to enhanced endothelial thrombosis (as a result of reduction in prostacyclin synthesis), sodium and water retention, and loss of the protective effects of COX-2 upregulation in the setting of MI, resulting in larger infarction size and thinning of the left ventricular wall in the infarct zone.
    - Timmers L, Sluijter JP, Verlaan CW, et al. Cyclooxygenase-2 inhibition increases mortality, enhances left ventricular remodeling, and impairs systolic function after myocardial infarction in the pig. Circulation. 2007;115:326-332.

CRS Type 2 (chronic CRS)

chronic heart failure leads to chronic kidney injury

Chronic CHF results in poor flow to kidney and chronic renal dysfunction

ESCAPE trial (Evaluation Study of CHF and Pulmonary Catheterization Effectiveness) found that only right heart pressures correlated with renal dysfunction, suggesting that renal vein pressure increases (CVP) lead to renal vascular congestion and loss of function.

Renal Syndromes related to Heart Disease

- Chronic Kidney Disease
  - Due to recurrent injuries from above insults
  - Chronic decrease in renal perfusion from poor pump function (cardiorenal syndrome)
  - Reduced effective arterial blood volume results in secondary increases in Renin/ AT and Aldosterone, leading to hypervolemia
  - Reduced EABV leads to increased ADH production which causes hyponatremia

CRS Type 3 (Acute Renocardiac Syndrome)

Abrupt worsening of kidney function leads to acute cardiac dysfunction, from fluid overload, Hyperkalemia, ischemia.

Uremia and acidosis lead to depressed cardiac contractility.

Angiotensin is a direct endothelial cell toxin and also causes myocardial cell injury.

Renal Artery Stenosis is a unique cause of CRS 3.

Causes flash pulmonary edema/ severe hypertension

Dialysis induced fluid and electrolyte shifts also cause acute cardiac dysfunction, arrhythmia.

CRS Type 4 (Chronic Renocardiac Syndrome)

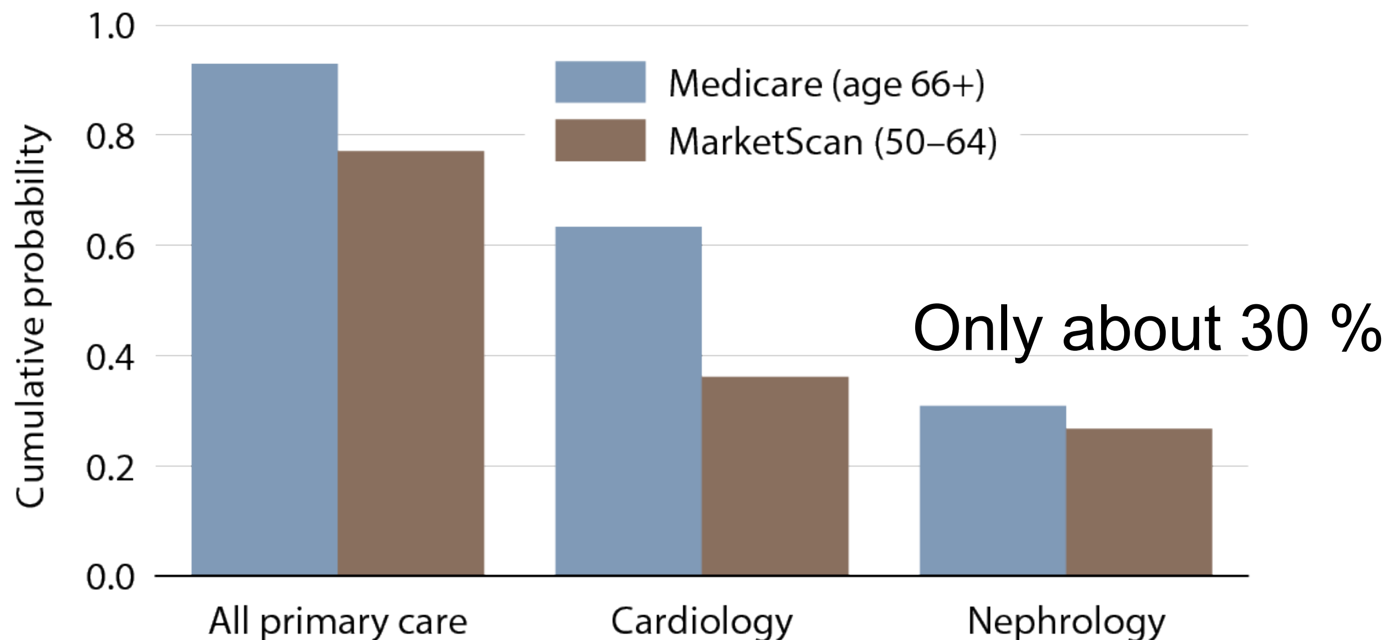
Primary CKD with resultant impact on the heart from HTN, Fluid overload, macroalbuminuria.

Leads to ventricular hypertrophy, diastolic dysfunction, marked increased risk of cardiovascular events.

Risk is heightened due to the reduced use of ACE, ARB, and contrast dye studies in pts with CKD. CKD pts are much less likely to be treated with these therapies, as well as B-blockers, Aspirin and Plavix.

Cumulative probability of a physician visit in the year following CKD diagnosis by physician specialty & dataset

Figure 2.10 (Volume 1)



Patients alive and eligible all of 2008, CKD diagnosis represents date of first CKD claim during 2008, physician claims searched during 12months following that date.

Renal Syndromes related to the heart (type 4 CRS)

- Cardiomyopathy
  - Due to uremia, acidosis (systolic)
  - Chronic hypertension leads to LVH (diastolic and systolic)
  - Diabetes also leads to LVH (diastolic)
  - Fluid overload (diastolic)
  - Can be confused with sleep apnea/ other causes of right heart failure

CRS Type 5 (Secondary CRS)

Systemic conditions which affect both the heart and the kidney include:

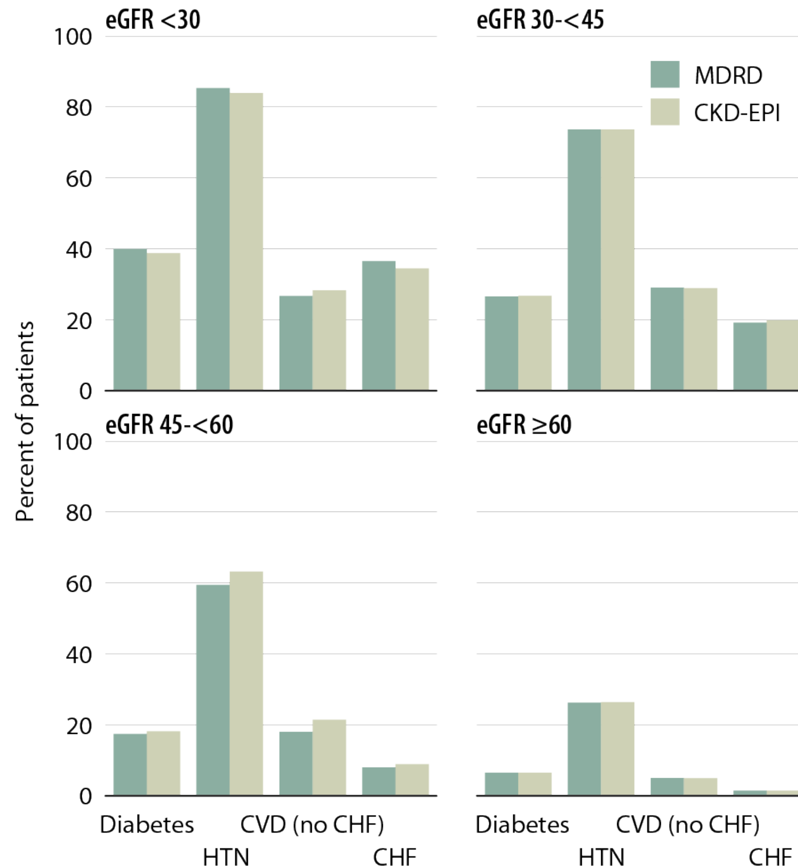
Diabetes,
Amyloidosis,
Vasculitis,
Sepsis,
SLE,
Sarcoidosis.

