CKD AND THE HEART

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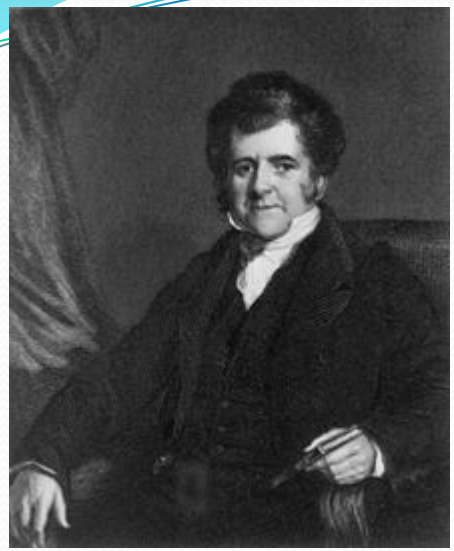
Città della Salute e della Scienza di Torino



Bright R. Cases and observations illustrative of renal disease accompanied with the secretion of albuminous urine. *Guy's Hospital Trans* 1836; **1**: 338–379.

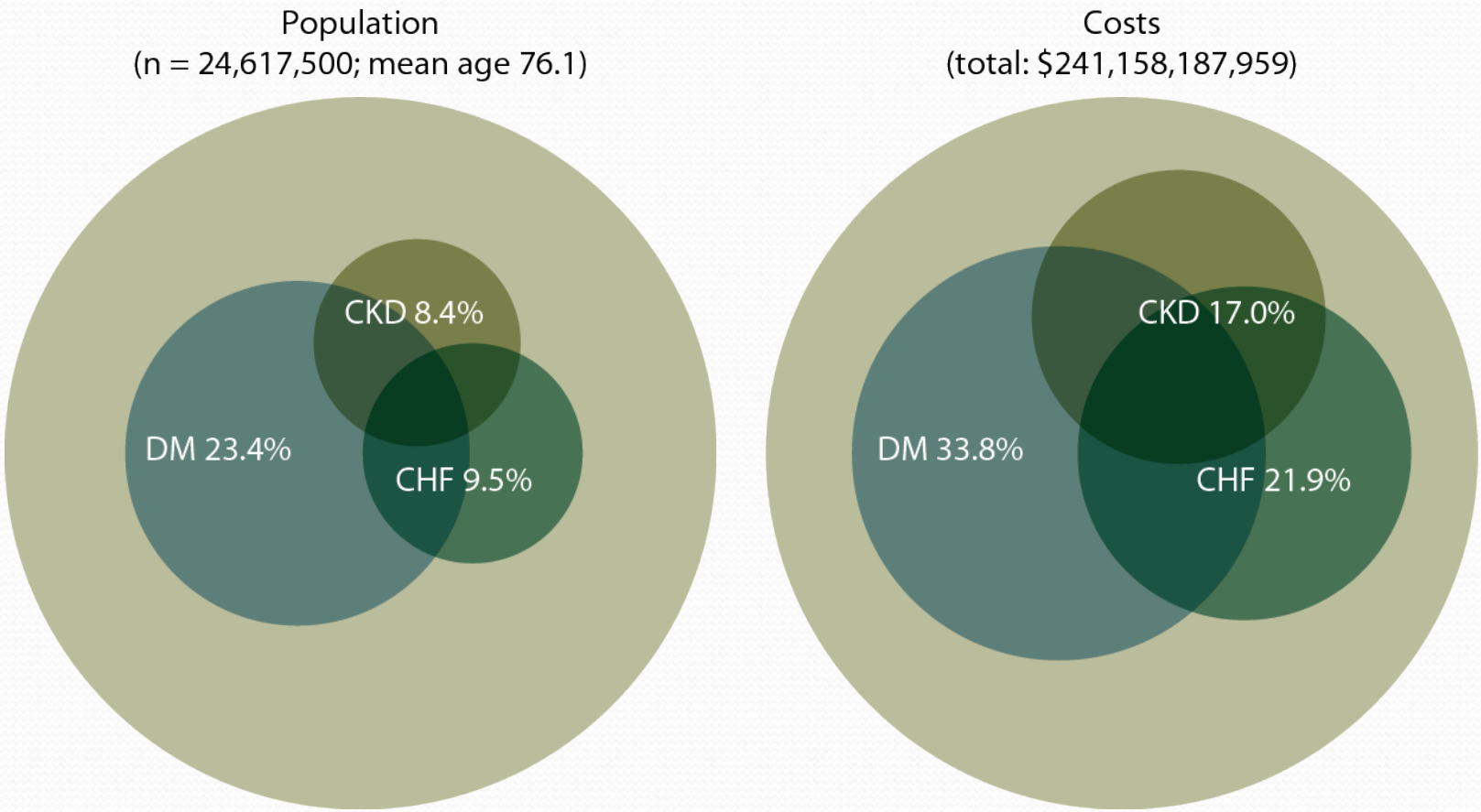
"It is observable, that the hypertrophy of the heart seems, in some degree, to have kept pace with the advance of disease in the kidneys; for in by far the majority of cases, when the heart was increased, the hardness and contraction of the kidney bespoke the probability of long continuance of the disease."

Prevalence of Chronic Kidney Diseases

Diseases	US Prevalence N (%)
CVD	**71,300,000 (34.2%)**
Hypertension	**65,000,000 (32.3%)**
CKD	**23,000,000 (11.6%)**
Diabetes	**20,600,000 (9.6%)**

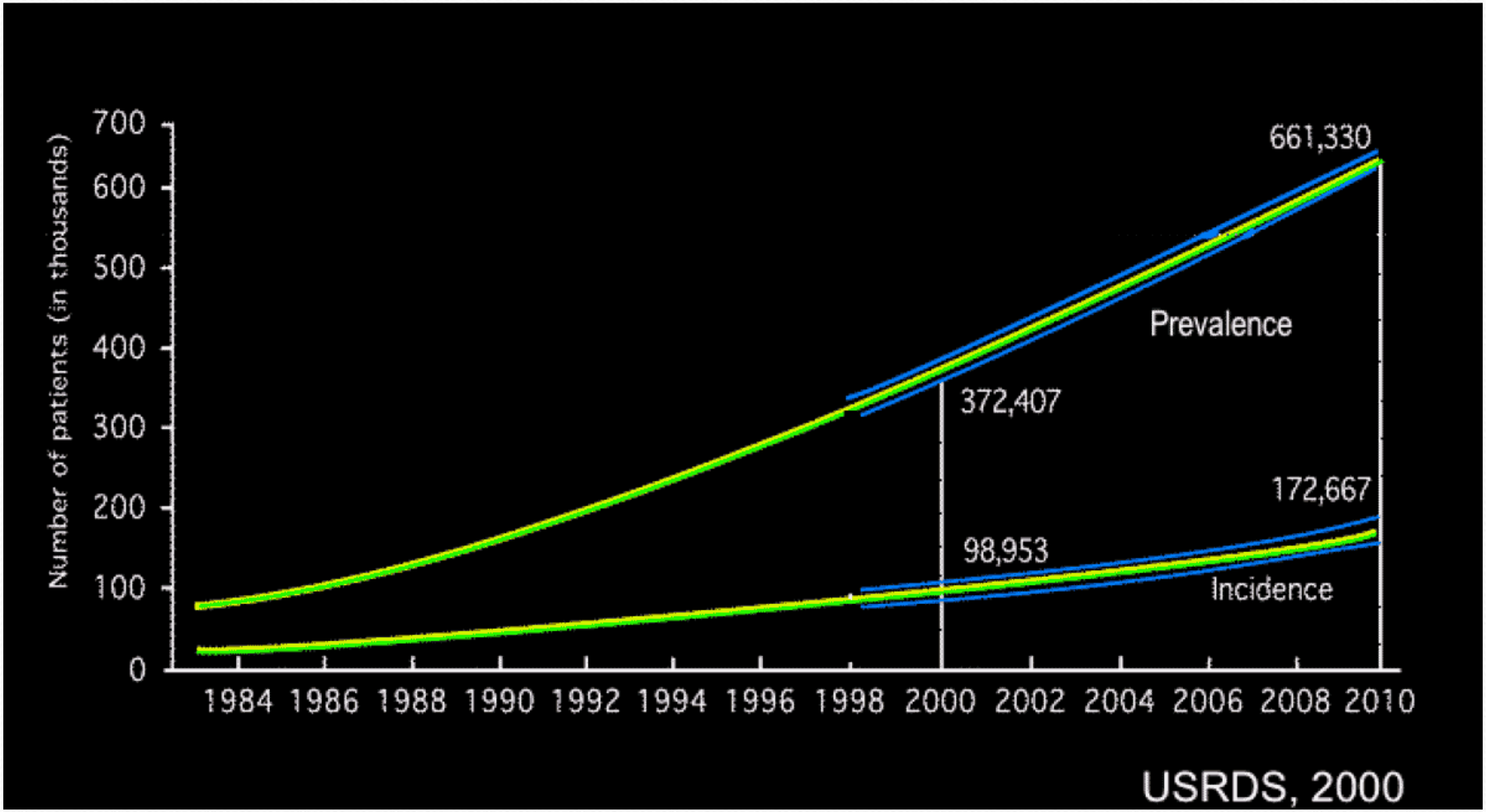
Levey, CDC Panel, AJKD 2009

Point prevalent distribution & annual costs of Medicare patients, age 65 & older, with diabetes, CHF & CKD

