Cardiovascular events and CKD

Cardiorenal syndrome

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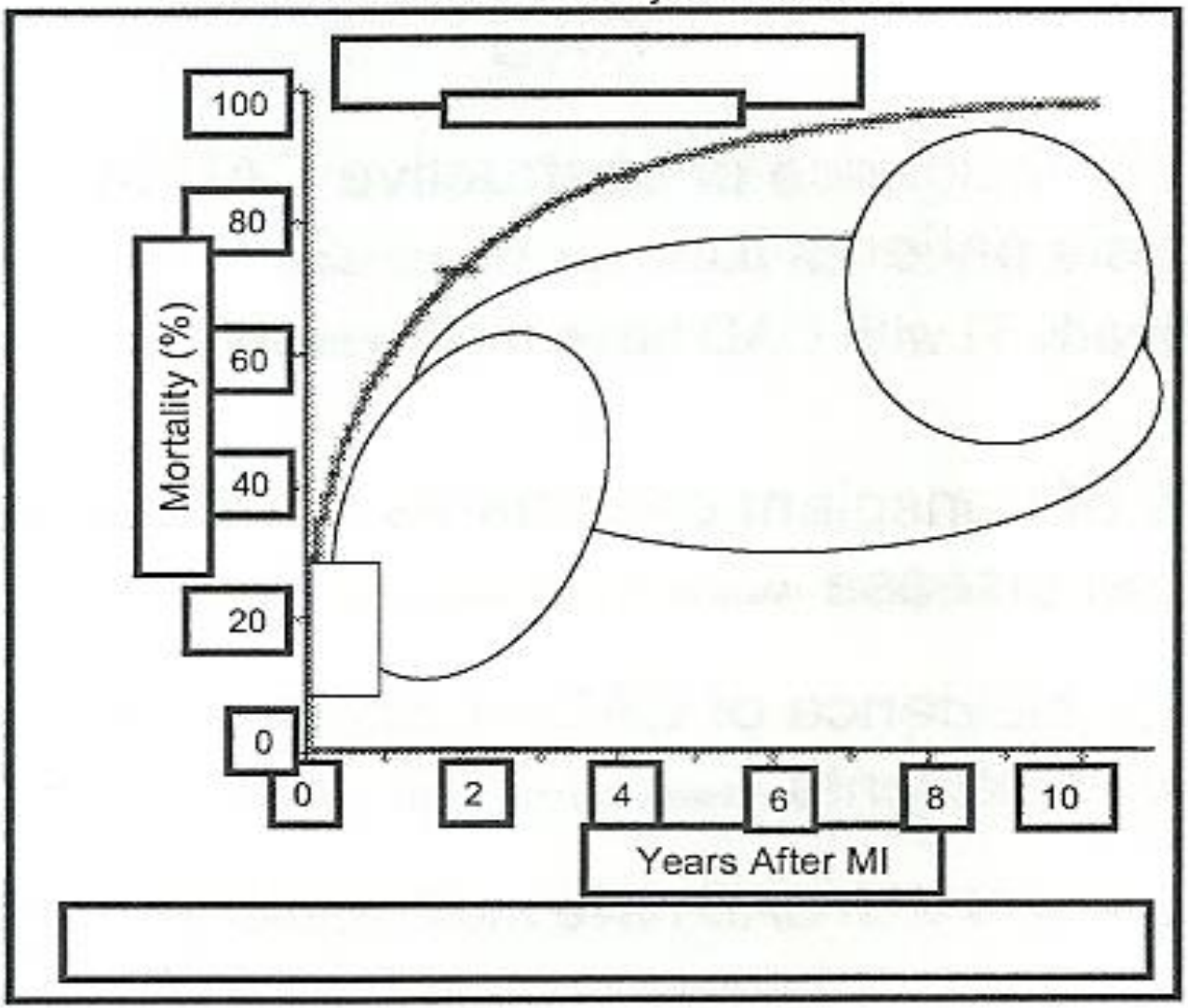
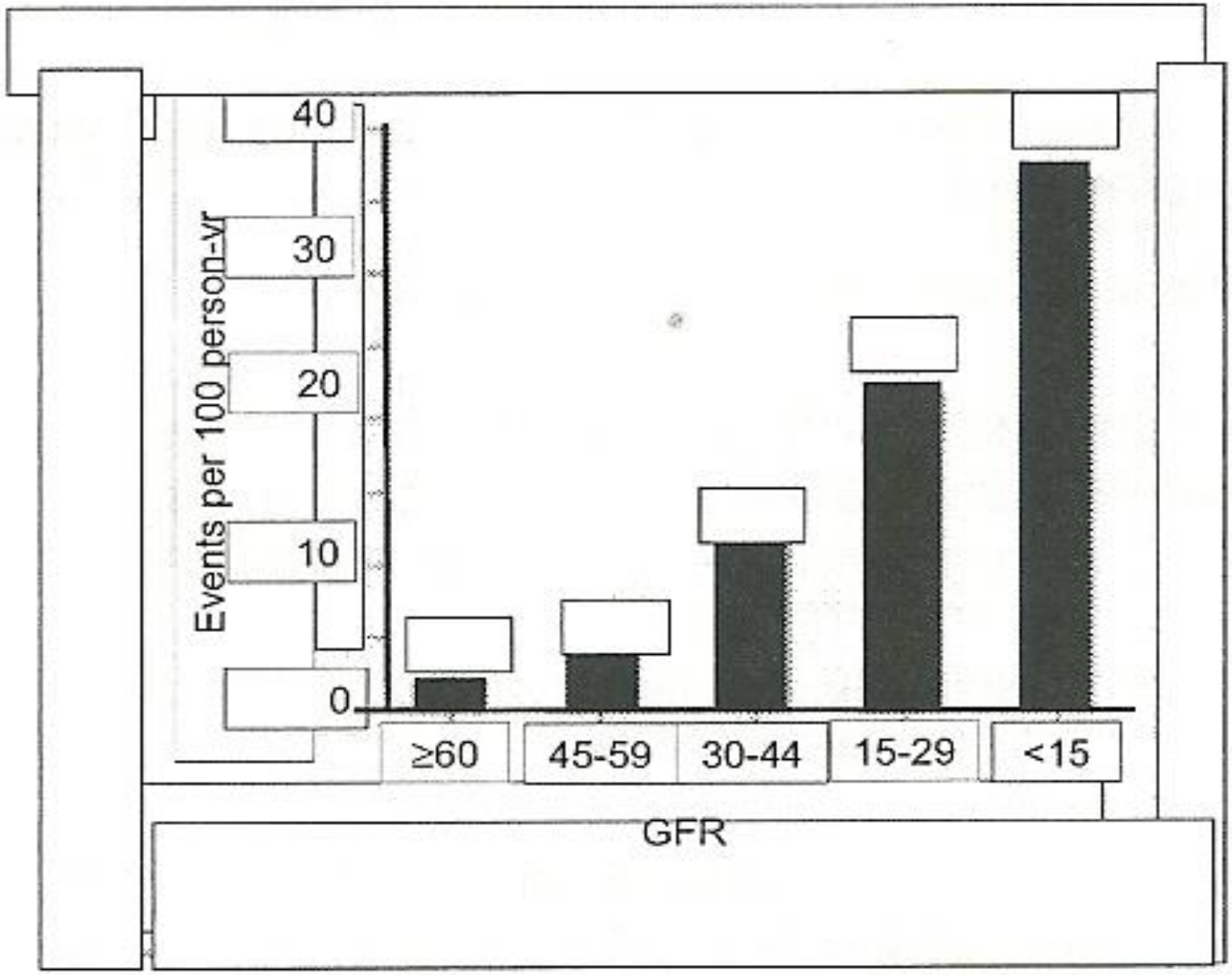
Estimated Cumulative Mortality Following First Myocardial Infarction in Chronic Dialysis Patients