Treatment of CRS

- Prevent contrast induced AKI
- Treatment considerations in diabetics
  - Use of coreg vs other beta blockers
- Treatment of Hypertension
- Recognize and Treat OSA
- Recognize risk factors for CRS
  - Microalbuminuria as marker of vascular disease
  - Use of novel agents

Prevalence of comorbidity in NHANES 2001–2008 participants, by risk factor, expanded eGFR categories, & method used to estimate GFR

Figure 1.5 (Volume 1)

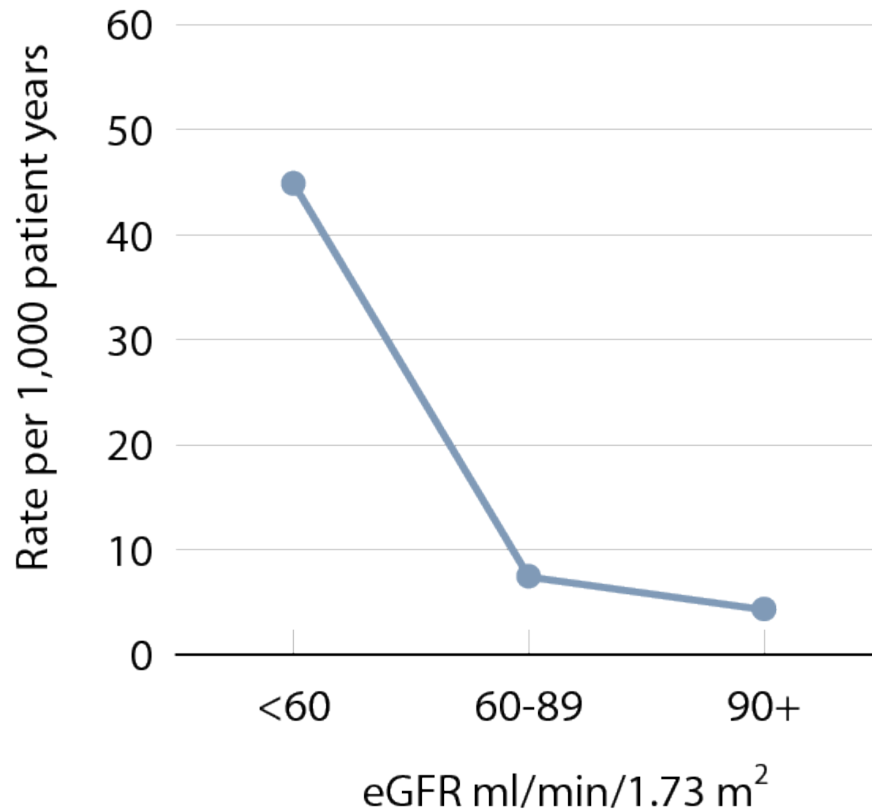


NHANES 2001–2008 participants age 20 & older.

Note how HTN is bigger problem as GFR falls

Mortality rates in NHANES 1999-2004 participants, by eGFR: MDRD equation

Figure 1.11 (Volume 1)



NHANES 1999–2004 participants age 20 & older.

How to improve CV Morbidity in CKD?

1. Early referral to Nephrology
2. Consider a patient with CKD 4 , 5, and ESRD as having the same risk as a patient who HAS ALREADY HAD THEIR FIRST HEART ATTACK.

Beta Blocker
Aspirin
Statin
restart ACE inhibitor or ARB once pt on dialysis

To prevent a vessel wall thrombus

Hall Thrombus

Seen in most teaching hospitals

Risk Factors for Contrast Nephropathy

- Age over 60
- Diabetes
- Pre-Renal States
  - CHF
  - NSAIDS, ACE Inhibitors, Diuretics
- Proteinuria Includes, but not limited to Myeloma.
- Pre-existing Renal Disease

Etiology of Contrast induced AKI
Two phases of injury:

- Immediate phase:
  - Contrast load (similar to Gentamicin or Amphotericin) causes intense renal vasoconstriction with immediate oliguria
  - Fluid shifts into vascular space, so patients can go into flash pulmonary edema
  - Can be treated with dialysis
  - Prevented by giving any sodium containing fluid – bicarb is not magical

Etiology of Contrast induced AKI
Two phases of injury:

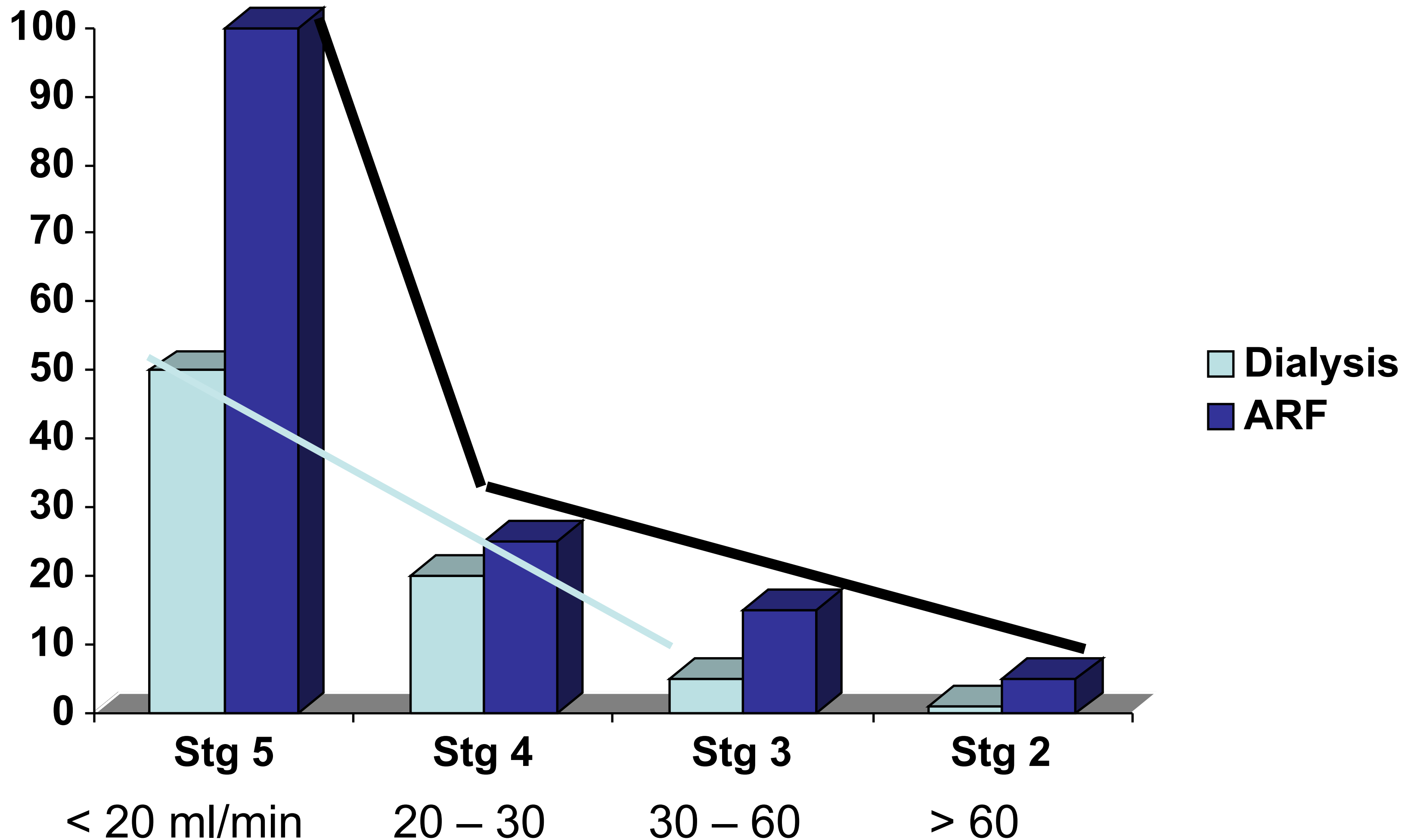
- Delayed/ secondary phase
  - Occurs at the time of the contrast infusion, but creatinine starts climbing 3-7 days after the contrast exposure
  - Due to direct tubular toxicity of the contrast (or gent/ Amphotericin)
  - Due to reactive oxygen radicals
  - Prevented by mucomyst

Etiology of Contrast induced AKI Two phases of injury:

- Delayed/ secondary phase
  - Prevented by mucomyst
  - Mucomyst provides sulfhydryl groups to the Pentose Phosphate shunt, which makes NADP and other free oxygen scavengers
  - PPS runs concurrently with the Krebs cycle, which is producing ATP and a lot of free oxygen radicals.