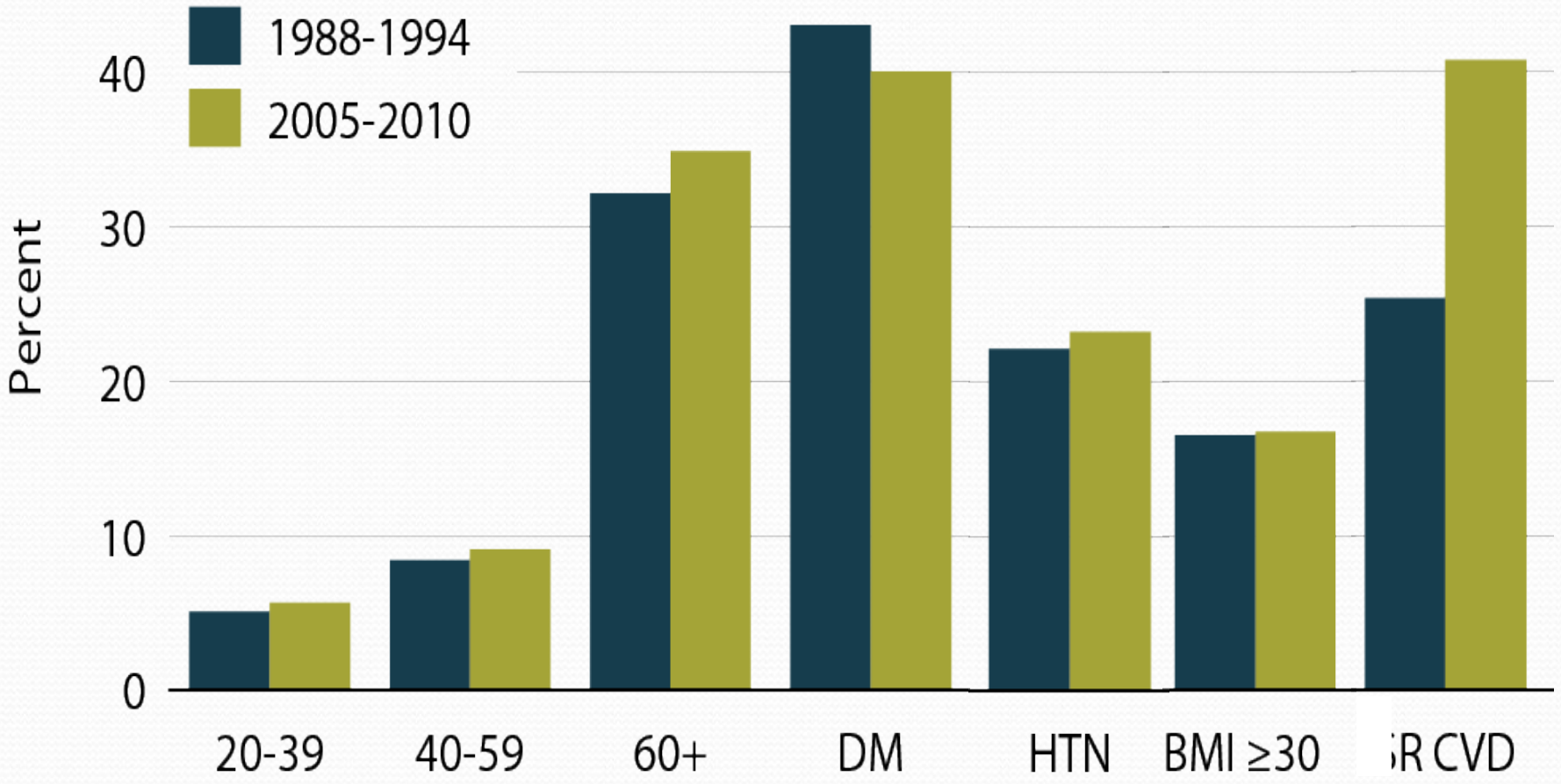


USRDS 2012 ADR

CHRONIC RENAL FAILURE (CRF): A RISING CLINICAL PROBLEM



NHANES participants with CKD by age & risk factor categories



USRDS 2012 ADR

Stages and Prevalence of Chronic Kidney Disease (Age 20)

Stage	Description	GFR (mL/min/1.73m^2)	Prevalence*	
	At increased risk	90 (with CKD risk factors)	N(1000s)	%
1.	Kidney damage with normal or ↑ GFR	90	5,900	3.3
2.	Kidney damage with mild ↓ GFR	60-89	5,300	3.0
3.	Moderate ↓ GFR	30-59	7,600	4.3
4.	Severe ↓ GFR	15-29	400	0.2
5.	Kidney Failure	<15 (or dialysis)	300	0.1

*Data for Stages 1-4 from NHANES III (1988-1994). Population of 177 million adults age 20 years. Data for Stage 5 from USRDS (1998) include approximately 230,000 patients treated by dialysis, and assume 70,000 additional patients not on dialysis. GFR estimated from serum creatinine using MDRD Study equation based on age, gender, race and calibration for serum creatinine. For stages 1 and 2, kidney damage estimated by spot albumin-to-creatinine ratio >17 mg/g in men or >25 mg/g in women on two measurements.

K/DOQI Clinical Practice Guidelines for Chronic Kidney Disease: Evaluation, Classification, and Stratification. Am J Kidney Diseases 2003;42: S1-S201.

Renal function as a risk indicator for cardiovascular events in 3216 patients with manifest arterial disease

Liesbeth Bax [a], Ale Algra [b,c], Willem P.Th.M. Mali [a], Michael Edlinger [b], Jaap J. Beutler [d], Yolanda van der Graaf [b,*], on behalf of the SMART study group [1]

Atherosclerosis 200 (2008) 184–190

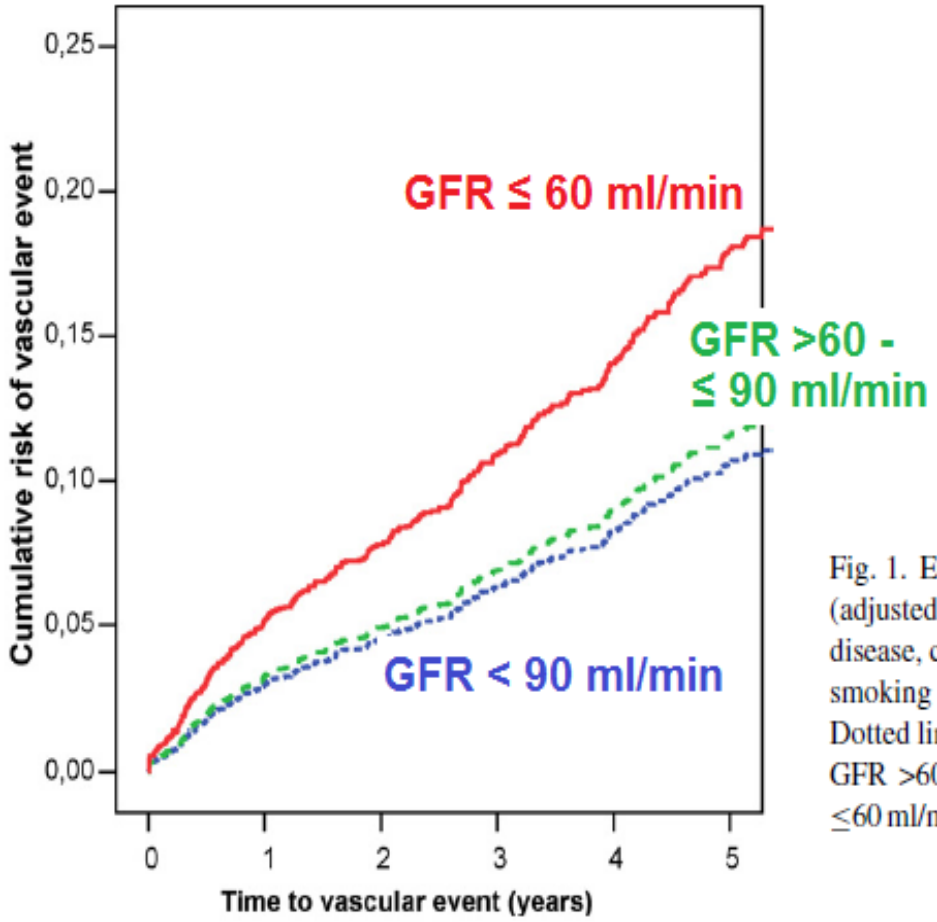


Fig. 1. Estimated survival curves for vascular events in MDRD-categories (adjusted for age, gender, body mass index, hypertension, coronary artery disease, cerebral disease, peripheral artery disease, AAA, diabetes mellitus, smoking and the use of ACE inhibitor and A-II antagonist medication). Dotted line: estimated GFR <90 ml/min per 1.73 m^2; dashed line: estimated GFR >60 and ≤90 ml/min per 1.73 m^2; continuous line: estimated GFR ≤60 ml/min per 1.73 m^2.

Chronic Kidney Disease and the Risks of Death, Cardiovascular Events, and Hospitalization

Alan S. Go, M.D., Glenn M. Chertow, M.D., M.P.H., Dongjie Fan, M.S.P.H., Charles E. McCulloch, Ph.D., and Chi-yuan Hsu, M.D.

