New Insights in Chronic Kidney Disease

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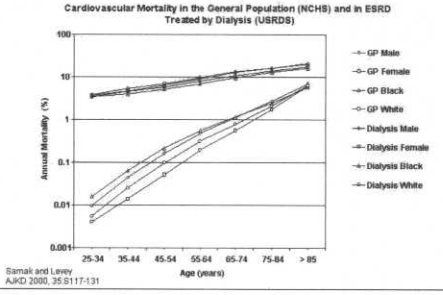
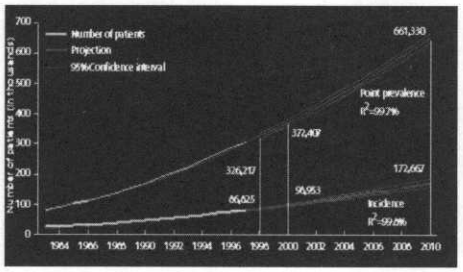
What is the burden of disease?

CVD Is Recognized as the Major Cause of Mortality in ESRD

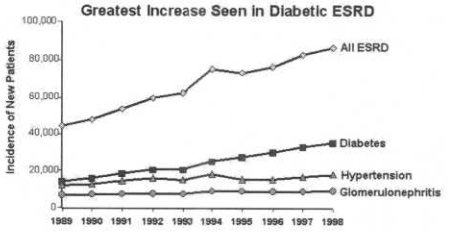


USRDS Projections



The Incidence of ESRD Is Increasing

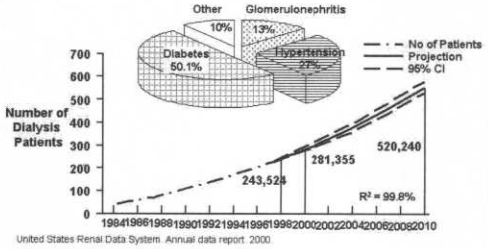
Greatest Increase Seen in Diabetic ESRD



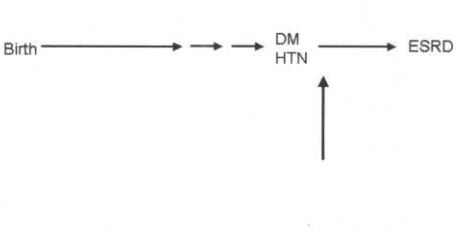
US Renal Database System. *2000 Atlas of ESRD in the United States*

Diabetes: The Most Common Cause of ESRD

Primary Diagnosis For Patients Who Start Dialysis



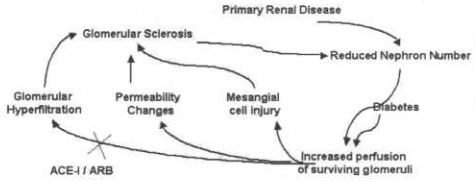
United States Renal Data System. Annual data report. 2000.



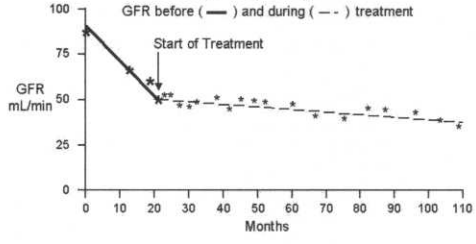
In The Beginning, CKD Research Focused on Two Important Questions

- Why was chronic kidney disease progressive?
- Were there therapeutic strategies that would favorably impact disease progression?

The Hyperfiltration Hypothesis

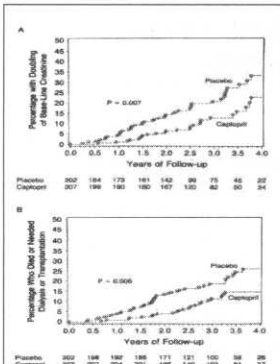


Impact of Antihypertensive Therapy on GFR in a Patient with Diabetic Nephropathy



Mogensen CE. *Pract Card*. 1983;9:156.