Risk of CN By Stage of CKD

The Kaufhold Nomogram



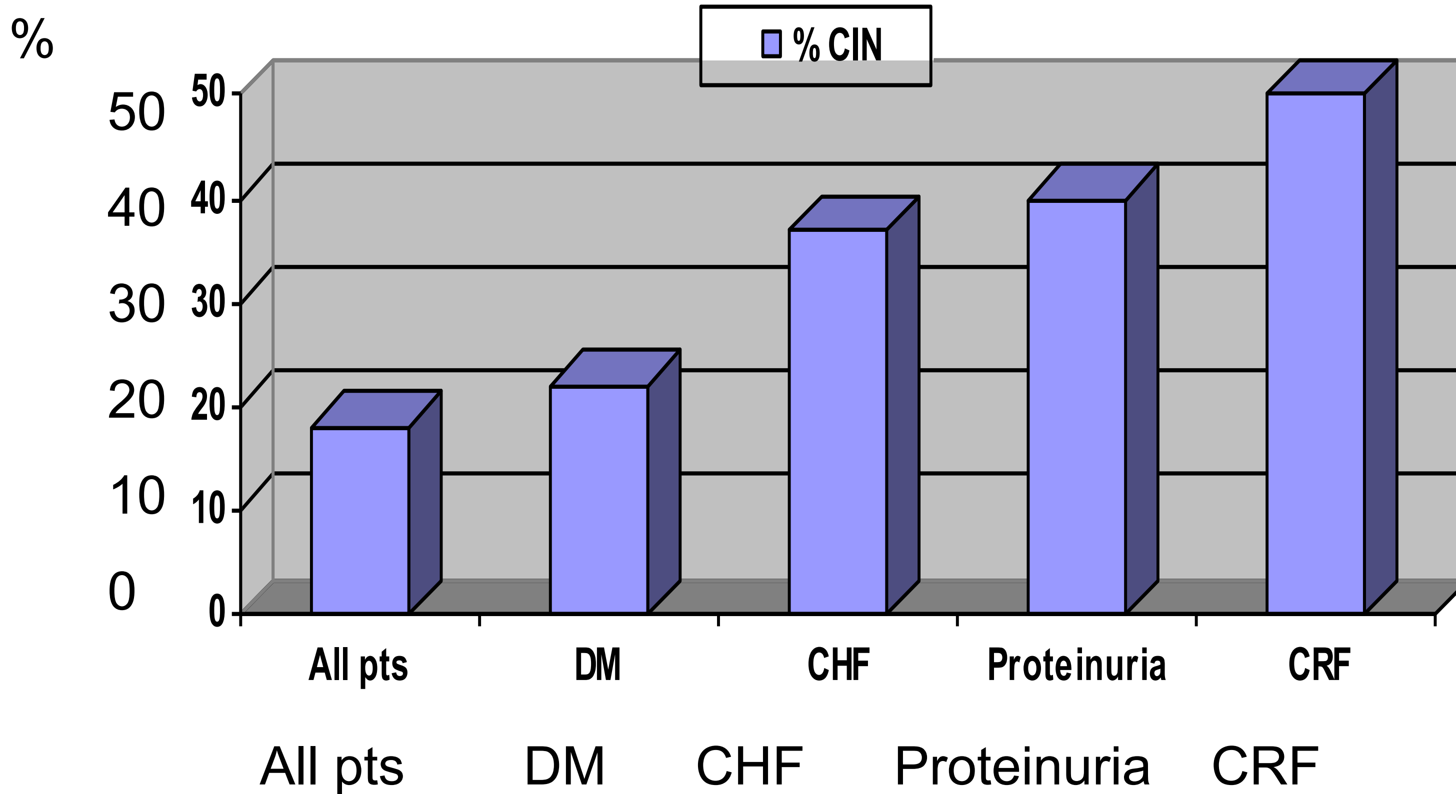
Incidence of CN
NAOD study 2005

- Nationally 4%

- GVH 2005 18%
- GVH 2006 5

- DHH 4%

Contrast Nephropathy at GVH 2005

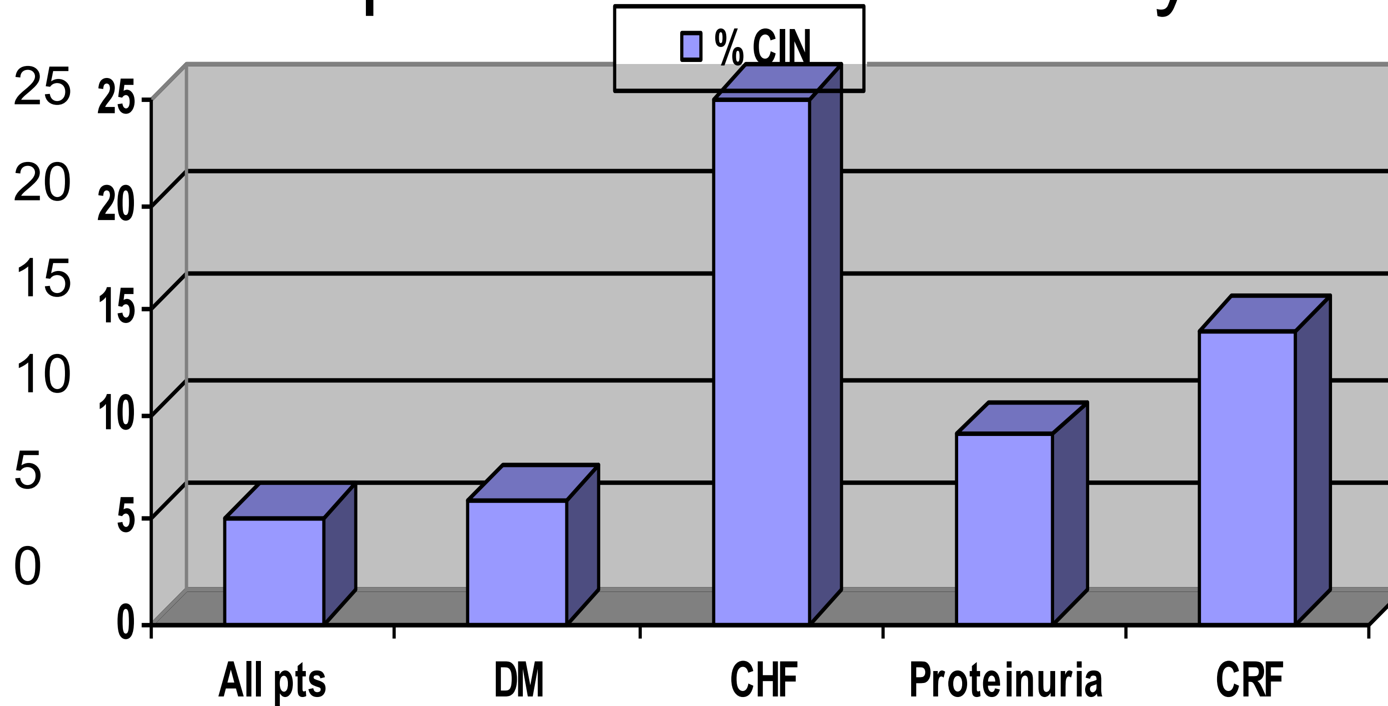


Policy / Recommendations

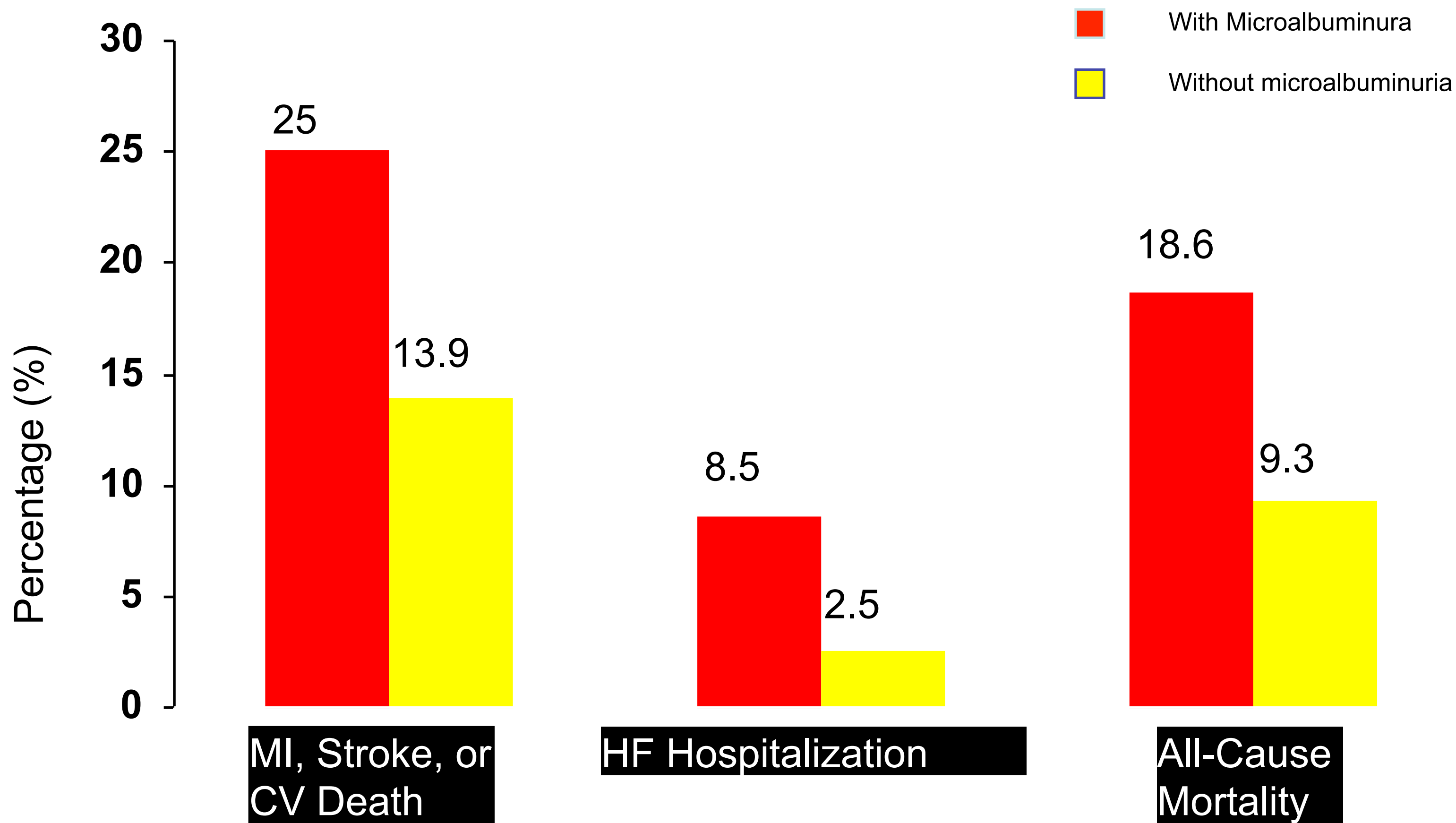
- Stop ACE/ ARB, NSAIDs, Diuretics day before procedure
- IVF for everyone
  - NS for low risk pts
  - Bicarb for high risk pts?
- Urinalysis for all pts/ calculate Creat Clear for all pts.
  - Proteinuria or creat clear < 40 considered High risk.
- Mucomyst for High risk pts
- Limit volume of contrast in High Risk Pts.
- Consider Nephrology consult if considering Mannitol, Corlepam, or identified as high risk.