Herzog CA. NEJM 1998; 339: 799-805

Cardiovascular Events Rates According to the Estimated GFR



Go, A. S. et al. N Engl J Med 2004;351:1296-1305

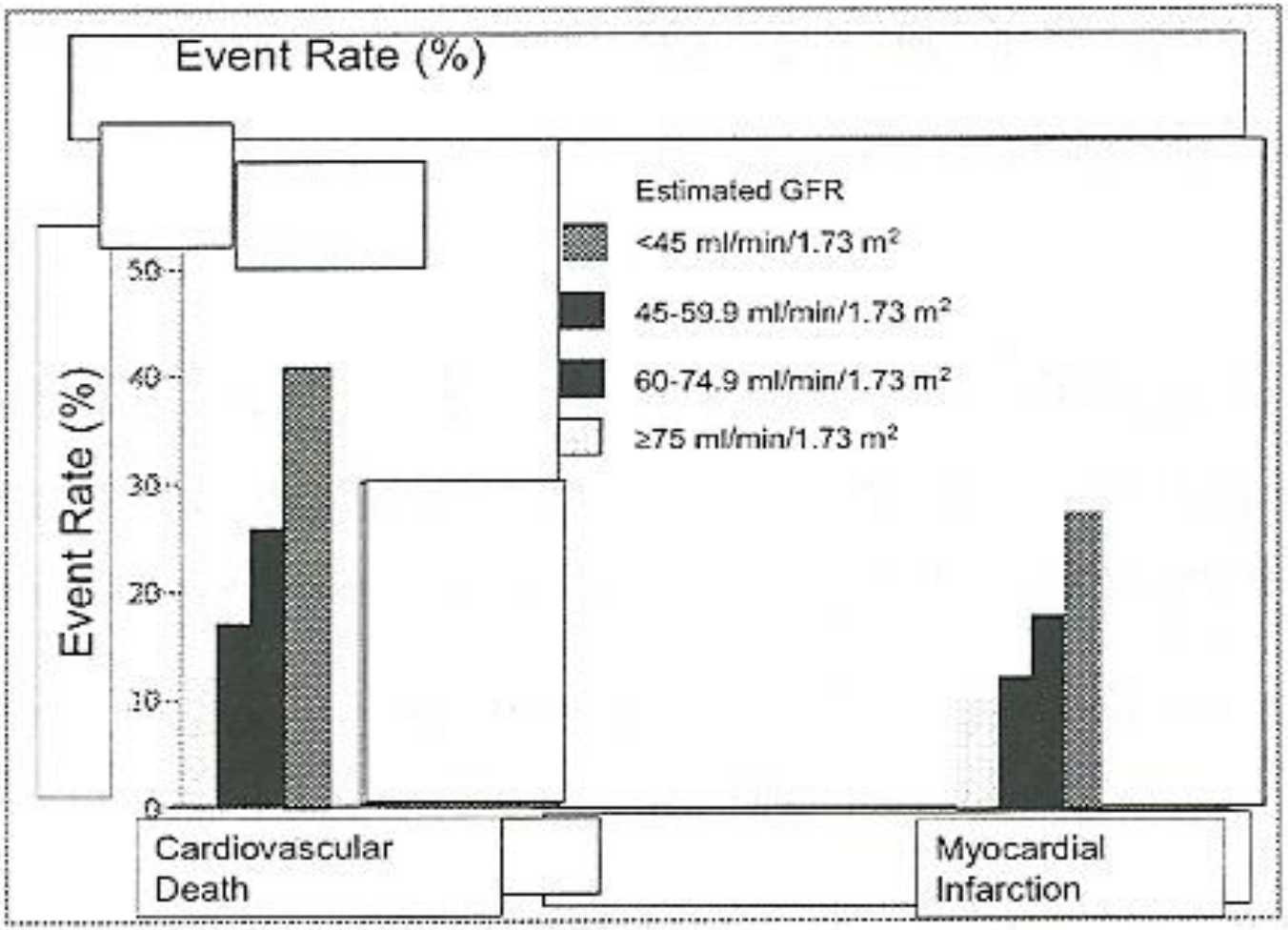
Relative Risk of ESRD vs. CV Death in Elderly Patients with CKD