ACEi in DN



- Type 1 DM (n=409)
- ≥ 500 mg/24hrs
- SCr ≤ 2.5 mg/dl
- Captopril 25 TID
- ~ 4 years f/u

Lewis et al. NEJM 1993

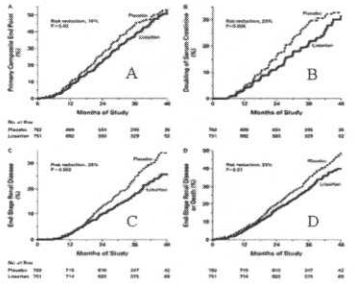
RENAAL

A- Doubling SCr or ESRD

B- Doubling SCr

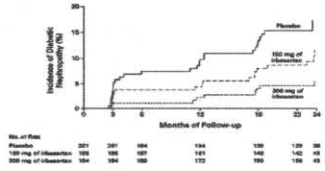
C- ESRD

D- ESRD or Death



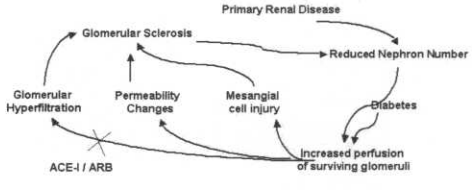
Irbesartan for MA- IRMA

- 590 patients with T2DM and MA, SCr ≤ 1.5 men, 1.1 in women
- Irbesartan 150 or 300 mg/d, 24 month study
- Primary outcome - Diabetic Nephropathy (AER > 200 mcg/min)
  - 29% and 70% reduced risk in treated arms
  - 44% and 68% reduced risk after adjusting for baseline MA and BP

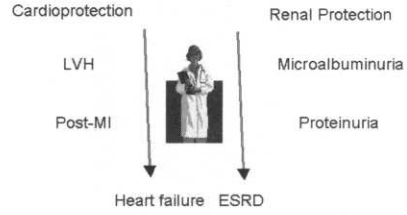


Parving H, NEJM 2001;345:870-8

The Hyperfiltration Hypothesis

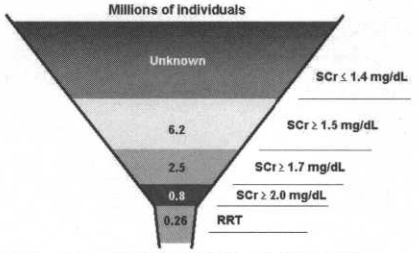


Diabetes & Hypertension: Risk Factors for CKD and CVD



Modified from Harris. In: *Diabetes in America*. 2nd ed. 1995.

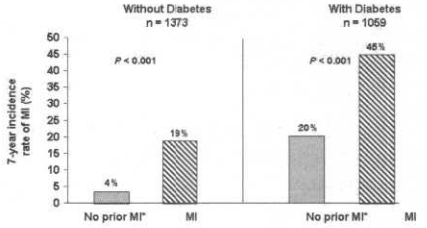
Estimates of CRI in the US Based on NHANES III Data



Jones et al. *Am J Kidney Dis*. 1998;32:992-999 (published correction in *Am J Kidney Dis*. 2000;35:178). US Renal Data System. *2000 Atlas of ESRD in the United States*.

Diabetics Are At Increased Risk for MI

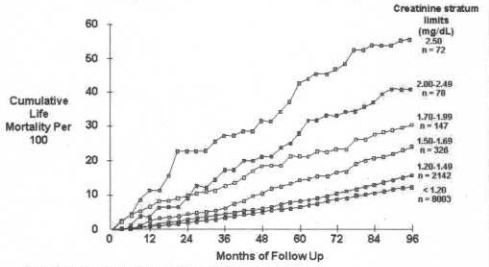
Type 2 Diabetes and CVD: 7-Year Incidence of Fatal/Nonfatal MI (East-West Study)



* These patients had no prior MI at baseline.
Haffner et al. *N Engl J Med*. 1998;339:229.

Serum Creatinine Predicts Mortality

Hypertension Detection and Follow-up Program



Shulman NB et al. *Hypertension*. 1989;13:80-93.

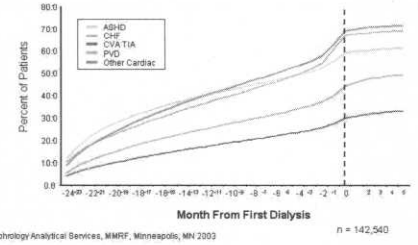
Outcome from CVD in CKD Patients

- **HOPE Trial:**
  - Myocardial infarction (MI) was 60% more common in patients with mild CKD (Cr 1.4 - 2.3 mg/dL).
  - CKD conferred a 1.4 independent risk for death, MI or stroke.
- **SOLVD Trial :**
  - Using MDRD equation, a 10 ml/min/1.73 m^2 decrease in GFR conferred a 6.4% increased risk of death.
  - An independent effect of anemia was also found.