Contrast Nephropathy GVH 2006

% • After Implementation of Policy

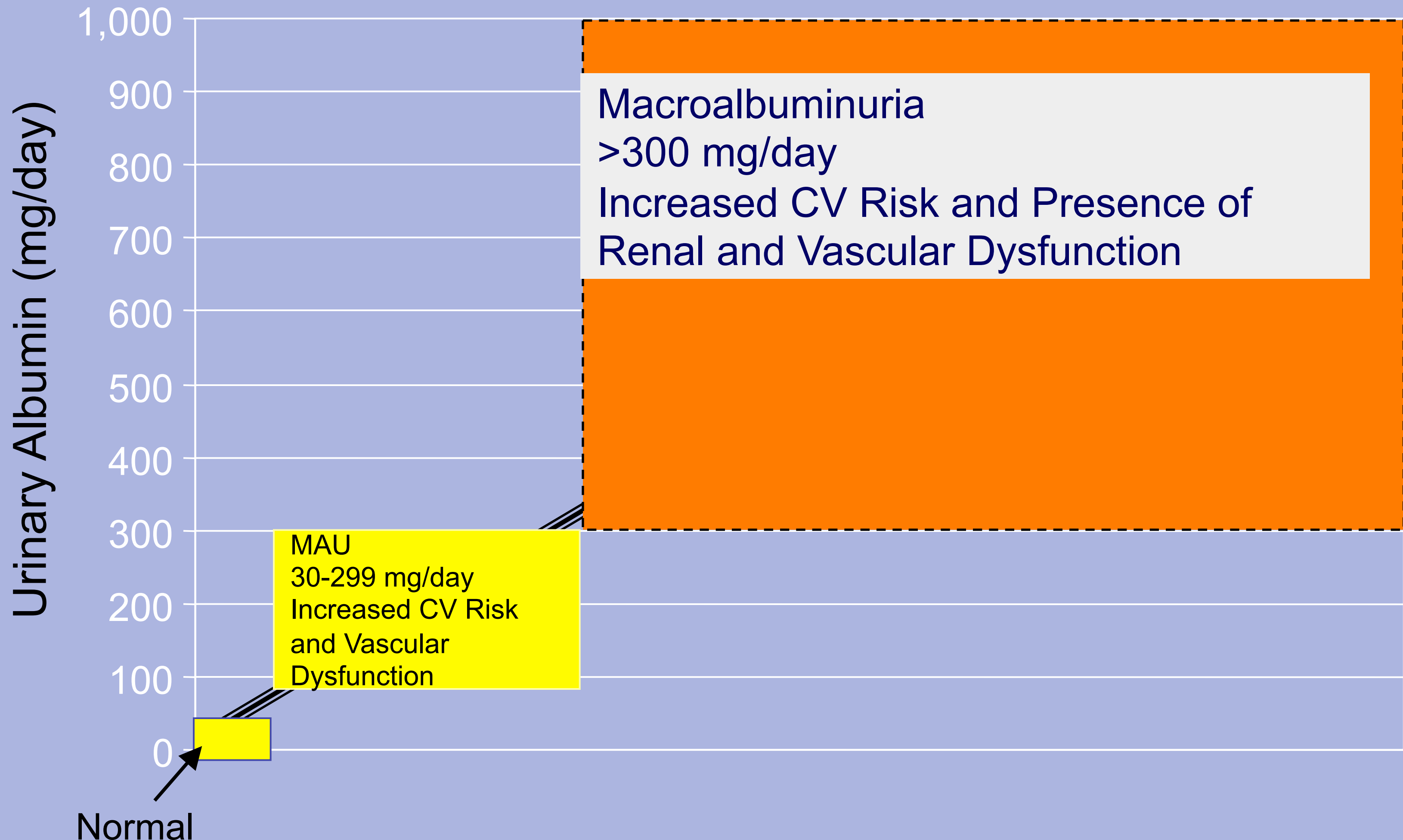


Association of Microalbuminuria With CV Events in Patients With Diabetes



Gerstein HC et al. JAMA. 2001;286:421-426

Presence of MAU Indicates a Potential Increased Risk for CV Events



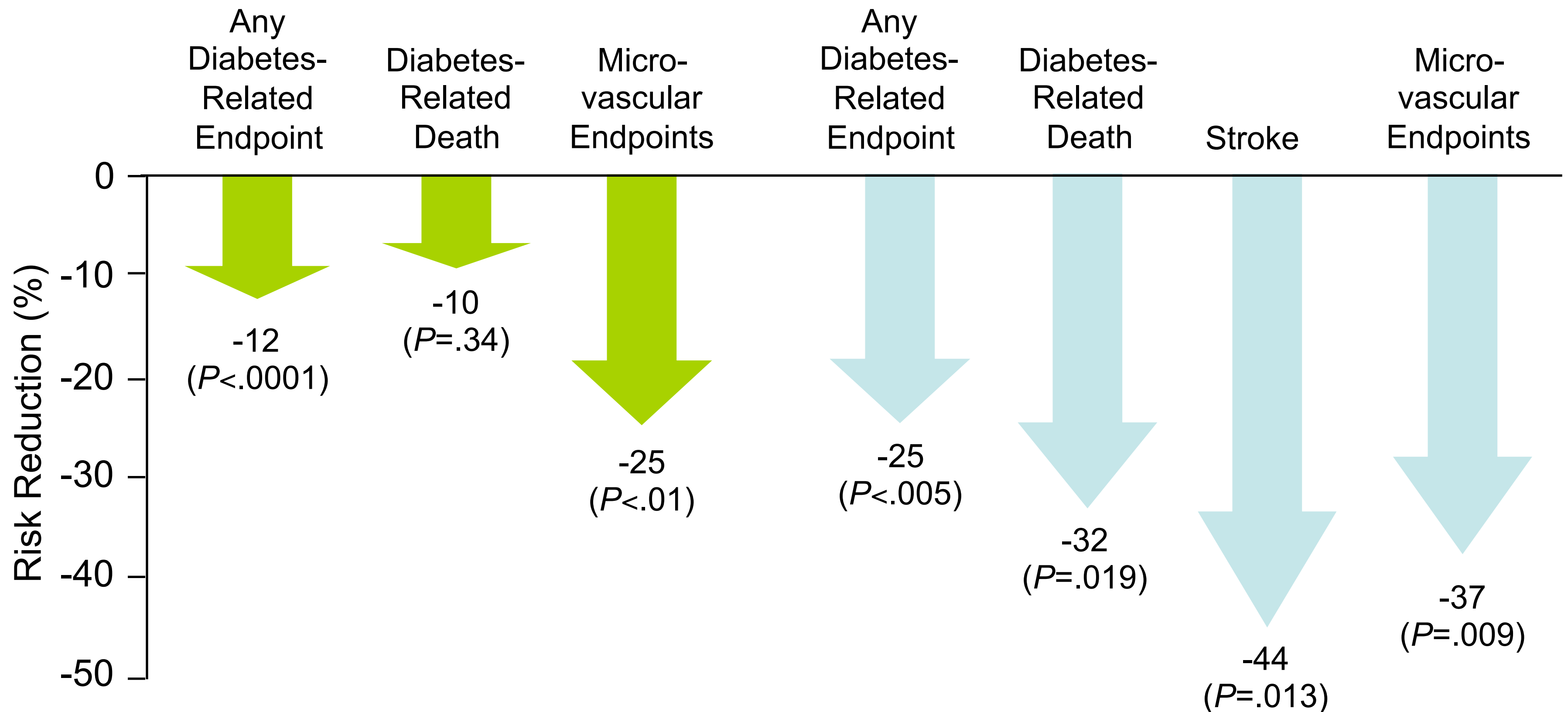
Garg JP et al. *Vasc Med*. 2002;7:35-43. Eknoyan G et al. *Am J Kidney Dis*. 2003;42:617-622.

Treatment Goals for Diabetic Hypertensive Patients

- Control blood pressure
  - 130/80 mm Hg for most patients