2 Year Incidence Rates

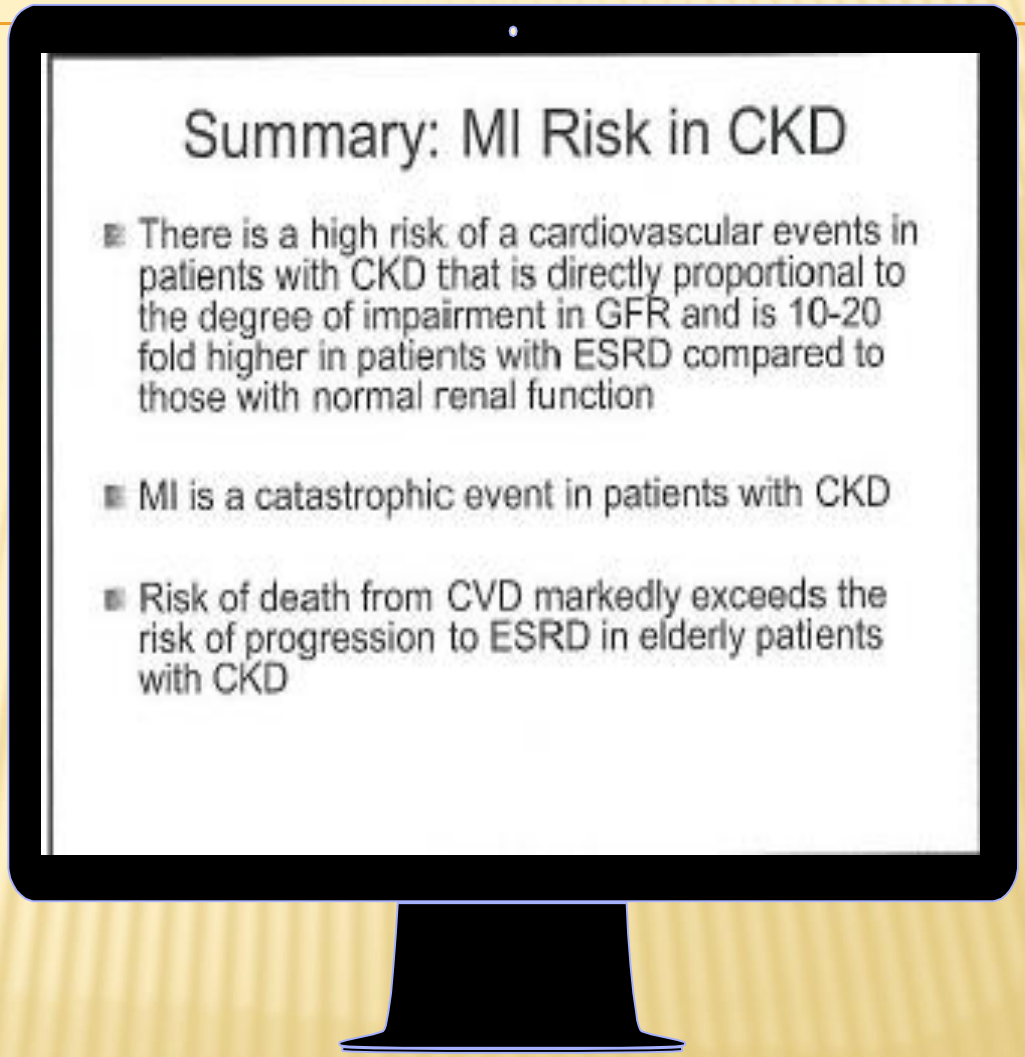
	CV Death	ESRD
CKD(+)/DM(+)	32.3%	6.1%
CKD(+)/DM(-)	29.5%	2.9%
CKD(-)/DM(-)	10.3%	0.1%

Collins AJ. KI 2003;64(S87):S24-31

Estimated Cardiovascular Death and Reinfarction Rates Three Years after MI in Patients with Pre-ESRD CKD



Anavekar NS. N Engl J Med 2004;351:1285-1295


Summary: MI Risk in CKD
There is a high risk of a cardiovascular events in patients with CKD that is directly proportional to the degree of impairment in GFR and is 10-20 fold higher in patients with ESRD compared to those with normal renal function
MI is a catastrophic event in patients with CKD
Risk of death from CVD markedly exceeds the risk of progression to ESRD in elderly patients with CKD

Etiology of Increased Risk of CVD Events CKD

- High burden of fixed CAD
- Inflammation
- Oxidative stress
- Coronary artery calcification
- Traditional CV risk factors (lipids, diabetes, hypertension, age)
- Poor performance of diagnostic tests
- Underutilization of standard CV therapies

Incidence of Obstructive CAD in Advanced CKD

- 60.2% incidence of obstructive CAD in new dialysis patients (Jokl, N. NDT. 1997;12:718-23)
  - Nearly ¾ with CAD have multi-vessel involvement
- 42% of transplant candidates have at least one-vessel disease (Marwick, TH. Transplantation. 1990;49:100-103)
- ~50% incidence of CAD in asymptomatic dialysis patients (Ohtake, T. JASN. 2005;16:1141-8. DeFilippi C. JAMA/ 2003; 290:353-9.)
  - Nearly ¾ with CAD have multi-vessel involvement

Inflammation, Oxidative Stress and CKD

- All biomarkers of oxidative stress and inflammation are elevated in patients with stage 3-5 CKD (Payson BP, KI. 2004;65:1009-1016)
  - No significant correlation with eGFR

- Both transient and persistent elevations in inflammatory markers are associated with a doubling in the risk of CV death in HD patients
  (Wanly PL. NDT. 2006;21:1658-1665. Wanner C. NDT. 2005;17:2034-2047)
  - CRP persistently elevated to >10mg/L 20% and transiently elevated in 26%

- Elevated CRP is associated with doubling of mortality in stage 3-4 CKD patients (Mason V. KI. 2005;68:766-72)

Coronary Calcification ?