N Engl J Med 2004;351:1296-305.

Table 2. Adjusted Hazard Ratio for Death from Any Cause, Cardiovascular Events, and Hospitalization among 1,120,295 Ambulatory Adults, According to the Estimated GFR.*

Estimated GFR	Death from Any Cause	Any Cardiovascular Event	Any Hospitalization
	adjusted hazard ratio (95 percent confidence interval)		
≥60 ml/min/1.73 m²†	1.00	1.00	1.00
45–59 ml/min/1.73 m²	1.2 (1.1–1.2)	1.4 (1.4–1.5)	1.1 (1.1–1.1)
30–44 ml/min/1.73 m²	1.8 (1.7–1.9)	2.0 (1.9–2.1)	1.5 (1.5–1.5)
15–29 ml/min/1.73 m²	3.2 (3.1–3.4)	2.8 (2.6–2.9)	2.1 (2.0–2.2)
<15 ml/min/1.73 m²	5.9 (5.4–6.5)	3.4 (3.1–3.8)	3.1 (3.0–3.3)

Estimated glomerular filtration rate and albuminuria for prediction of cardiovascular outcomes: a collaborative meta-analysis of individual participant data

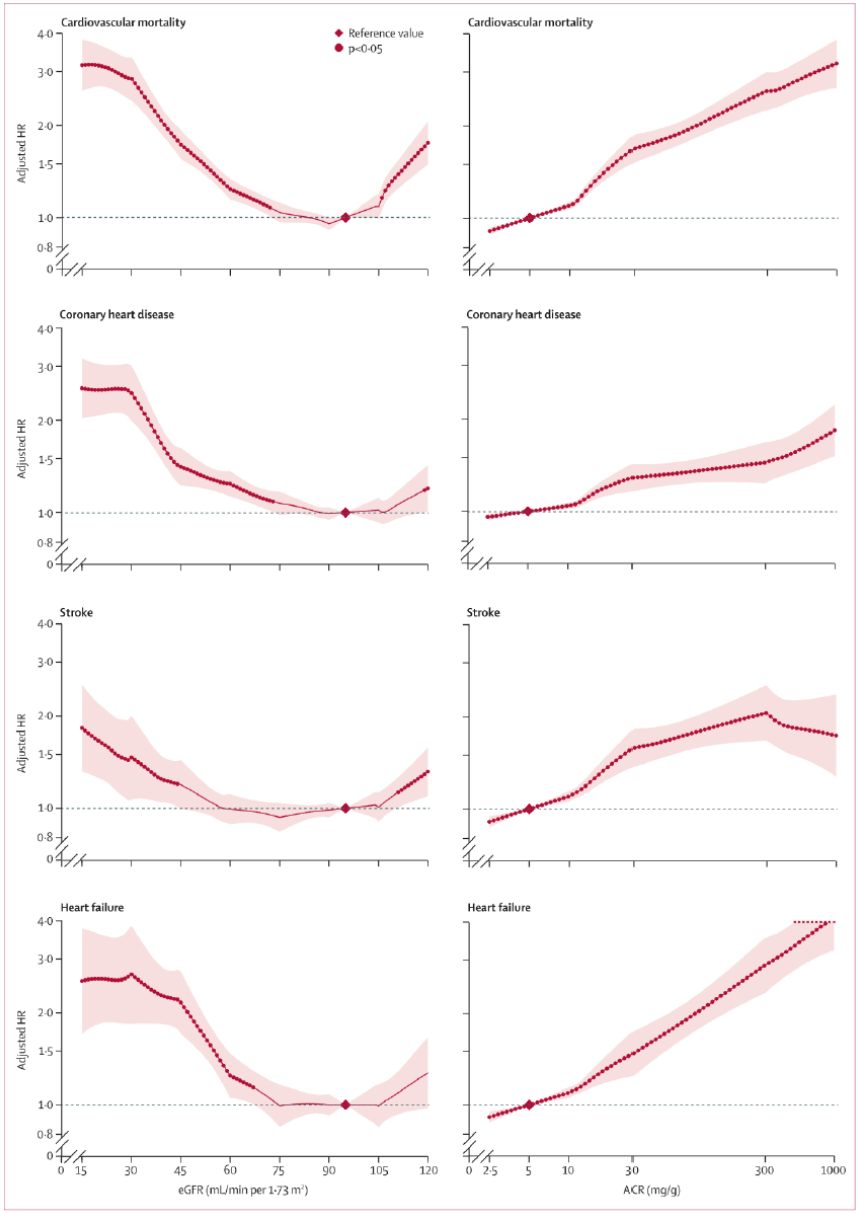
Kunihiro Matsushita, Josef Coresh, Yingying Sang, John Chalmers, Caroline Fox, Eliseo Guallar, Tazeen Jafar, Simerjot K Jassal, Gijs W D Landman, Paul Muntner, Paul Roderick, Toshimi Sairenchi, Ben Schöttker, Anoop Shankar, Michael Shlipak, Marcello Tonelli, Jonathan Townend, Arjan van Zuilen, Kazumasa Yamagishi, Kentaro Yamashita, Ron Gansevoort, Mark Sarnak, David G Warnock, Mark Woodward, Johan Ärnlöv, for the CKD Prognosis Consortium

Lancet Diabetes Endocrinol 2015;
3: 514–25

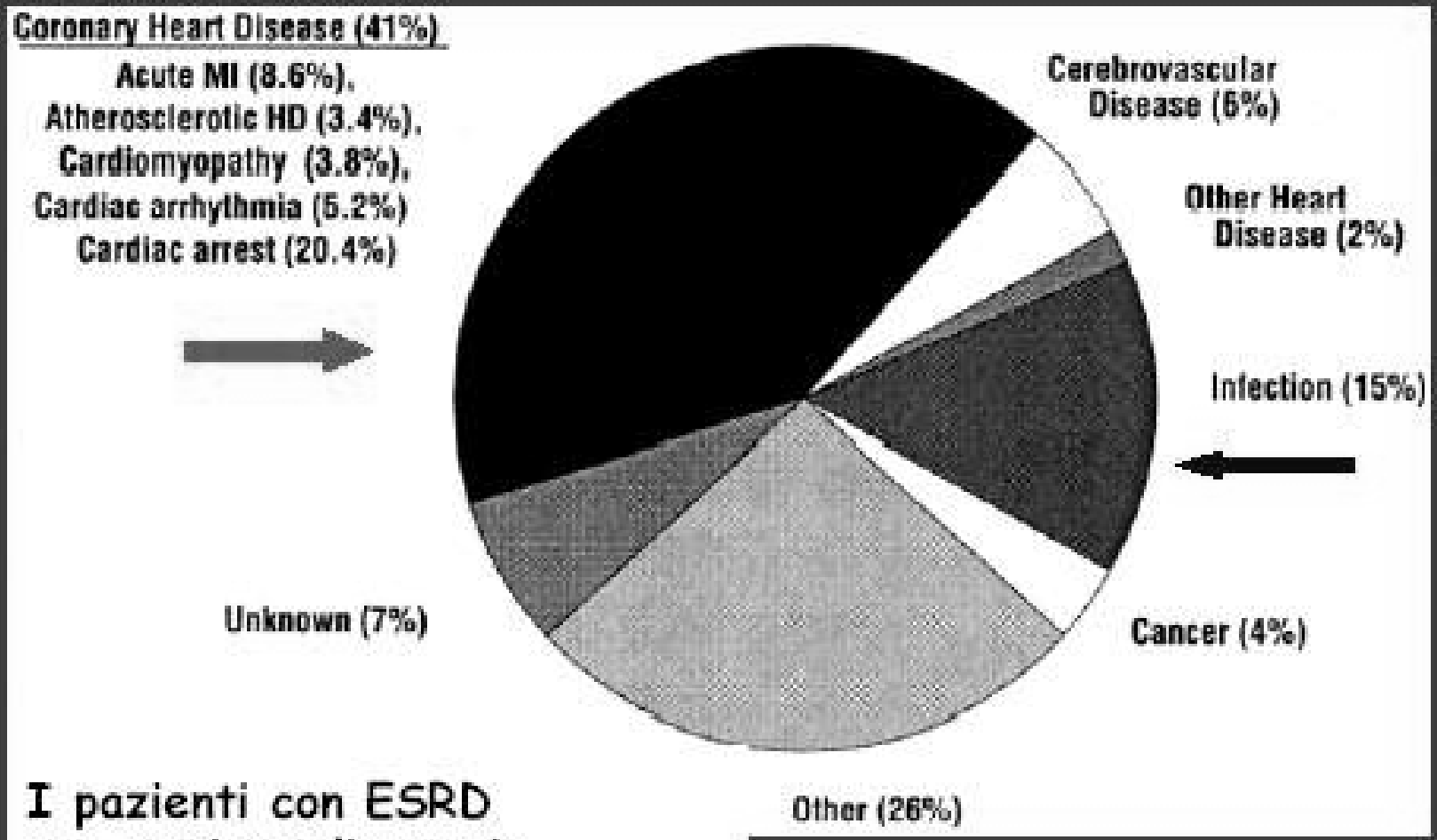
637 315 individuals without a history of cardiovascular disease