  - 125/75 mm Hg for patients who have proteinuria >1 g/d and renal insufficiency
- Reduce the risk of end-organ failure
- Reduce the risk of CV events
  - MI
  - CV death
- Delay or prevent the progression to HF

JNC 7 Report. *JAMA*. 2003;289:2560-2572. Bakris GL et al. *Am J Kidney Dis.* 2000;36:646-661. ADA. *Diabetes Care.* 2003;26(Suppl 1):S33-S49.

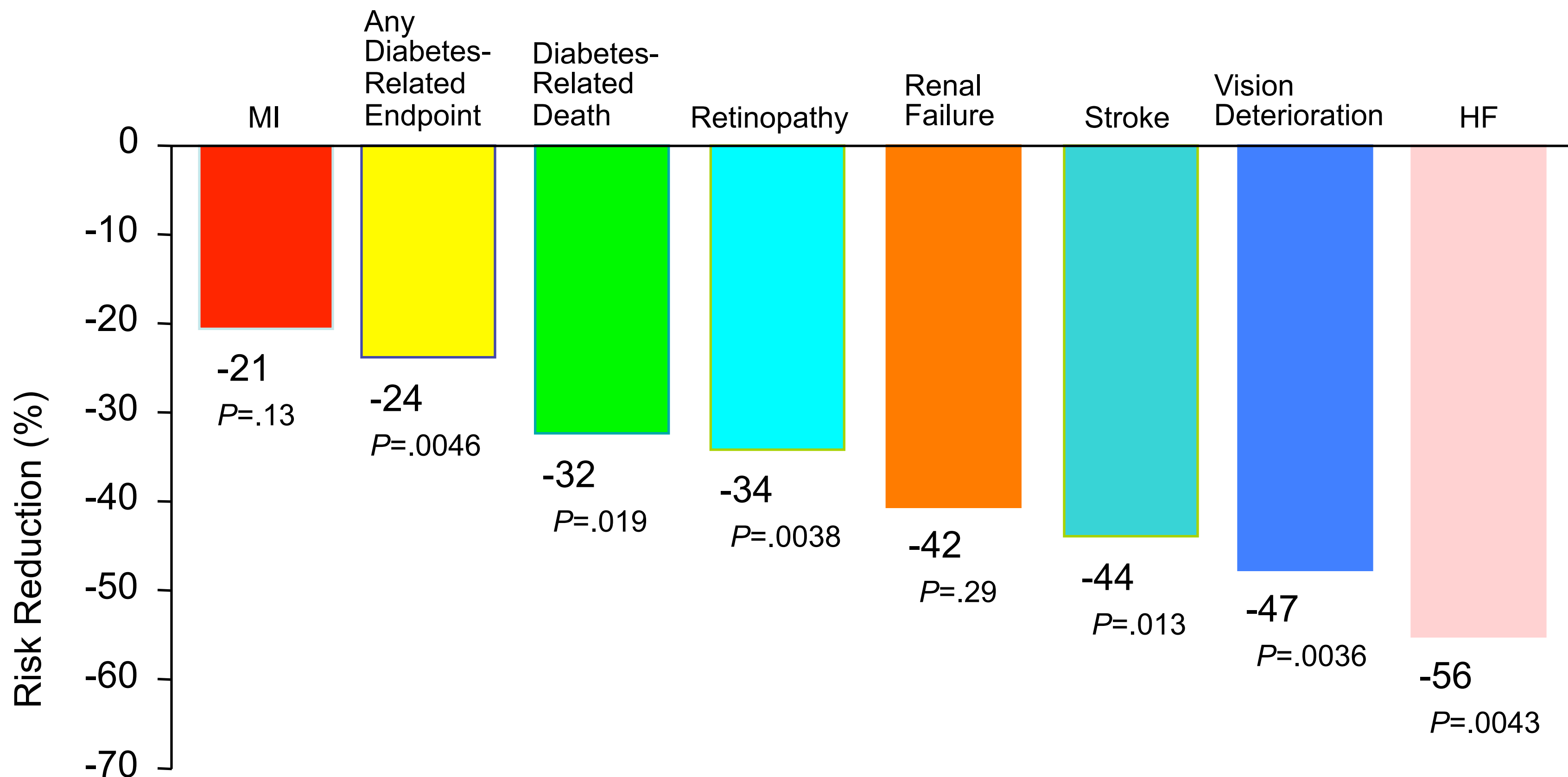
United Kingdom Prospective Diabetes Study (UKPDS): Results



UK Prospective Diabetes Study Group 38. *BMJ*. 1998;317:703-713.

UK Prospective Diabetes Study Group 33. *Lancet*. 1998;352:837-853.