- Coronary artery calcification is more common in patients with ESRD or CKD than patients with normal renal function, particularly among those with diabetes (Goodman WG. NEJM. 2000;18:1478-83, Kwan H. JASN 2006;18:507-13)
- Presence of Coronary calcification is independently linked to risk of CV death in patients with ESRD as well as in general population (Marzocka M. Clin Exp Nephr 2004;8:54-58. Block GA. KI 2007. Block GA. KI 2007;78:478-41)

BUT

- Variable correlation of coronary artery calcification with the presence of CAD
  - Sensitivity and specificity for detection of CAD vary widely depending on cut point used for calcium score and test performance is poor (Fujimoto N. Clin Chem Acta 2006;367:98-102. Shaplin EJ. AJKD 2004;43:313-19)
- No significant effect on mortality when patients given non-calcium containing binders compared with calcium containing binders in long-term study (Kidney Int. 2007;72:1130-7.)
- No significant relationship of eGFR or Cystatin C with CAC score among patients with mild to moderate CKD in MESA study of >6000 participants (Ix JH. JASN 2008;19:575-83)

Coronary Calcification Summary

- Excellent marker of risk of all-cause and cardiovascular mortality

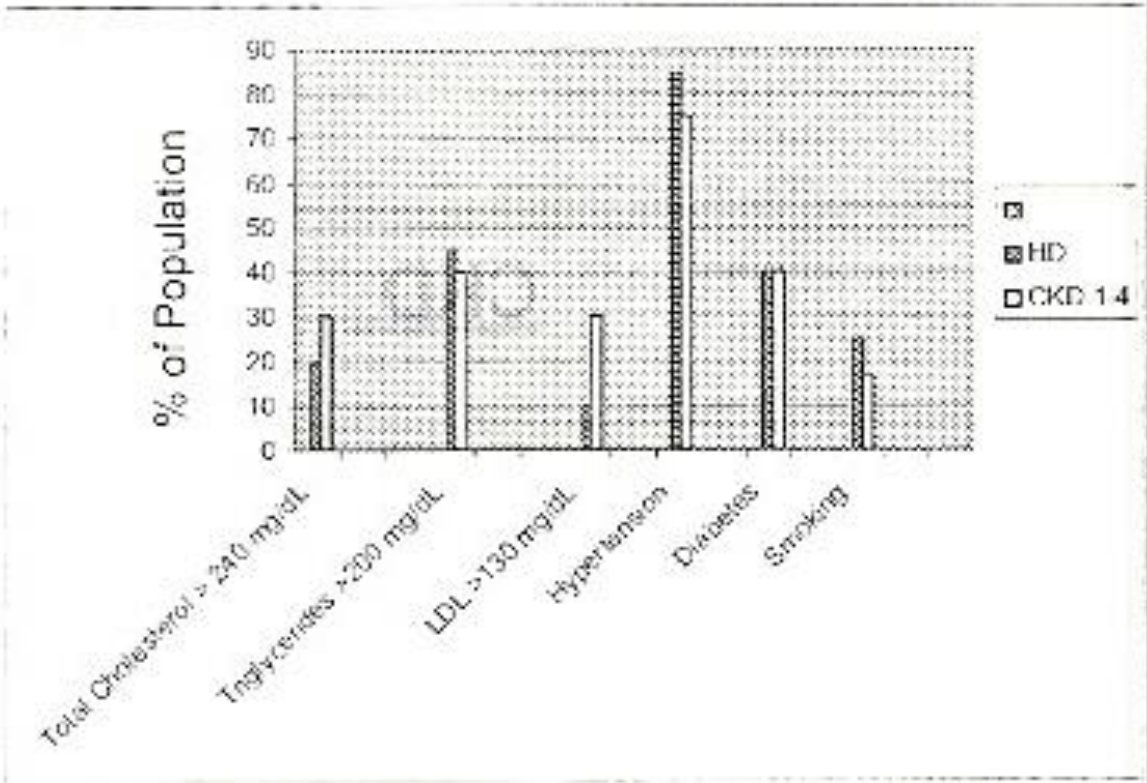
- Pathogenic role remains uncertain
  - Experimental studies suggest that calcification stabilizes coronary plaque (H. Vliegani R, Younis H, Burke AP, Kamm RD, Lee RT. Circ 2001;103:1051-1056)
  - Lack of effect of sevelamer vs. calcium-therapy in large randomized trial

Traditional Risk Factors and CKD

- Most traditional risk factors such as advanced age, hypertension, hyperlipidemia are common in patients with CKD

Levey A. Semin Dial 2003;16:118-127

- But Framingham risk score is poorly predictive in CKD (5 year-c statistic only 0.62 in men) and standard factors only partly account for elevated CV mortality rates in CKD patients



Weiner D. JACC 2007;50:217-24
Fleischman E.H. Clin Nephrol 200156:221-230.