1. Mann et al. Annals Int Med. 2001; 134: 629-636.
2. Al-Ahmad et al. J Am College Card. 2001; 38: 955-962.

Cardiovascular Co-morbidities Are Common in CKD

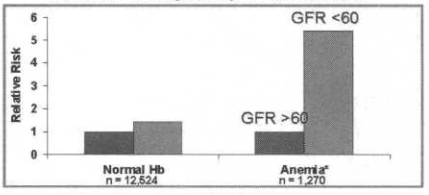
CVD As Well As CKD Are Progressing



Nephrology Analytical Services, MMRF, Minneapolis, MN 2003 n = 142,540

Anemia Increases the Relative Risk of Stroke in CKD Patients

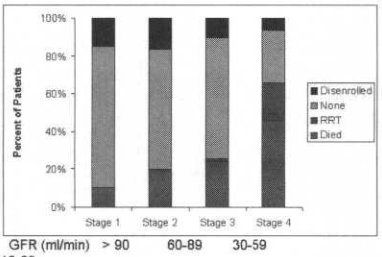
Risk of Stroke According to Kidney Function and Hb Level



*Anemia defined as Hb < 12g/dL for women and < 13 g/dL for men
CrCl = creatinine clearance

Abramson JL, et al. *Kidney Intl*. 2003;64:610-615.

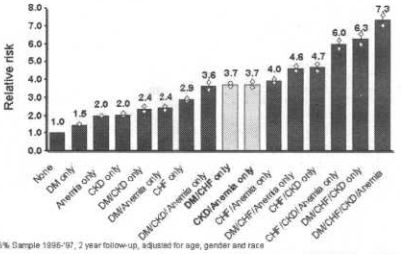
CKD Patients Are More Likely To Die Than Progress To ESRD



JASN 2002, Kaiser Permanente, 1996 cohort, 5 yr follow up

Anemia Is A Mortality Multiplier

DM/CHF Have The Same Mortality Risk As CKD/Anemia



Medicare 5% Sample 1995-'97, 2 year follow-up, adjusted for age, gender and race

CHF and CKD: Clinical Benefit of Anemia Correction

126 anemic CHF patients (91% CKD) referred to Nephrology clinic for anemia management, mean intervention period 12.4 months (5-27)

	Before	After
Hemoglobin (g/dL)	10.3	13.1
Serum creatinine (mg/dL)	2.4	2.3
ΔGFR (mL/min/month)	-0.95	0.27
NYHA class (0-4)	3.8	2.7
Fatigue/SOB index (0-10)	8.9	2.7
Hospitalizations	3.7	0.2
Systolic BP (mmHg)	132	131
Diastolic BP (mmHg)	75	76

Silverberg, et al. Peritoneal Dial Int. 21(sup3):s236-40.

Lessons From RENAAL: Baseline Characteristics Predict Clinical Outcomes

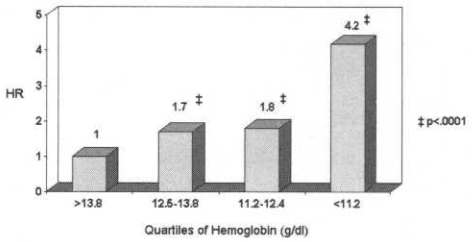
VARIABLE	p VALUE
Proteinuria *	<.0001
Serum Creatinine	<.0001
Serum Albumin	~.0003
Hemoglobin **	~.0069

* Modifiable risk factors

Multivariate analysis on primary endpoint

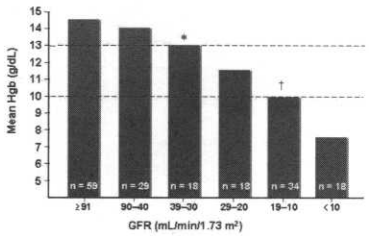
Keane et al. Kidney Int; 63: 1499-1507

RENAAL Trial: Effect Of Hemoglobin On Combined Renal Endpoint (DsCr/ESRD)



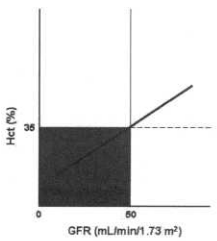
Mohanram et al. JABN; 13: 8A

Anemia Develops and Worsens With Declining Kidney Function



* = 25%-40% of kidney function. † = 10%-15% of kidney function.
Adapted from Radtke et al. *Blood*. 1979;54:877-884.