24 cohorts

median follow-up 4·2–19·0 years



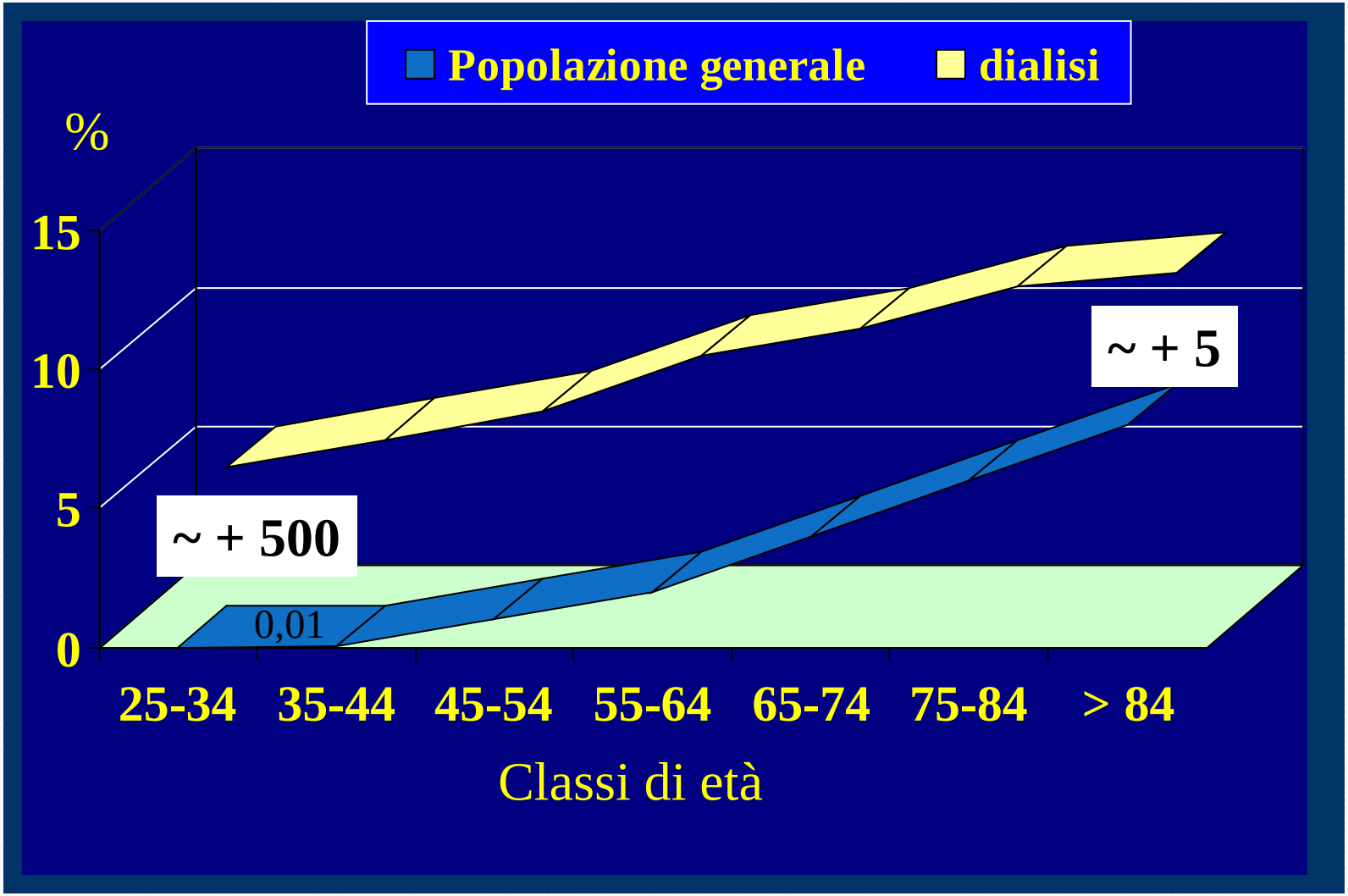
CAUSE OF DEATH IN ESRD PATIENTS



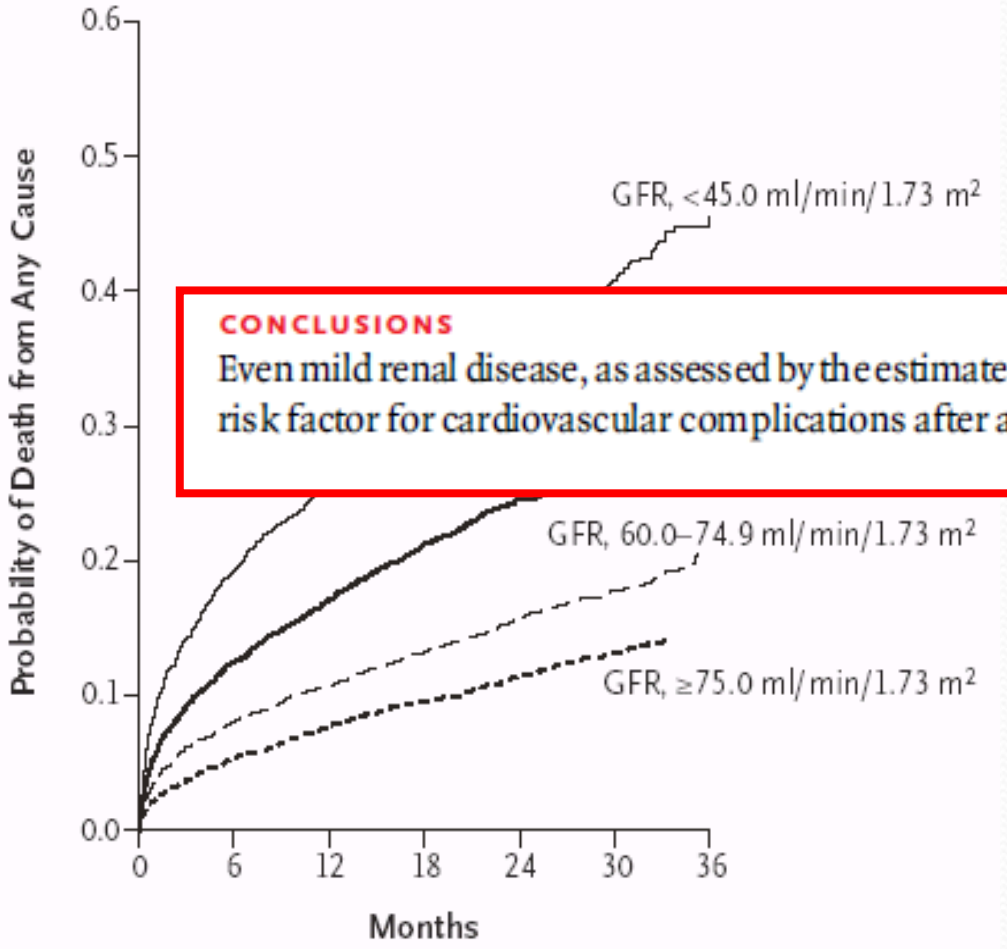
I pazienti con ESRD
non muoiono di uremia,
ma di malattie cardiovascolari,
come la popolazione generale

Dati USA - NKF

ANNUAL MORTALITY FOR CV DISEASE USRDS



RENAL DYSFUNCTION AND CARDIOVASCULAR OUTCOMES AFTER AMI: THE VALIANT TRIAL



n=14,527

CONCLUSIONS

Even mild renal disease, as assessed by the estimated GFR, should be considered a major risk factor for cardiovascular complications after a myocardial infarction.