Summary: Dx of CAD

- Diagnosis of CAD/MI can be challenging in CKD patients
- Standard non-invasive tests may have low negative and positive predictive values
- Maintenance of a high index of suspicion is crucial

Utilization of Cardiovascular Therapies in CKD

	CKD	No CKD	P
Angiography			
All Patients	25.2%	46.8%	<0.0001
Appropriate Candidates	29.6%	49.6%	<0.0001
Revascularization After Angiography	54.7%	62.0%	<0.0001

Chertow G. JASN 2005;15:2462-2468

Treatment of Stable CAD in the General Population

- Standard of care derived from large, randomized clinical trials
  - ASA/anti-platelet agents
  - Statins
  - ACE-I/ARB
  - Beta blocker
  - Percutaneous/surgical revascularization

Anti-Platelet Agents

- No randomized evidence for CAD endpoints in ESRD population
- 2-fold increase of the risk of bleeding with Clopidogrel + full dose ASA in ESRD (Kauffman JS. JASN 2003;14:2313-2321)
- Risk of CV death/MI decreased in general population of patients with hx of CVD administered Clopidogrel 75 mg/day + ASA (75-162 mg/day) vs ASA alone (Bhatt, DL. NEJM. 2006)
- Retrospective analyses suggest that relative efficacy of ASA is similar in patients with vs. without CKD (McCullough PA. Am Heart J 2002;144:226-232, Berger AK. JACC 2003;42:201-8)

- Recommendations:
  - ASA-all patients
  - Clopidogrel-consider with low dose ASA for patients with documented CAD and low bleeding risk

Statins

- 4D Trial (Wanner, C. NEJM 2005;353:238-248)
  - 1297 Diabetic HD patients with LDL 80-190 mg/dL
    - Lipitor 20 mg/day vs. placebo, well powered
    - HR for CV events 0.92 (0.77-1.10)
    - No difference in non-fatal MI (11% vs. 12%)
    - Small increase in CVA (10% vs. 7%)
    - Safety: No cases of rhabdomyolysis or severe liver disease
- Multiple trials/subgroup analyses demonstrating efficacy in general population and moderate CKD population
- Recommendation:
  - Statins for most patients with LDL>70
  - May consider holding in diabetic ESRD patients with LDL 100-160

ACE Inhibitors/ARB

- Fosodial Trial (Zannad, F. Kl. 2006;70:1318-24)
  - 397 HD patients on HD > 6 months
  - Fosinopril vs. placebo
  - HR for CV events 0.93 (0.68-1.26) but underpowered due lower than expected event rate

- Recommendation:
  - ACE-I/ARB-consider for all patients with stage 3-5 CKD
  - Efficacy in ESRD unknown

Beta-Blockers

- Carvedilol in ESRD (Cice, G. JACC.2003;41:1438-44)
  - 114 HD patients with dilated cardiomyopathy, EF<35% & NYHA class II or III CHF
  - Carvedilol ≤25 mg QD vs. Placebo for 24 months
  - HR for all-cause mortality 0.51 (0.32-0.82)
    - CV death HR 0.32 (0.18-0.57)
    - Non-fatal MI (11% vs. 12%)
    - Safety: side effects in < 10%
- Recommendation
  - Administer to all patients with low EF (grade 1 recommendation)
  - Consider for all patients post-MI regardless of EF

"Cardiorenal" for 100 Years

- Sir Thomas Lewis (1881-1945)

A Clinical Lecture

ON

PAROXYSMAL DYSPNOEA IN CARDIO-RENAL PATIENTS:

WITH SPECIAL REFERENCE TO "CARDIAC" AND "URAEMIC" ASTHMA.

DELIVERED AT UNIVERSITY COLLEGE HOSPITAL, LONDON, NOVEMBER 12TH, 1913.

BY THOMAS LEWIS, M.D., D.SC., F.R.C.P.

ASSISTANT PHYSICIAN AND LECTURER IN CARDIAC PATHOLOGY, UNIVERSITY COLLEGE HOSPITAL; PHYSICIAN TO OUT-PATIENTS, CITY OF LONDON HOSPITAL.