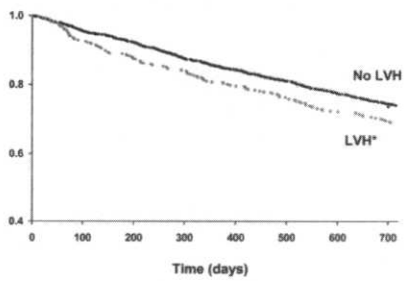
Causes of the Anemia of CKD



- Erythropoietin deficiency
- Suppression of RBC synthesis by uremic toxins
- Short RBC survival
- Iron deficiency
  - Blood loss
    - GI tract
- Nutritional deficiency (B_{12}, folate)
- Hyperparathyroidism
- Chronic inflammation
- Infection
- Aluminum bone disease

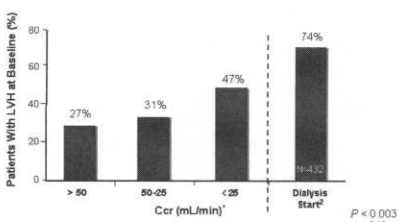
Drueke et al. *Clin Nephrol*. 1999;51:1-11.

Estimated Survival



Stack et al: Am J Kidney Dis 2002

Prevalence of LVH Increases With Decreased Kidney Function



P < 0.003
n = 246

¹Rate calculated using Cockcroft-Gault formula.
1. Levin et al. *Am J Kidney Dis*. 1999;34:125-134. 2. Foley et al. *Kidney Int*. 1995;47:186-192.

Anemia Linked to LVH Independent of BP

446-Patient CRI Study

	LVH (n = 84)	No LVH (n = 162)	*P* value
Ccr (mL/min)	32.1	37.7	0.001
Hgb (g/dL)	**12.1**	**13.0**	**< 0.0001**
SBP (mm Hg)	141.3	150.3	< 0.0003

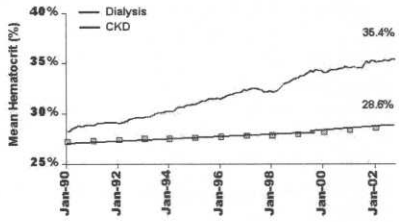
Levin et al. *Am J Kidney Dis*. 1999;34:125-134.

Clinical Trials to Support Decreases in LVMI Following Treatment of Anemia

Study	Duration (months)	Hemoglobin (g/dL) Pre to post	Δ LVMI (%)	P value
Portoles et al.1997[1]	6	9.0 to 11.7	-17	<0.05
Silberberg et al. 1990[2]	6.3	6.3 to 11.4	-5	.0004
Zehnder et al. 1992[3]	8.6	8.6 to 11.4	-20	<.001
London et al. 1989[4]	9	6.8 to 10.6	-17	<.05
Macdougall et al. 1990[5]	12	6.4 to 10.8	-22	<.01

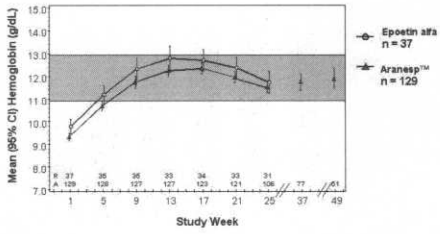
Am J Kidney Dis. 1997;29:541-548. 2. Can J Cardiol. 1990;6:1-4. 3. Nephron. 1992;61:21-25.
Kidney Int. 1988;36:878-82. 5. Lancet. 1990;335:489-493.

Anemia Management in CKD is Suboptimal



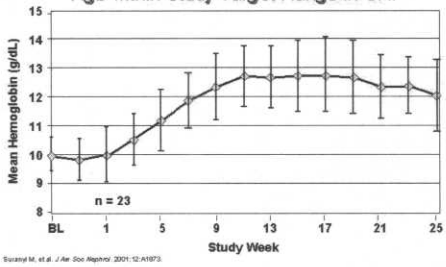
Adapted from Obrador et al. Kidney Int 2001;1875-1884

Once-a-Week Effectively Achieved Study Target Hgb Range in CRI Patients



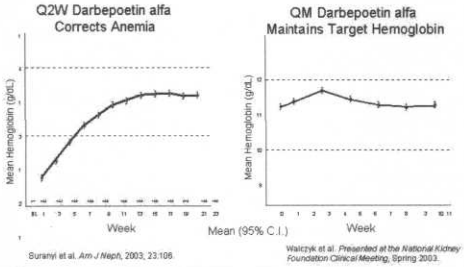
Locatelli F, et al. Kidney Int. 2001;60:741-747.