UKPDS: Blood Pressure Control Study in Type 2 Diabetes—Effect of Intensive BP Lowering on Risk of Micro- and Macrovascular Complications



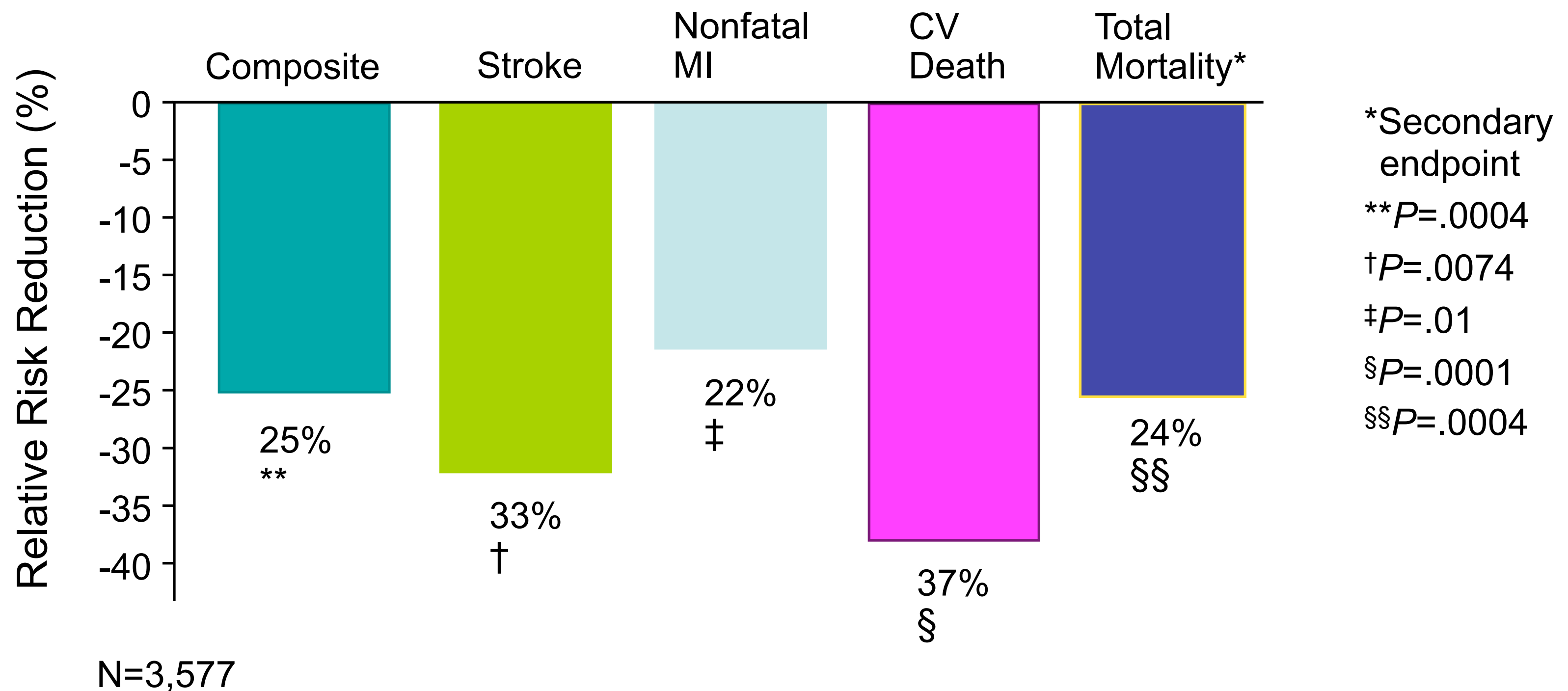
1,148 hypertensive patients with type 2 diabetes were allocated to tight (144/82 mm Hg, n=758) or less tight (154/87 mm Hg, n=390) and followed for a median of 8.4 years.

UKPDS Group. UKPDS 38. *BMJ*. 1998;317:703-713.

MICRO-HOPE: Outcomes in Diabetes

Ramipril's Effects Beyond Baseline Therapy

- Aspirin or other antiplatelets
- Lipid-lowering agents
- Diuretics
- β-blockers
- Glycemic control medications



HOPE Study Investigators. *Lancet.* 2000;355:253-259.

Physician Concerns About Adding β-Blockers in Patients With Diabetes

Metabolic

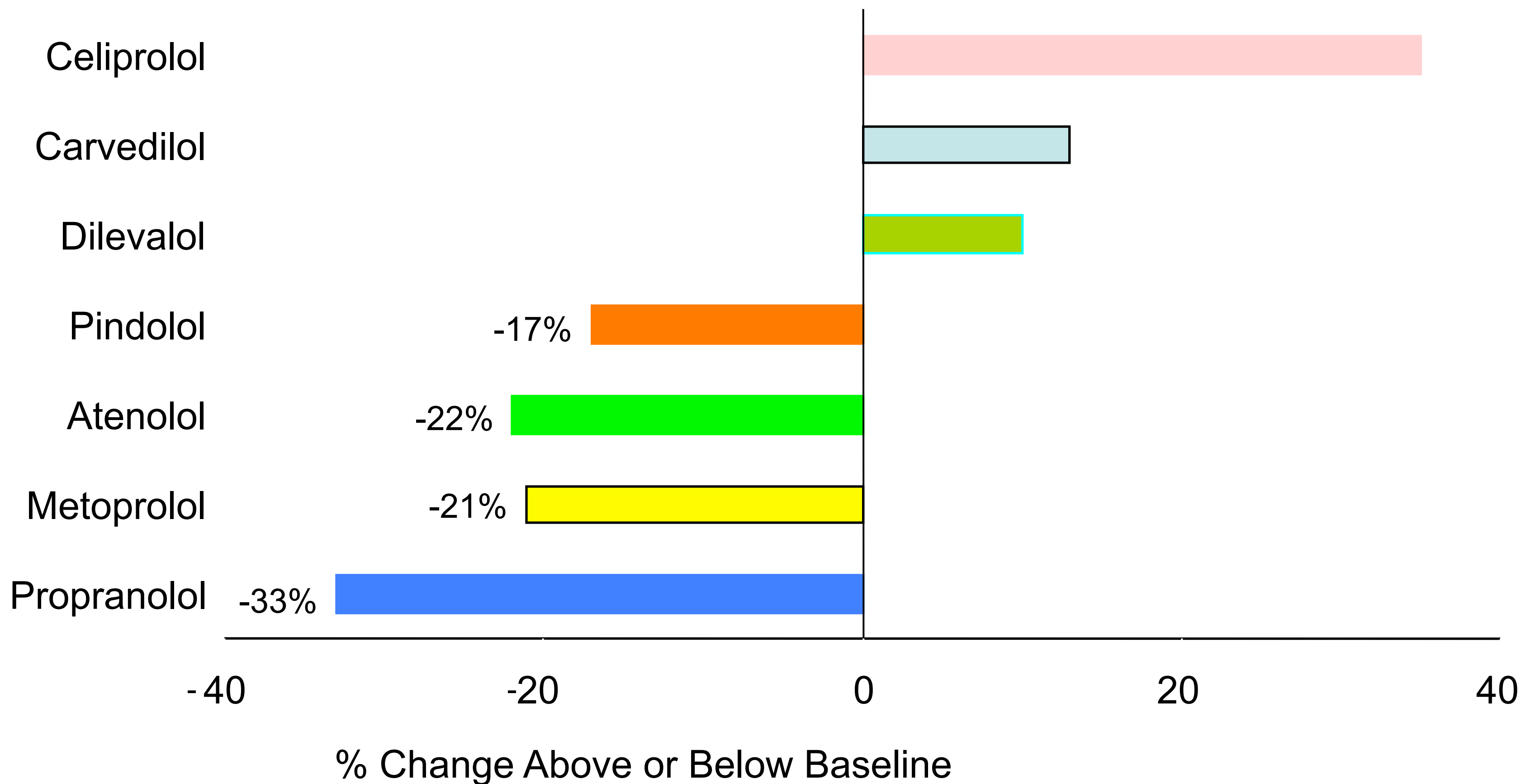
- Worsening HDL
- Increased Apo B
- Negative effects on glucose metabolism
- Negative effects on renal blood flow
- Masked hypoglycemia

Tolerability

- Fatigue
- Impotence
- Weight increase
- Peripheral vasoconstriction (cold extremities)
- Depression

Bell DS. *Endocr Pract*. 1999;5:51-53.