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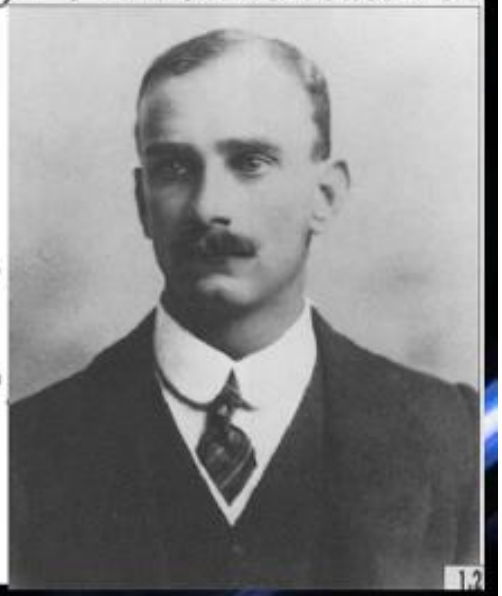
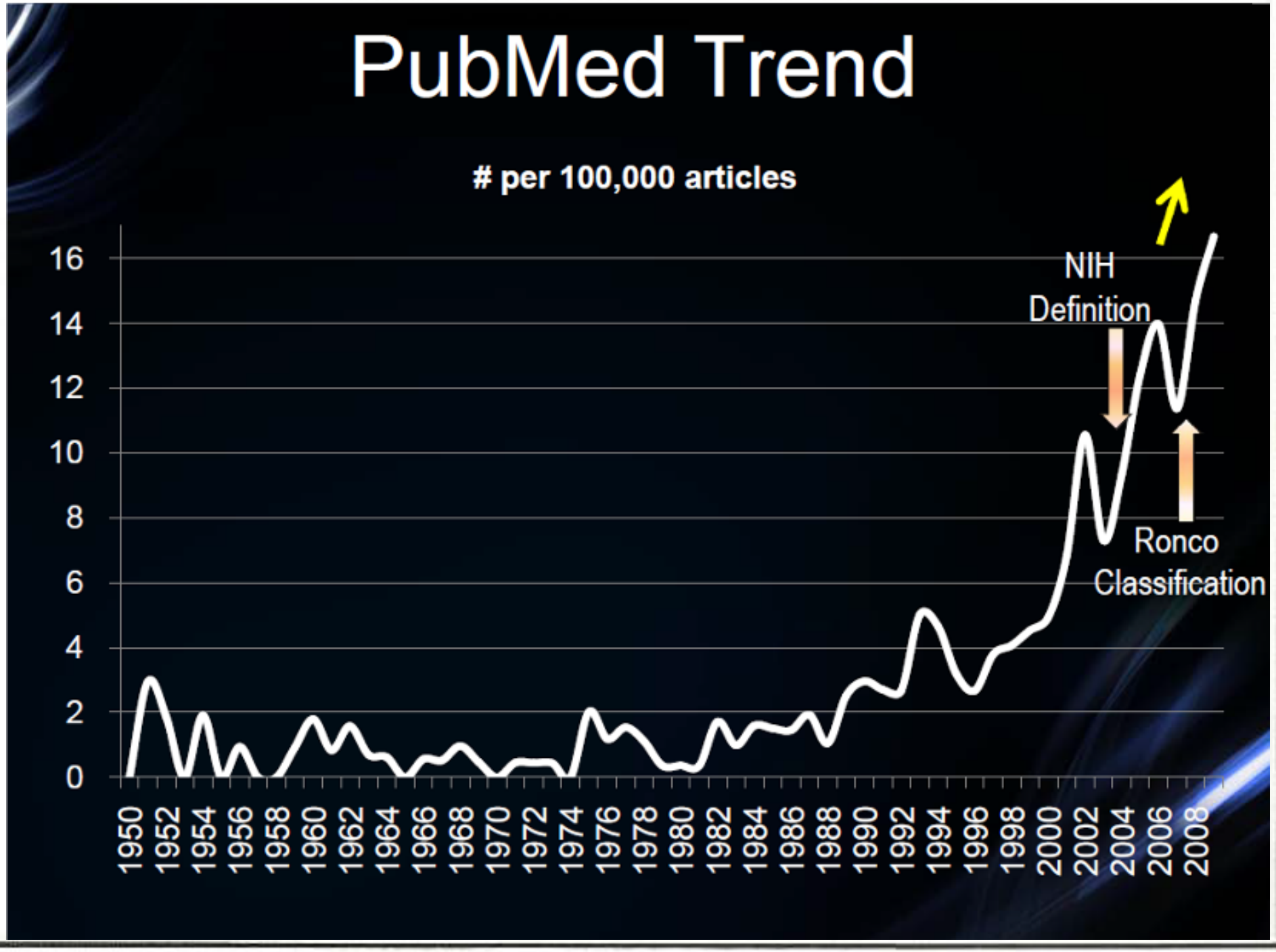


Lewis T., Br Med J 1913;2:1417-

PubMed Trend



Anemia, CKD and CHF Commonly Appear Together in Individual Patients

Observation that many patients with CKD and anemia also have CHF

Observed ~50% of patients with CHF have anemia and that low Hb is related to worse NYHA class

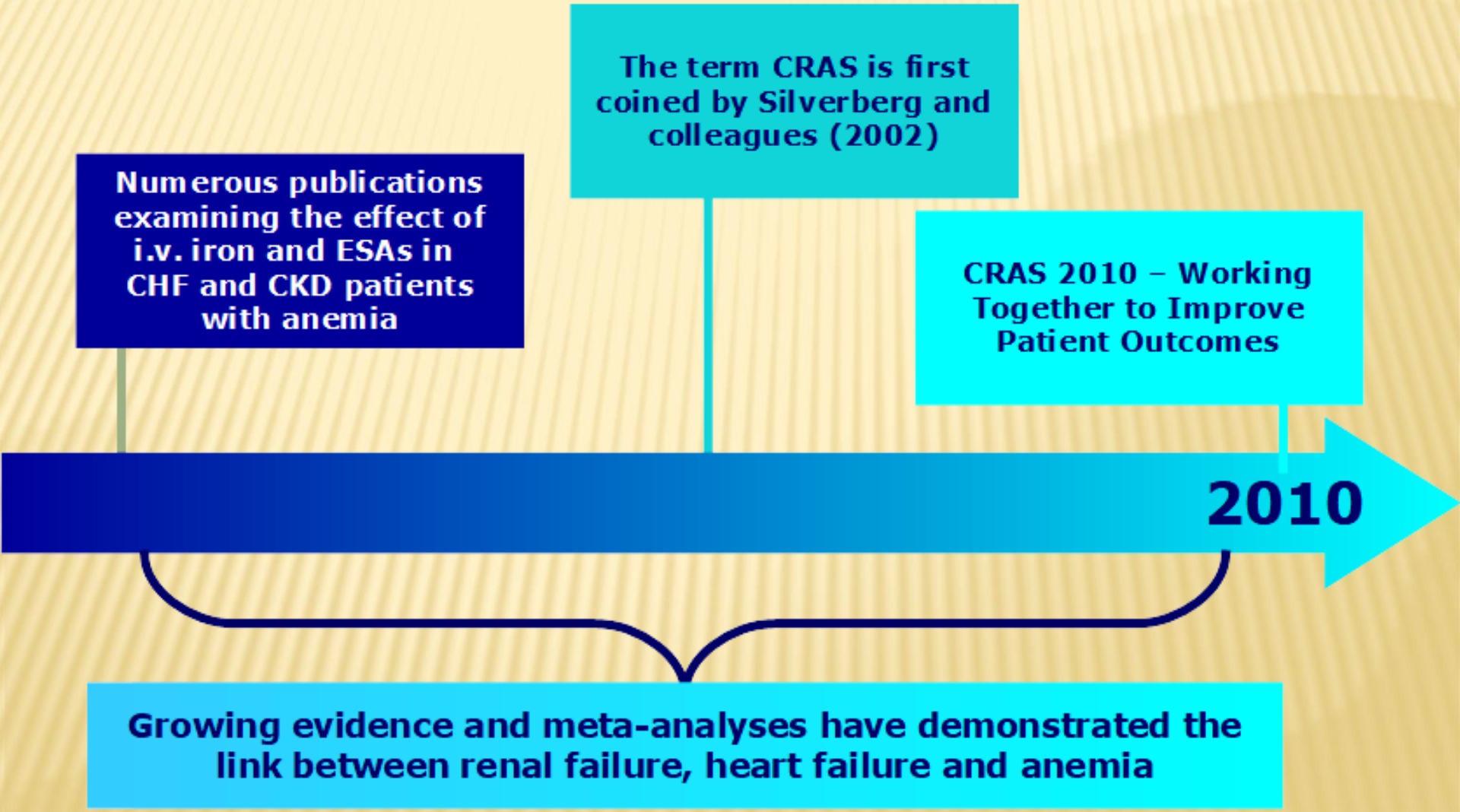
Correction of anemia with i.v. iron and ESA in patients with CKD positively affected CKD progression, NYHA class and QoL