Once-Every-Other-Week Effectively Achieved and Maintained Hgb within Study Target Range in CRI



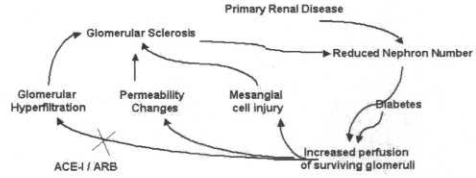
Suranyi M, et al. J Am Soc Nephrol. 2001;12:A1873.

Optimal Anemia Management Is Achievable



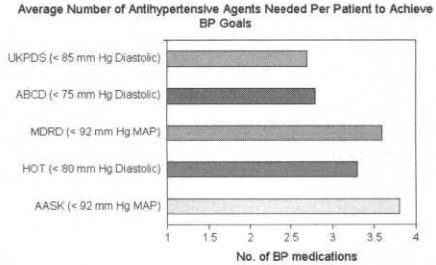
Suranyi et al. Am J Neph, 2003, 23:106.
Walczyk et al. Presented at the National Kidney Foundation Clinical Meeting, Spring 2003.

The Hyperfiltration Hypothesis



Optimal Management Of Hypertension Is Frequently Complex and Unachievable

Average Number of Antihypertensive Agents Needed Per Patient to Achieve BP Goals



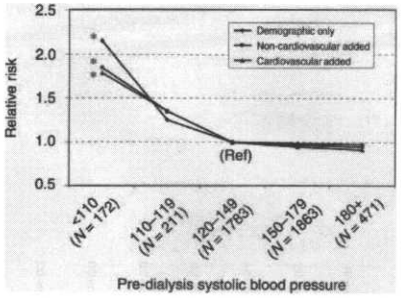
Bakris et al. Am J Kidney Dis. 2000;36:646.

RENAAL: The Challenge to Control Blood Pressure

- N 1513
- Baseline Blood Pressure 152.5 / 82.4 mm Hg
- Target Blood Pressure 140 / 90 mm Hg or less
- Achieved Blood Pressure 142 / 77 mm Hg
- Number of Anti-HTN Meds 4.5

Target Systolic Blood Pressure Was Not Achieved

Brenner et al. N Eng J Med. 2001;345:861.



ZADEH et al: Kidney Int, Volume 63(3).March 2003.793–808

Table 2. **Effect of Pravastatin Use on Incidence of Cardiovascular Events in Participants with Chronic Renal Insufficiency, as Defined by Creatinine Clearance of 75 mL/min or Less***

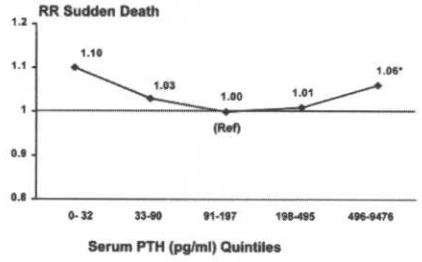
Event	Participants in the Placebo Group	Participants in the Pravastatin Group†	Adjusted Hazard Ratio with Pravastatin (95% CI)	P Value‡
	(%)			
Death from CHD or nonfatal MI§	126 (14.5)	89 (10.5)	0.72 (0.55–0.95)	0.02
Major coronary event	234 (27.0)	171 (20.3)	0.72 (0.59–0.88)	0.001
Total mortality	111 (12.8)	86 (10.2)	0.81 (0.61–1.08)	0.14
Fatal MI or confirmed nonfatal MI	90 (10.4)	65 (7.7)	0.73 (0.52–1.01)	0.06
CABG or PTCA	153 (17.6)	105 (12.4)	0.66 (0.50–0.85)	0.001
Unstable angina	142 (16.4)	133 (15.8)	0.93 (0.73–1.18)	>0.2
Stroke	46 (5.3)	29 (3.4)	0.62 (0.39–1.00)	0.051