Anavekar et al NEJM, 2004

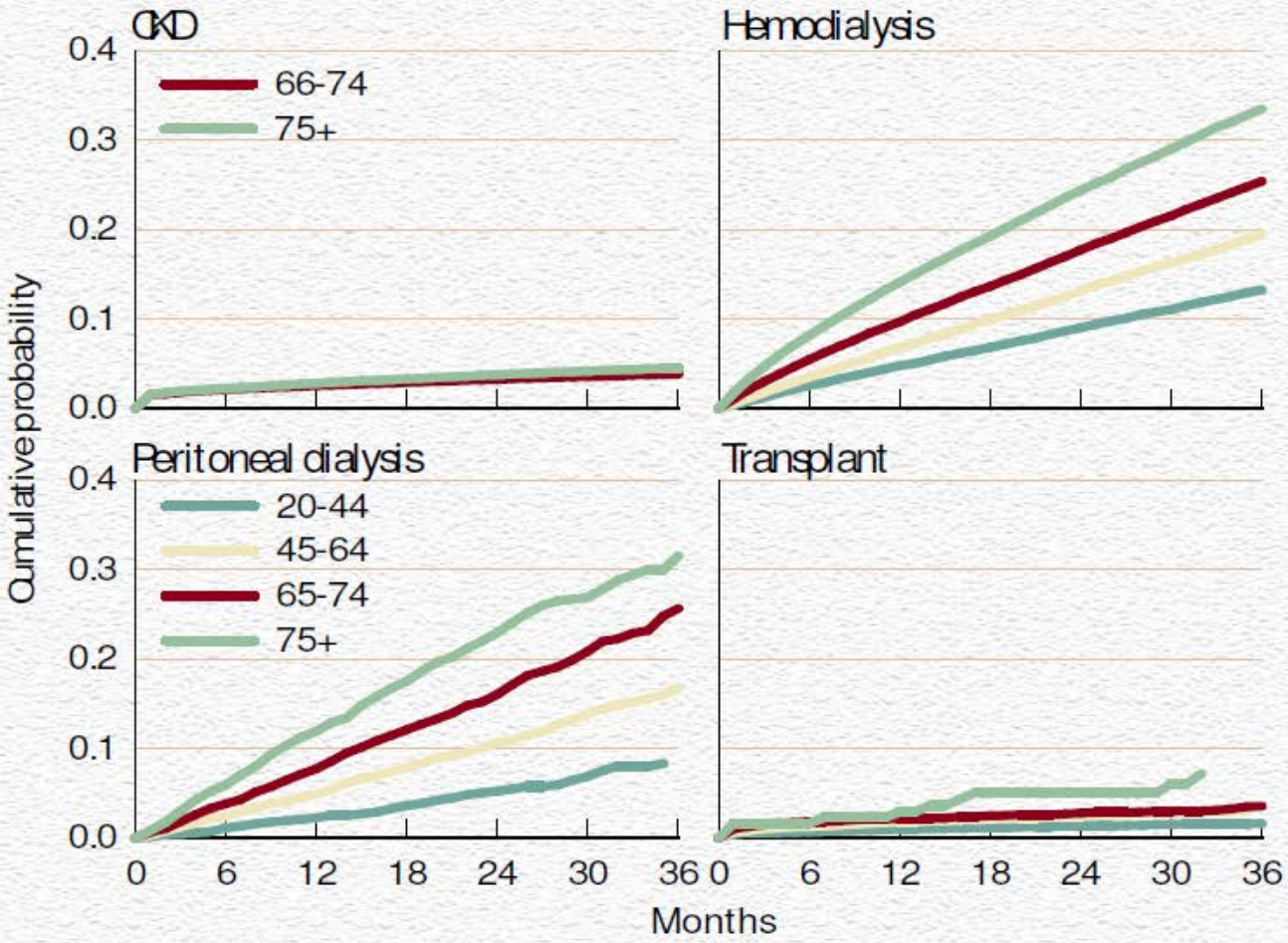
1. **More than a third of patients with HF has CKD**

(Cleland JGF,Eur Heart J 2003;24:442-463)
(Obialo Am J Cardiol 2007).
(Adams KF,Am Heart J 2005;149:209-216)

2. **CKD worsen HF prognosis :** every 0,5 mg/dl sCr increase leads to 15% increase in mortality

(GL Smith et al Renal impairment in heart failure, JACC 2006)

Probability of cardiac arrest in incident patients, by age



2006 ADR

USRDS

Clin Transplant 2009: 23: 653–659 DOI: 10.1111/j.1399-0012.2009.01018.x

Clinical Transplantation

Assessment of cardiovascular risk in waiting-listed renal transplant patients: a single center experience in 558 cases

G. Leonardi[a], M. Tamagnone[a], M. Ferro[b], G. Tognarelli[a], M. Messina[a], R. Giraudi[a], F. Fop[a], G. Picciotto[c], L. Biancone[a,d] and G.P. Segoloni[a,d]

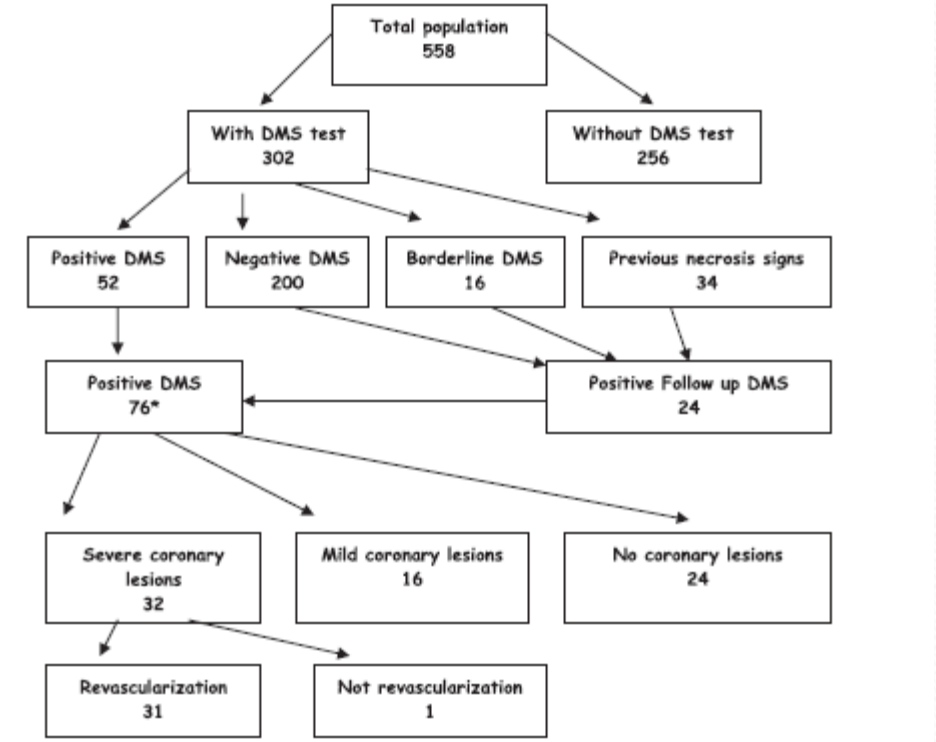


Table 3. Dipyridamole-stress sestamibi myocardial scintiscan (DMS) indications in the study population

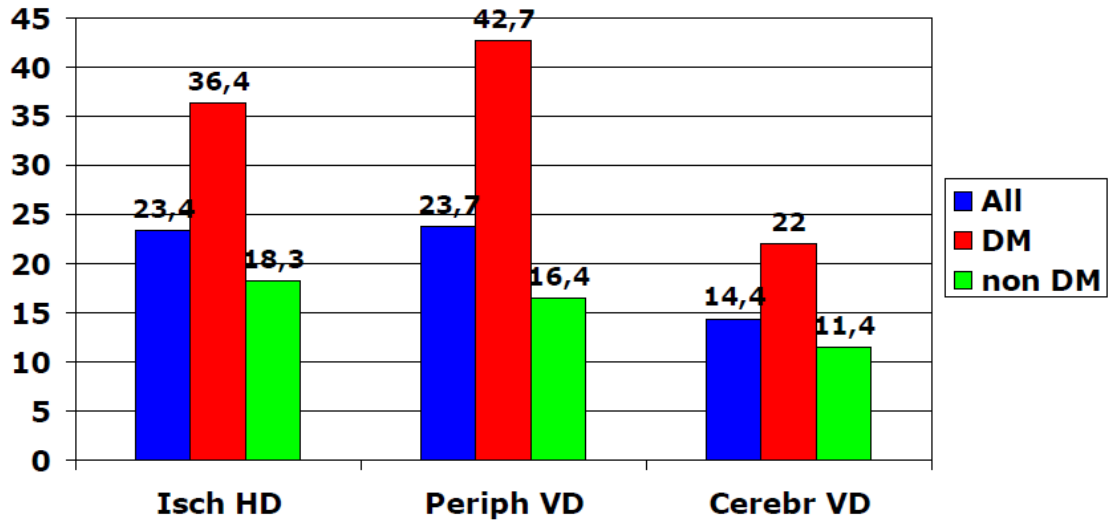
DMS indication[a]	Number of patients	%
Echocardiographic abnormality	10	3.3
Electrocardiogram abnormality	1	0.3
Age ≥55 yr[b]	152	50.3
Diabetes mellitus	6	2.0
Severe dyslipidemia	1	0.3
≥20 yr on dialysis treatment	2	0.7
≥15 yr of arterial hypertension	38	12.6
≥15 yr of steroid therapy	4	1.3
As requested by the nephrologists	18	6.0
History of cardiac disease or symptoms	40	13.2
Others or multiple indications	30	9.9
Total	302	100

[a]Patients who had multiple indications for DMS are included in "Others or multiple indications."
[b]"Age ≥55 yr" includes all patients who performed DMS on the basis of age indication, even if they could have had some other indications.