Correction of anemia in patients with CHF produced similar results to those observed in patients with CKD and CHF

Late 1990s

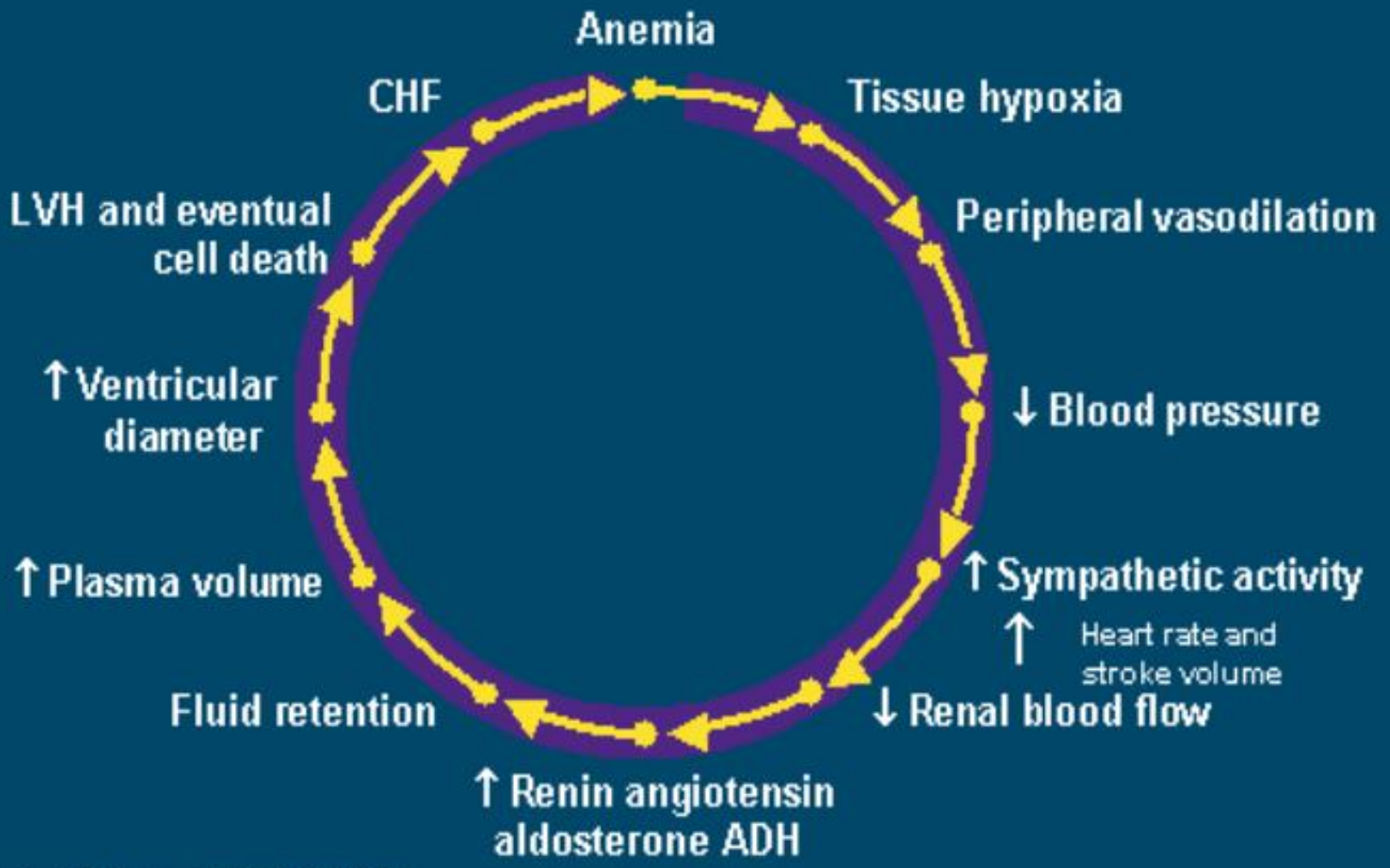
Hb, hemoglobin; NYHA, New York Heart Association; QoL, quality of life