* All models were based on complete data for 1711 participants (887 in the placebo group and 844 in the pravastatin group). Hazard ratios and *P* values were derived from Cox proportional hazards models. Patient-specific data were used to compute *P* values and confidence intervals. CABG = coronary artery bypass grafting; CHD = coronary heart disease; MI = myocardial infarction; PTCA = percutaneous transluminal coronary angioplasty.
† Percentages are cumulative incidences.
‡ Adjusted for age; sex; history of hypertension; smoking at baseline; diabetes mellitus; previous congestive heart failure; use of angiotensin-converting enzyme inhibitors, calcium-channel blockers, β-adrenergic blockers, and aspirin; prerandomization systolic and diastolic blood pressure; baseline high-density lipoprotein and low-density lipoprotein cholesterol levels; baseline triglyceride levels; serum albumin levels; body surface area; and pravastatin use.
§ This combined variable was the specified primary end point.

Lipid Lowering Therapy in patients with CKD

Tonelli et al Annals of Internal Medicine 2003

Other risk factors for CVD



Ganesh et al. J Am Soc Nephrol 12:2131-2138, 2001

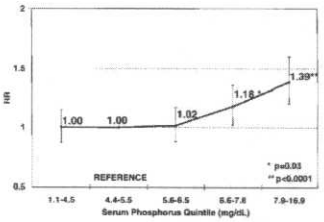
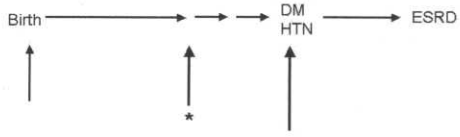


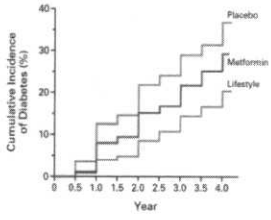
Fig 2. Relative mortality risk by serum phosphorus quintiles (N = 6,407). The vertical bars indicate the 5% to 95% confidence intervals.

Am J Kidney Dis 1998 Apr;31(4):607-17
Block GA

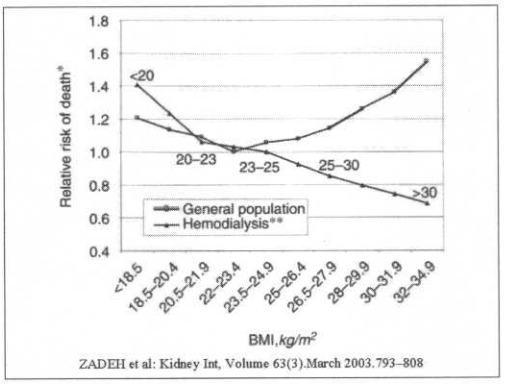
What to pay attention to as CKD progresses

1. Intrinsic renal disease
2. BP
3. LVH
4. Anemia
5. Lipids
6. DM management
7. Ca/P/PTH

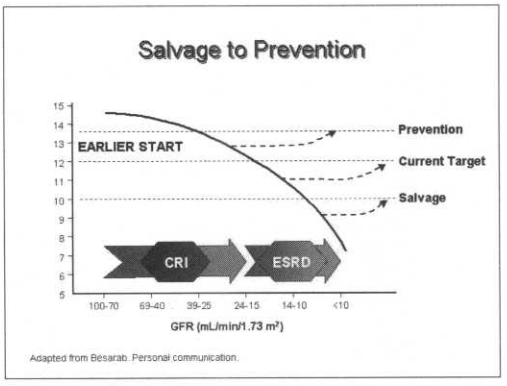




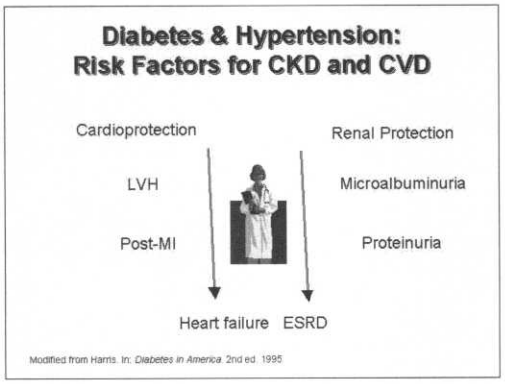
DPP NEJM Feb 2002



ZADEH et al: Kidney Int, Volume 63(3).March 2003.793–808



Adapted from Besarab. Personal communication.



Modified from Harris. In: *Diabetes in America*. 2nd ed. 1995