Effect of β-Blockers on Insulin Sensitivity in Hypertensive Patients



Jacob S et al. *Am J Hypertens*. 1998;11:1258

Carvedilol Versus Metoprolol for CHF+diabetes

	Total No. Randomized	No. of Deaths Placebo/β-blockade
CIBIS II		
Diabetes	312	33/27
Non-diabetes	2 335	195/129
All	2 647	228/156
MERIT-HF		
Diabetes	985	61/50
Non-diabetes	3 006	156/95
All	3 991	217/145
COPERNICUS		
Diabetes	589	
Non-diabetes	1 700	
All	2 289	190/130
All 3 studies		
Diabetes	1 886	
Non-diabetes	7 041	
All	8 927	635/431

Deedwania, *Am Heart J* 2005;149:159

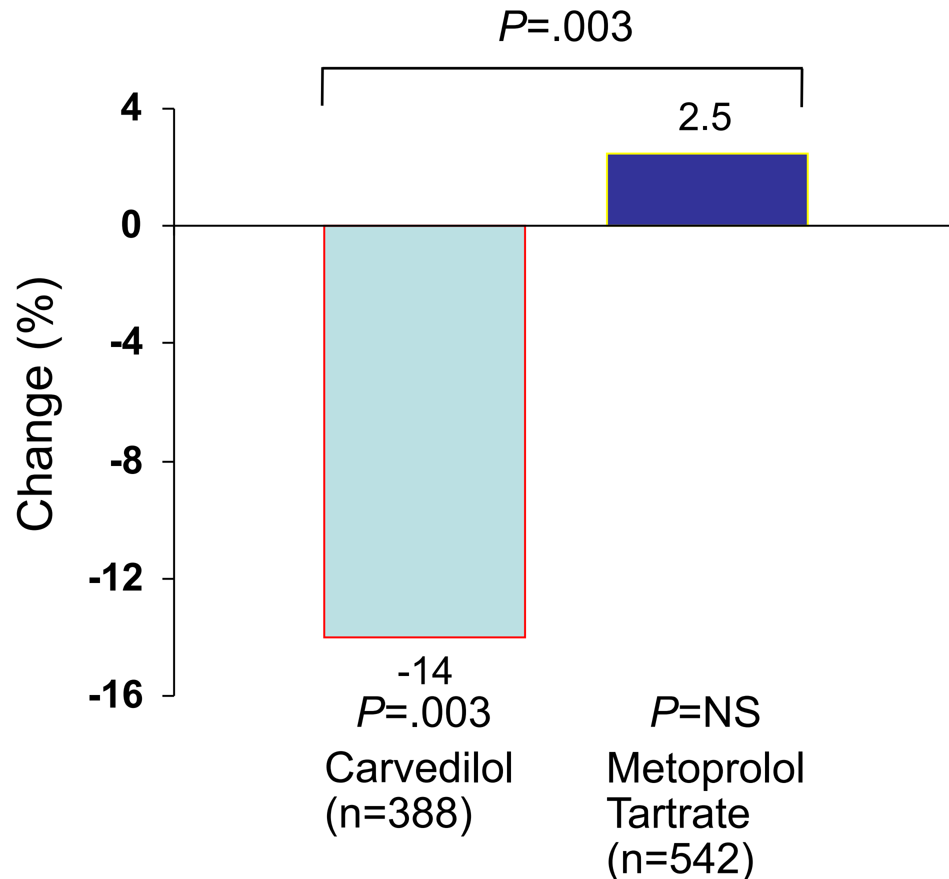
COMET Diabetes

Diabetes yes
no
Overall

Carvedilol better | Metoprolol better

0.50 0.75 1.00 1.25 1.50

Albumin:Creatinine Ratio

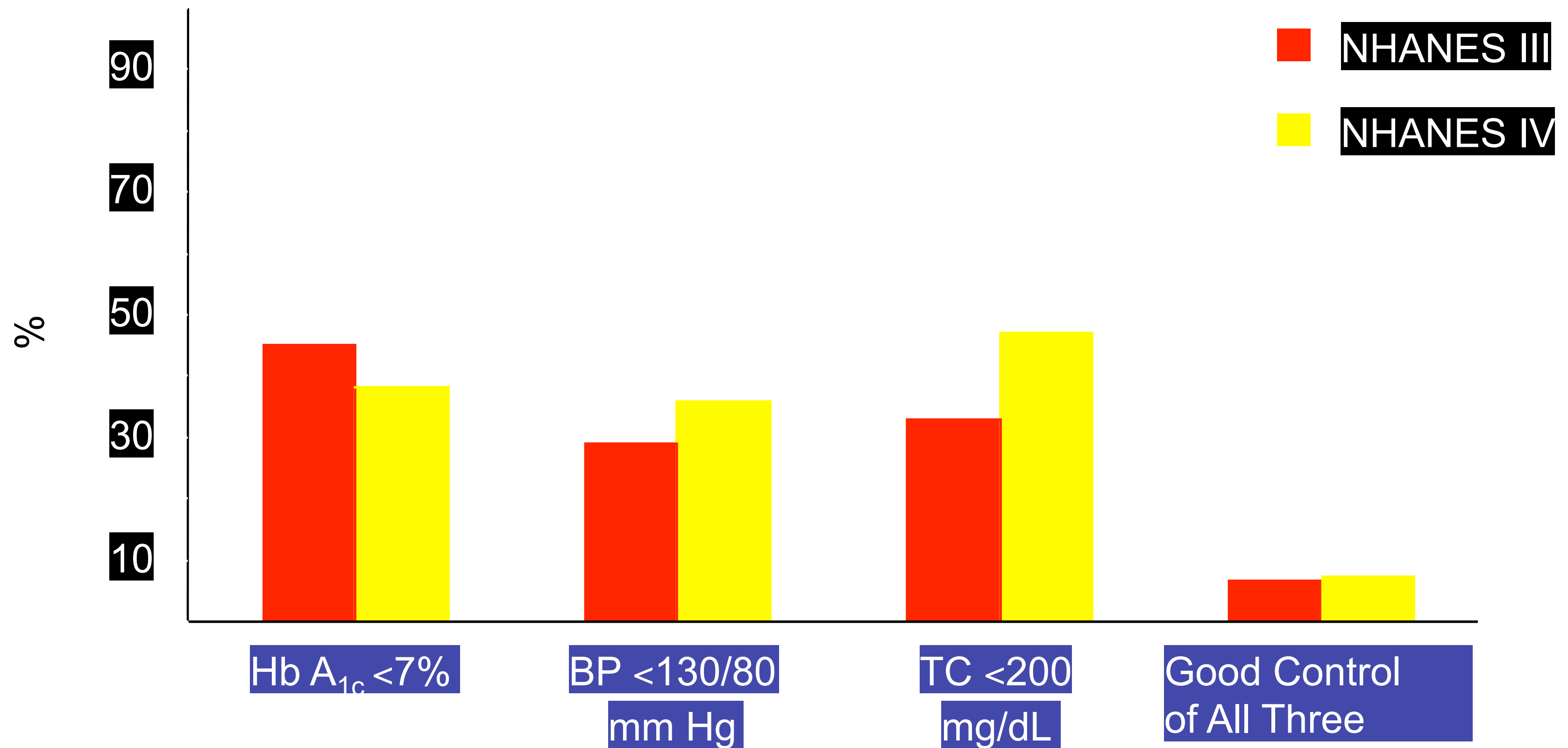


Bakris GL et al. *JAMA*. 2004;292:2227-2236. Data on file. GlaxoSmithKline.