Increased prevalence of CVD

ERA-EDTA Registry data (5 countries – 1994 to 2001)

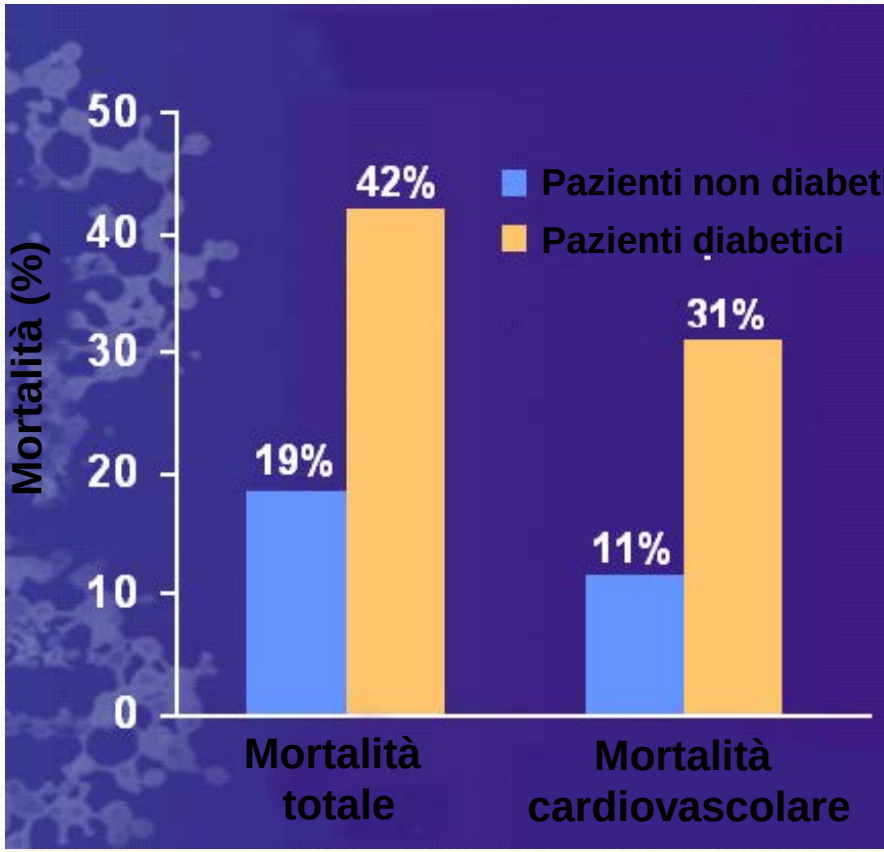
Prevalence of cardiovascular co-morbidity at the start of dialysis



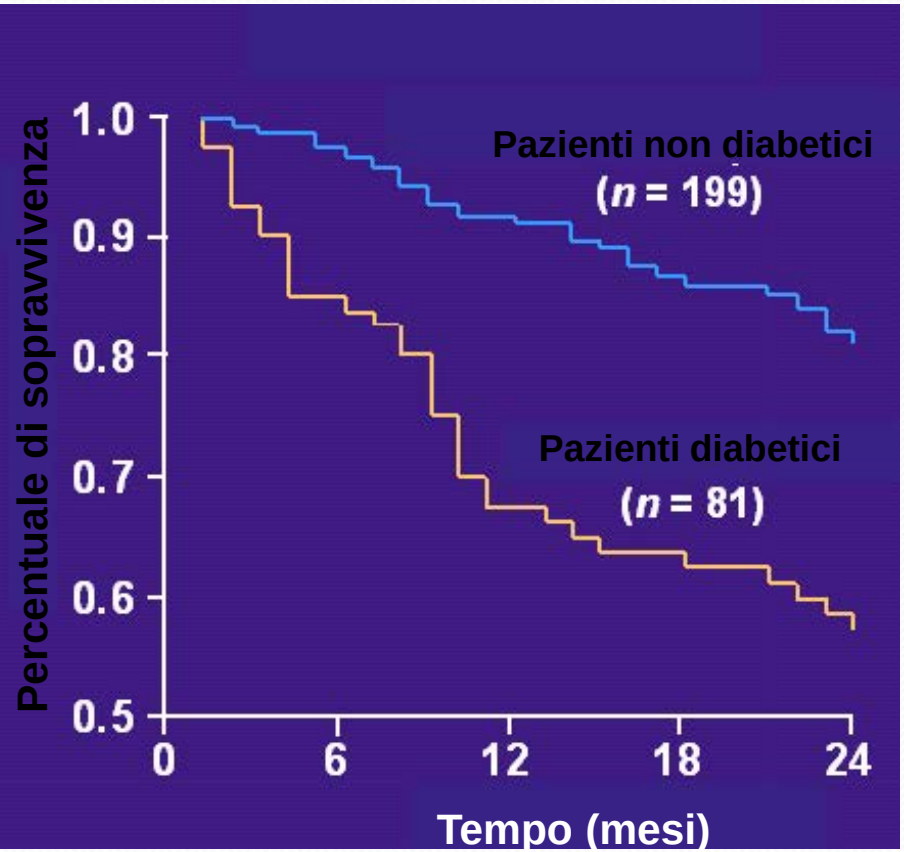
Stel VS et al. Prevalence of co-morbidity in different European RRT populations and its effect on access to renal transplantation. NDT 2005: 2803–2811

Mortalità tra i pazienti emodializzati con insufficienza renale terminale

Mortalità a 2 anni

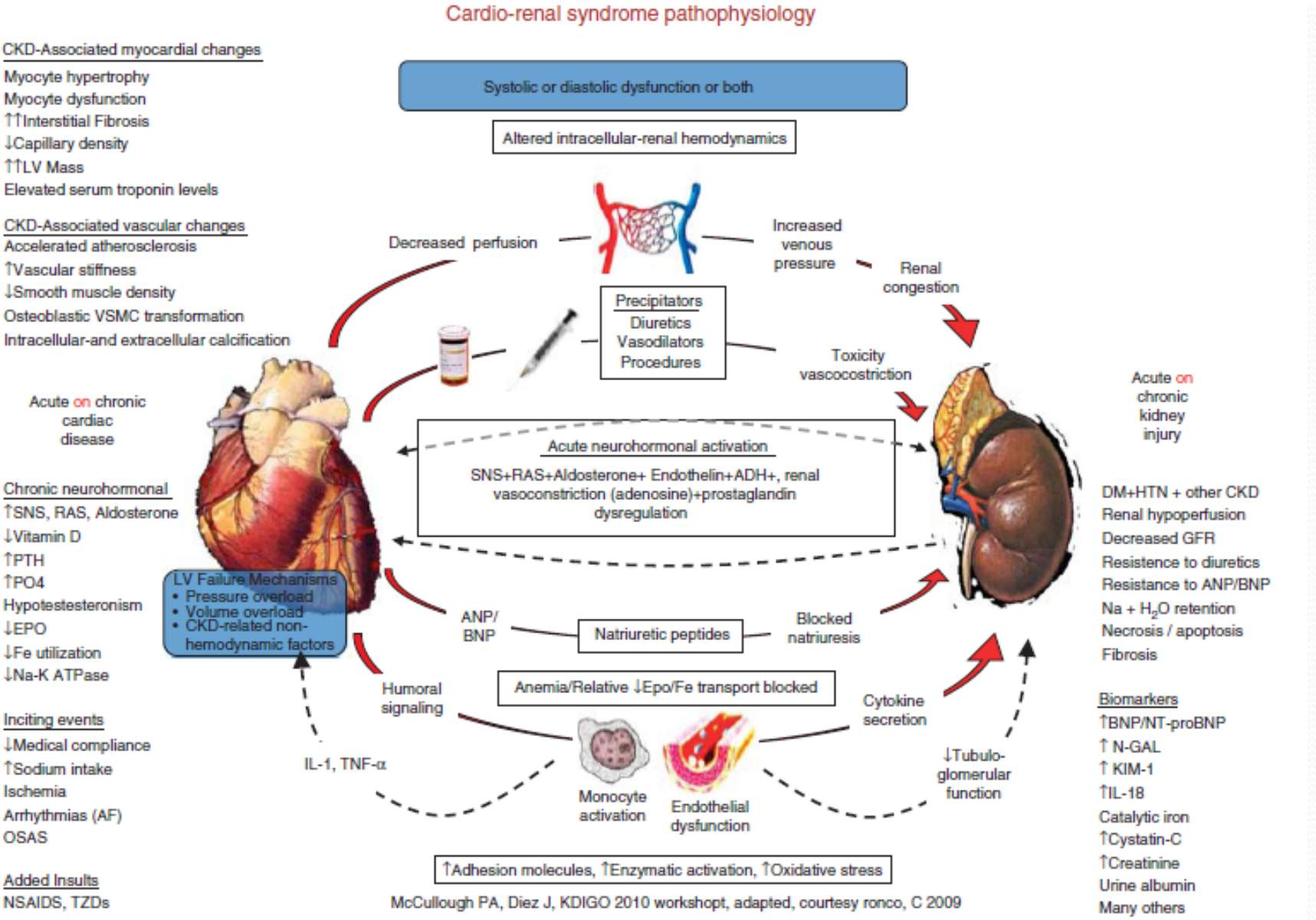


Sopravvivenza a 2 anni



Cardiovascular disease in chronic kidney disease. A clinical update from Kidney Disease: Improving Global Outcomes (KDIGO)

Kidney International (2011) 80, 572–586



Journal of the American College of Cardiology
© 2008 by the American College of Cardiology Foundation
Published by Elsevier Inc.

Vol. 52, No. 19, 2008
ISSN 0735-1097/08/$34.00
doi:10.1016/j.jacc.2008.07.051

STATE-OF-THE-ART PAPER

Cardiorenal Syndrome

Claudio Ronco, MD,* Mikko Haapio, MD,† Andrew A. House, MSc, MD,‡ Nagesh Anavekar, MD,§ Rinaldo Bellomo, MD¶

Vicenza, Italy; Helsinki, Finland; London, Ontario, Canada; and Melbourne, Australia

CRS, general definition
A complex pathophysiologic disorder of the heart and kidneys where acute or chronic dysfunction in one organ may induce acute or chronic dysfunction in the other organ

***CRS type I** (acute CRS)*
Abrupt worsening of cardiac function (e.g. acute cardiogenic shock or acute decompensation of chronic heart failure) leading to kidney injury

***CRS type II** (chronic CRS)*
Chronic abnormalities in cardiac function (e.g. chronic heart failure) causing progressive chronic kidney disease

***CRS type III** (acute renocardiac syndrome)*
Abrupt worsening of renal function (e.g. acute kidney failure or glomerulonephritis) causing acute cardiac disorder (e.g. heart failure, arrhythmia, or pulmonary edema)

***CRS type IV** (chronic renocardiac syndrome)*
Chronic kidney disease (e.g. chronic glomerular disease) contributing to decreased cardiac function, cardiac hypertrophy and/or increased risk of adverse cardiovascular events

***CRS type V** (secondary CRS)*
Systemic condition (e.g. diabetes mellitus or sepsis) causing both cardiac and renal dysfunction

SINDROME DISTINTA IN 5 SOTTOGRUPPI DIFFERENTI PER FISIOPATOLOGIA.