Studies and Meta-analyses Demonstrate the Links Between CHF, CKD and Anemia



I.v., intravenous; ESA, erythropoiesis-stimulating agent

Anemia and cardiovascular disease



Anand et al Brit Ht J 1993; 70:357

THE COMPLICATED PUZZLE OF UREMIC CVD

Red- traditional (*i.e.*, Framingham) risk factors

Blue – inflammatory biomarkers

Green – endothelial dysfunction

Orange – vascular ossification

Brown – surrogate oxidative markers

Purple – adiopkines

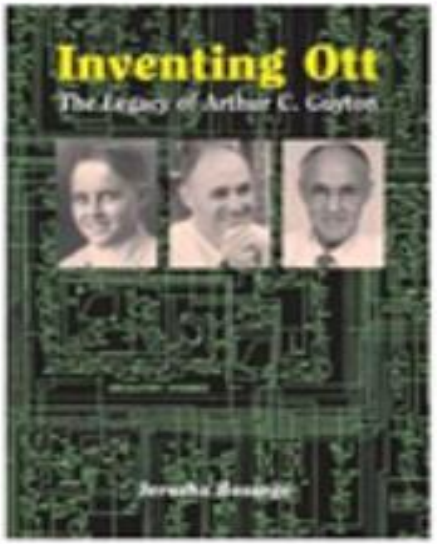
Grey - others

Clin J Am Soc Nephrol 2008;3: 505-521.

Arthur C. Guyton

(1919) – (2003)

"Father" of Modern Cardiovascular Physiology



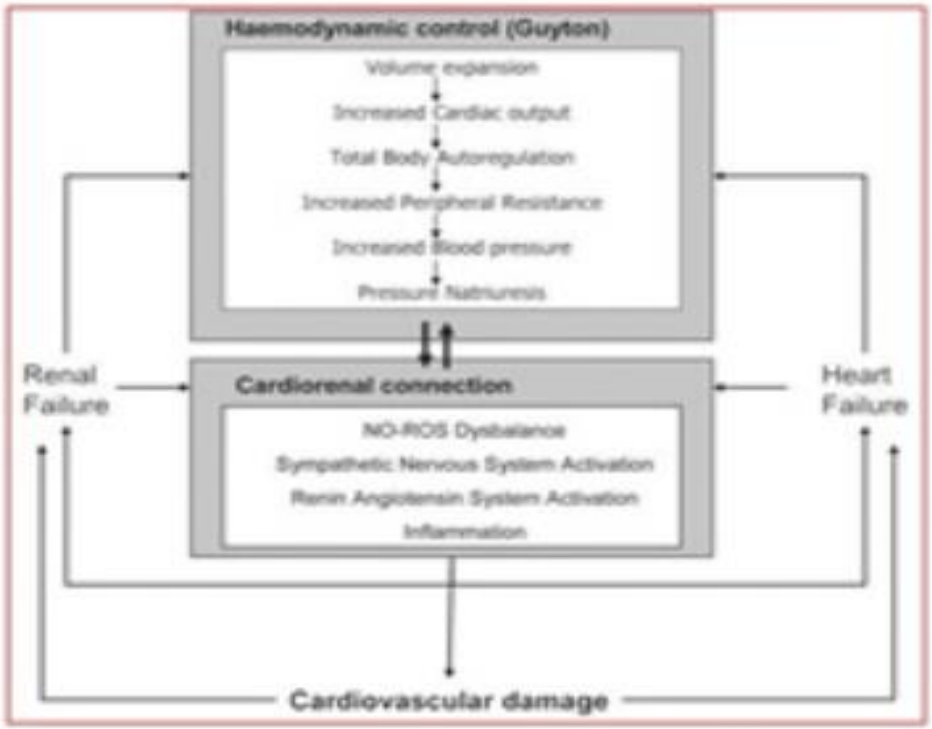
In 1950, Dr. Guyton did research that proved that the cardiac output was controlled by the body tissues' need for oxygen and not by the heart itself. In addition, he developed a computer model of the circulatory system and used it to demonstrate that the kidneys provided a long-term control of the blood pressure. He dedicated most of his research to the heart-kidney interactions.

GUYTON MODEL REVISITED

Bongartz, L., G. et al. Eur Heart J 2005 26:11-17

Severe cardiorenal syndrome represents a pathophysiological condition in which combined cardiac and renal dysfunction amplifies progression of failure of the individual organ, so that cardiovascular morbidity and mortality is increased.

Guyton has provided an excellent framework describing the physiological relationships between cardiac output, extracellular fluid volume control, and blood pressure. While this model is sufficient to understand systemic haemodynamics in combined cardiac and renal failure, not all aspects of the observed accelerated atherosclerosis, structural myocardial changes, and further decline of renal function can be explained.



Since increased activity of the renin-angiotensin system, oxidative stress, inflammation, and increased activity of the sympathetic nervous system seem to be cornerstones of the pathophysiology in combined chronic renal disease and heart failure, we have explored the potential interactions between these cardiorenal connectors. As such, the cardiorenal connection is an interactive network with positive feedback loops, which, in our view, forms the basis for the SCRS.

Conclusions

When you treat the failing heart well you also save the failing kidneys-they are Siamese twins

When you treat the failing kidneys well you also save the failing heart

When you correct the anemia in CHF or CKI you save both the failing heart and the failing kidneys

Cardiologists, other internists and nephrologists should work together in patients with CHF and CKI

"A Fatal Dance of Two Noble Organs"

Burl, D, *UCDavis, 2008.*

Before I came here I was confused about this subject. Having listened to your lecture I am still confused. But on a higher level.

-Enrico Fermi