Cardiovascular Protection as the Therapeutic Target in Diabetes

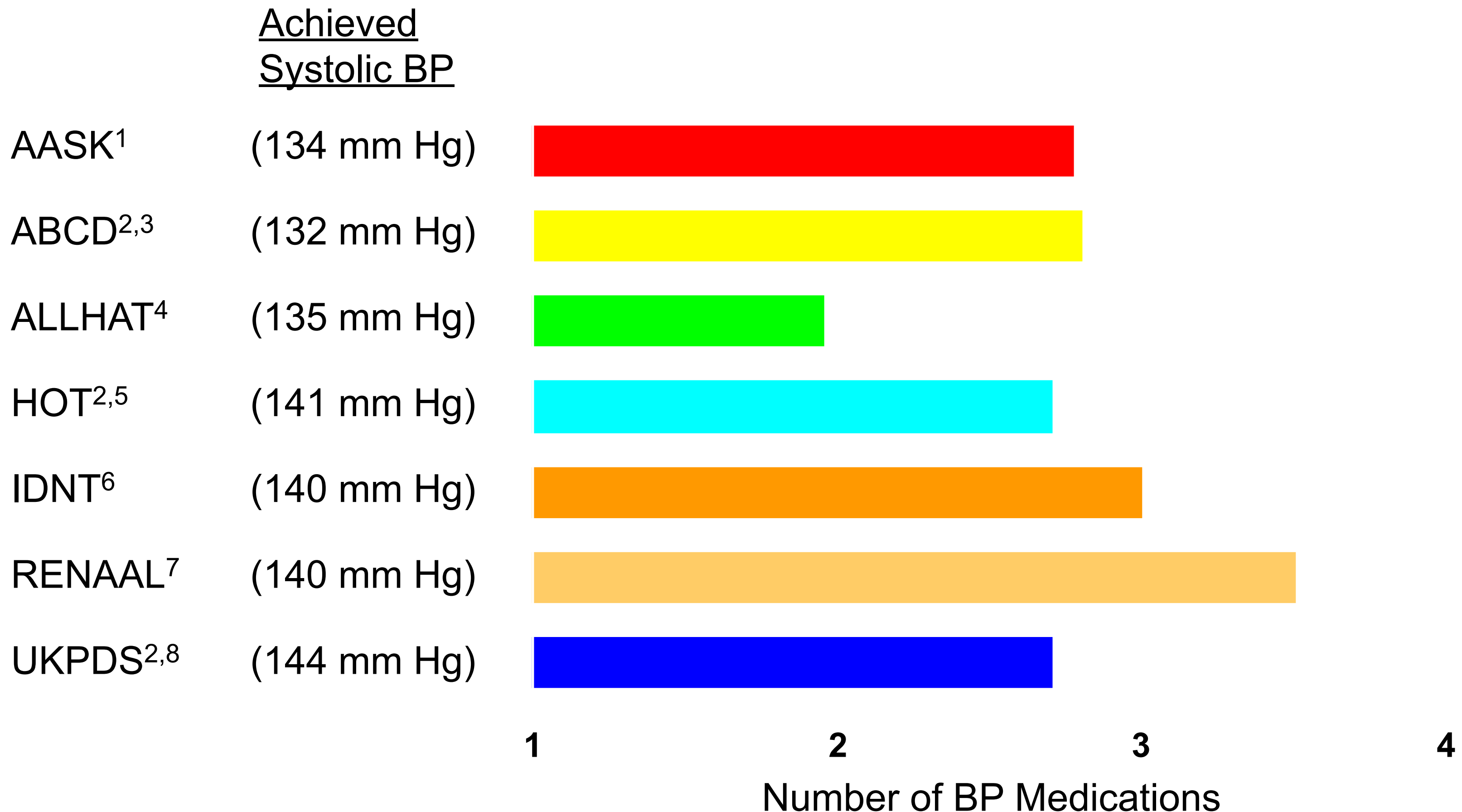
- Vasculo-protective/Cardio-protective
  - Aspirin or clopidogrel
  - ACE inhibitor/ARB
  - β-blocker – preferably Carvedolol
  - Statin
- Hemodynamic
  - Blood pressure control
- Metabolic
  - Blood sugar control

Percentage of Adults With Diabetes Who Achieved Recommended Levels of Vascular Risk Factors in NHANES



Saydah S et al. *JAMA*. 2004;291:335-342.

High-Risk Hypertensive Patients Require Multiple Agents to Achieve Goal



[1]Wright JT et al. *JAMA*. 2002;288:2421-2431. [2]Bakris GL. *J Clin Hypertens*. 1999;1:141-147. [3]Estacio RO et al. *N Engl J Med*. 1998;338:645-652. [4]The ALLHAT Officers and Coordinators. *JAMA*. 2002;288:2981-2997. [5]Hansson L et al. *Lancet*. 1998;351:1755-1762. [6]Lewis EJ et al. *N Engl J Med*. 2001;345:851-860. [7]Bakris GL et al. *Arch Intern Med*. 2003;163:1555-1565. [8]UK Prospective Diabetes Study Group. *BMJ*. 1998;317:703-713.

What Should "Treat patients with diabetes as if they have known CAD" Imply? Same is true for patients with CKD

- Aspirin (lowers risk of CV events in diabetes)
- β-blocker (lowers risk of MI, stroke, heart failure, and CV mortality in diabetes)
- ACE inhibitor (lowers risk of MI, stroke, heart failure, and CV mortality in diabetes)
- Statin (lowers risk of MI, stroke, heart failure, and CV mortality in diabetes regardless of LDL)

Smith SC Jr et al. *Circulation.* 2001;304:1577-1579.

Novel Agents for treatment of CHF

- Neprilysin Inhibitors
  - NEP (neutral endopeptidase) metabolizes ANP and BNP, (as well as bradykinin.)
    - So inhibitors increase levels of ANP/ BNP and bradykinin
    - Sacubitril or combo of Valsartan/ Sacubitril known as Entresto
    - Paradigm-HF study showed that pts who tolerated treatment had less readmission for CHF

Correction of Anemia in Diabetic CHF

- Diabetic patients with Hb less than 12.5 g% treated with erythropoetin and IV iron
  - NYHA class improved by 36.8%
  - Dyspnea improved by 69.7% on Visual Analogue Scale
  - EF improved by 7.6%
  - Hospitalizations decreased by 96.6%

Silverberg DS et al. *Nephrol Dial Transplant*. 2003;18:141-146.

Obstructive Sleep Apnea, Diabetes, and CHF

- OSA is more prevalent in both diabetes and CHF
- Increased sympathetic tone is the common denominator
- Increased sympathetic activity increases BP, myocardial stress, and insulin resistance
- CPAP treatment decreases sympathetic activity and afterload and ANP, and increases LVEF and stroke volume

CPAP=continuous positive airway pressure.

Somers VKK et al. *J Clin Invest*. 1995;96:1897-1904. Kaye DM et al. *Circulation*. 2001;103:2336-2338.

Treatment: Digoxin and Diuretics

- Improve clinical manifestations of HF
- Improve quality of life for HF patient
- No effect on mortality
- To improve mortality, the remodeling process must at least be halted and, preferably, reversed

Guidelines Comparison: Blood Pressure Goals in Hypertensives

JNC 7	130/80 mm Hg
NKF	130/80 Hg
with CKD	125/75 mm Hg*
ADA	130/80 mm Hg

*Lower blood pressure levels are recommended for people who have proteinuria >1 g/d and renal insufficiency.

JNC 7 Chobanian A et. Al Hypertension 2003. ADA. *Diabetes Care.* 2002;25(Suppl 1):S33-S49. Bakris GL et al. *Am J Kidney Dis.* 2000;36:646-661.

Stages of Hypertension

• Normal	• < 120 / 80
• Prehypertension	• 120 -139 / 80-89
• Stage 1	• 140-159 / 90-99
• Stage 2	• > 160 / >100

Treatment of Hypertension

- Stage 1 or Single agent – HCTZ for most pts. B-Blocker for females/ high heart rate.
- Stage 2 I start with DHP CCB (Nifedipine XL)
- plus one or both of above.
- Resistant HTN I look for CLASSES of agents

Classes of Antihypertensives

- Diuretics
- Rate control agents BBlocker, Verapamil, Diltiazem
- ACE/ ARB's
- Vasodilators Dihydropyridines, Hydralazine, Alpha blockers, Minoxidil
- Central agents: clonidine, aldomet.

Nephrology level htn

- I tell the pt that we’ll need to control the main route plus the main detours causing the HTN.
- Average of 3.1 medications to achieve control
- Rate control (pulse < 78)
- Diuretic
- Vasodilator DHP CCB, Hydralazine, Cardura, Minoxidil.
- ACE / ARB (accept 30% increase in creat if BP responds)

Refer to Nephrologist

- If unable to control on 3 drug regimen which includes Rate control, diuretic.
- If you are considering Minoxidil or renal angio.

- If creatinine climbs more than 30 % or if creatinine is over 2.0.

References

http://www.kidneyfailurerisk.com/

Ronco, Haapio, House e al. Cardiorenal Syndrome, JACC, Vol 52, No 19, 2008 page 1527-39.

New Insights into CV Risk Reduction in the patient with Diabetes. Online. March 6 2005.

JNC 7 Report 2003

Eckardt KU, Gillespie IA, Kronenberg F. High cardiovascular event rates occur within the first weeks of starting hemodialysis. Kidney Int. 2015;88:1117-1125.

Post Test

- Which Treatment has the LEAST impact on progression of renal disease?
  - A. Use of ACE inhibitors
  - B. Referral to a nephrologist
  - C. Use of DHP calcium Channel Blocker
  - D. Control of Diabetes to A1c < 8.0
  - E. The nature of the underlying renal Disease