DISORDINE DEL CUORE E DEI RENI NELLA QUALE LA DISFUNZIONE ACUTA O CRONICA DI UN ORGANO PUO' INDURRE DISFUNZIONE DELL'ALTRO.

I BIOMARCATORI POSSONO CONTRIBUIRE A PRECOCE DIAGNOSI DELLA SINDROME E AD INTERVENTI TERAPEUTICI PRECOCI.

L'UTILIZZO DI QUESTA CLASSIFICAZIONE PUO' AIUTAR A CREARE GRUPPI DI PAZIENTI PROVVEDENDO A REALIZZARE STRATEGIE SPECIFICHE INTERVENTISTICHE.

POSSIBILI FUTURI CLINICAL TRIALS SU POPOLAZIONE ATTENTAMENTE SELEZIONATA E STRATIFICATA.

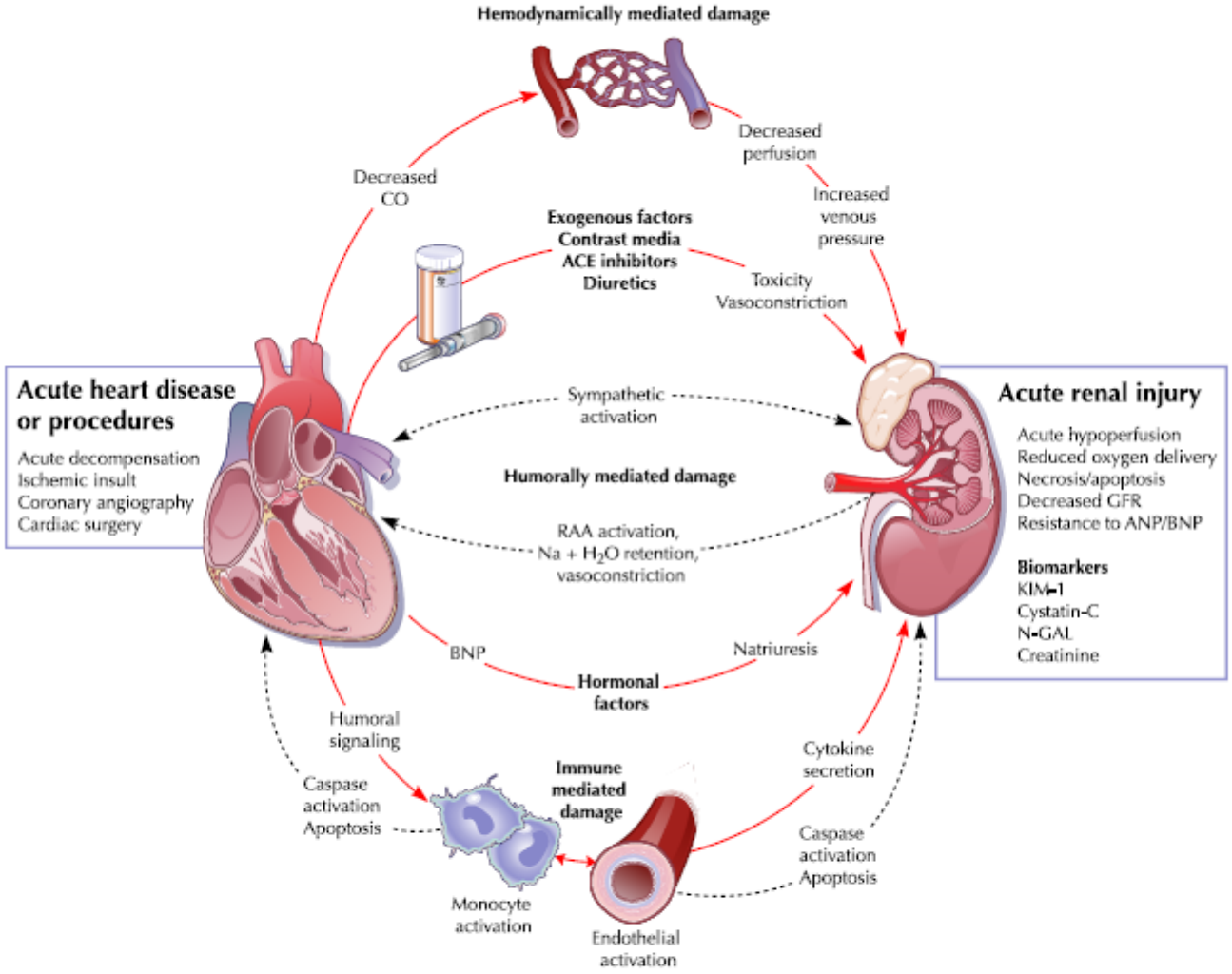
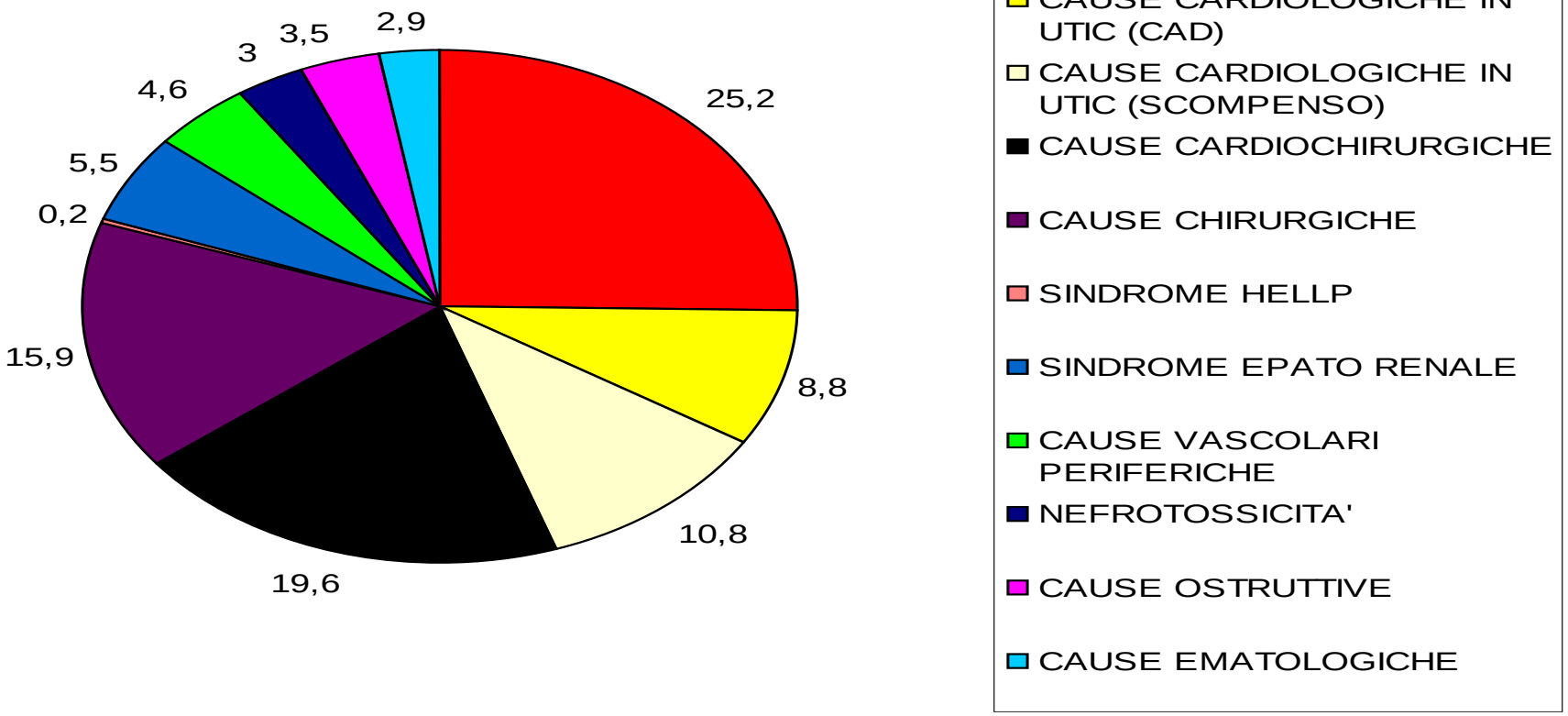


Figure 1 **CRS Type 1**

Pathophysiological interactions between heart and kidney in type 1 cardiorenal syndrome (CRS) or "acute CRS" (abrupt worsening of cardiac function, e.g., acute cardiogenic shock or acute decompensation of chronic heart failure) leading to kidney injury. ACE = angiotensin-converting enzyme; ANP = atrial natriuretic peptide; BNP = B-type natriuretic peptide; CO = cardiac output; GFR = glomerular filtration rate; KIM = kidney injury molecule; N-GAL = neutrophil gelatinase-associated lipocalin; RAA = renin angiotensin aldosterone. Figure illustration by Rob Flewell.

PERCENTUALE DI CAUSE PRINCIPALI DI IRA NELLA CASISTICA DELL'OSPEDALE SAN GIOVANNI BATTISTA - TORINO



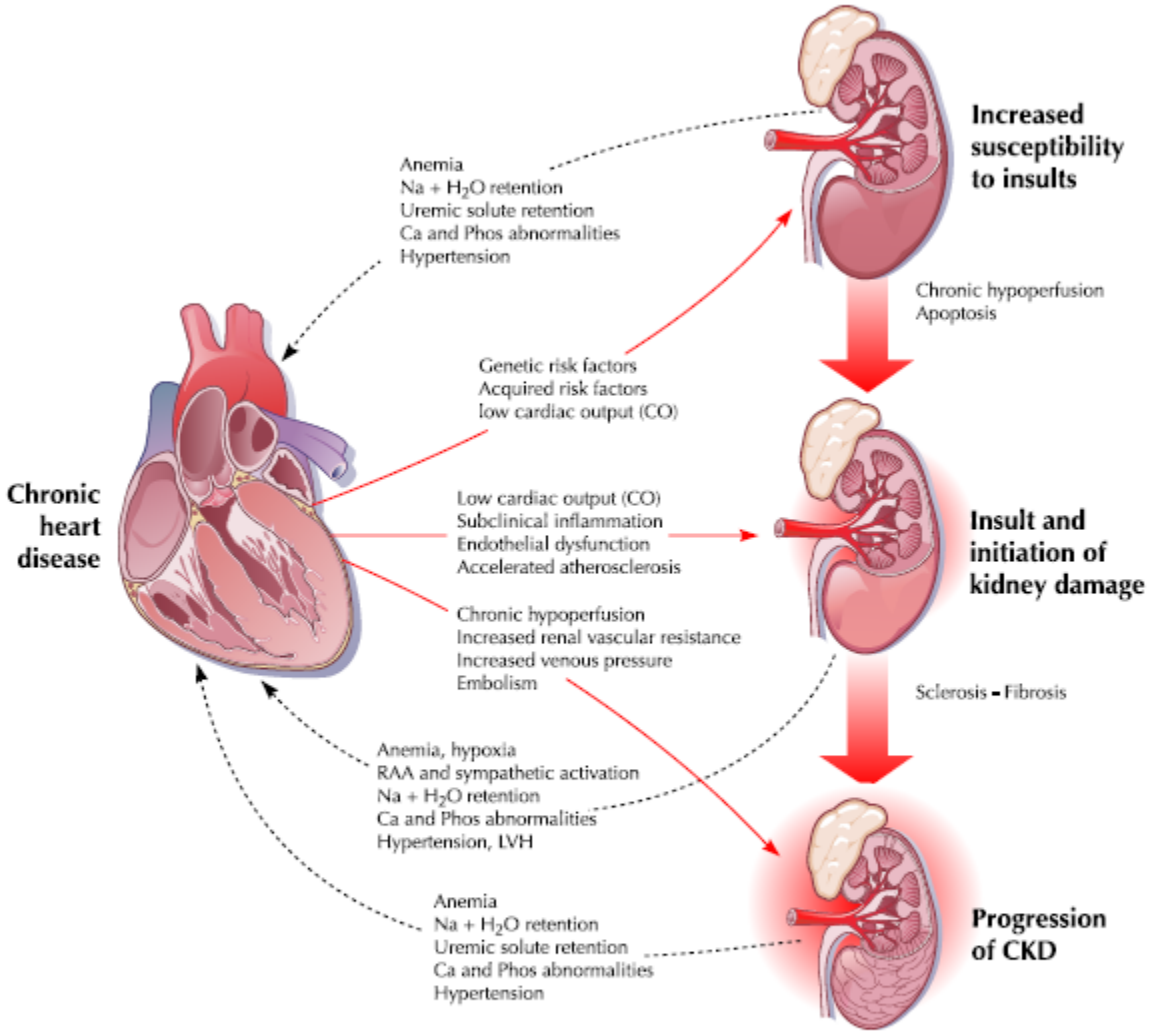


Figure 2 **CRS Type 2**

Pathophysiological interactions between heart and kidney in type 2 cardiorenal syndrome (CRS) or "chronic CRS" (chronic abnormalities in cardiac function, e.g., chronic heart failure) causing progressive chronic kidney disease (CKD). Figure illustration by Rob Flewell. LVH = left ventricular hypertrophy; RAA = renin angiotensin aldosterone.

The NEW ENGLAND JOURNAL of MEDICINE

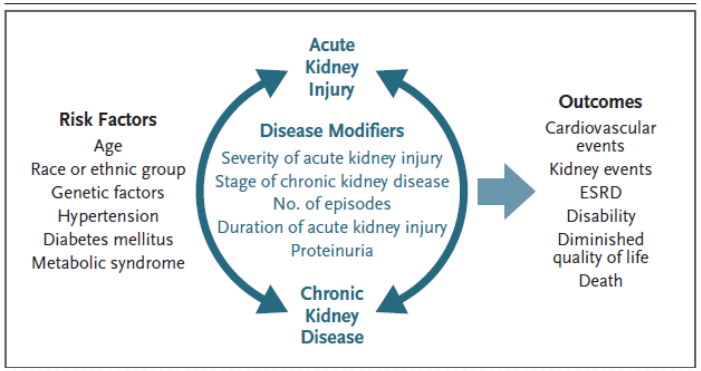
REVIEW ARTICLE

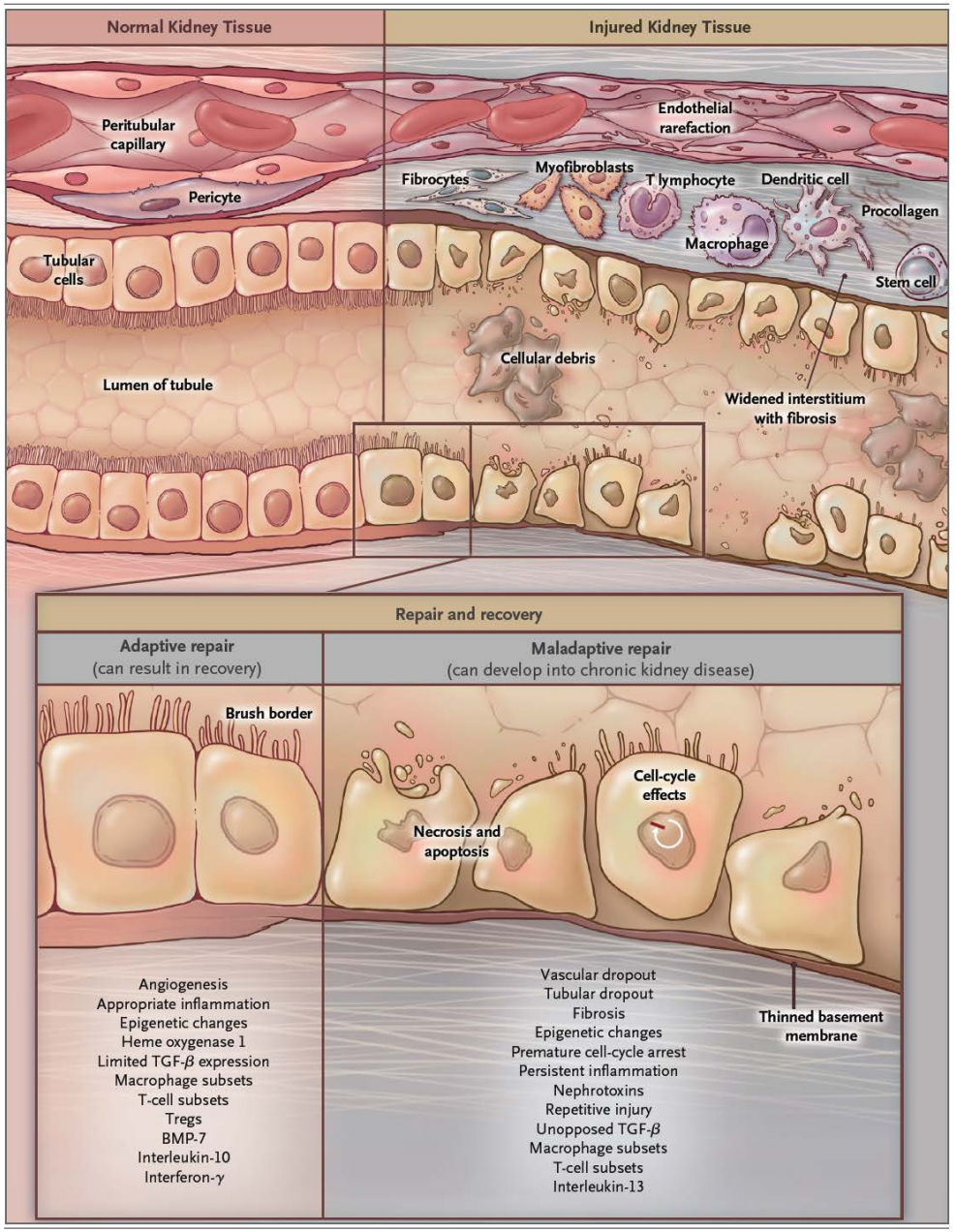
Julie R. Ingelfinger, M.D., *Editor*

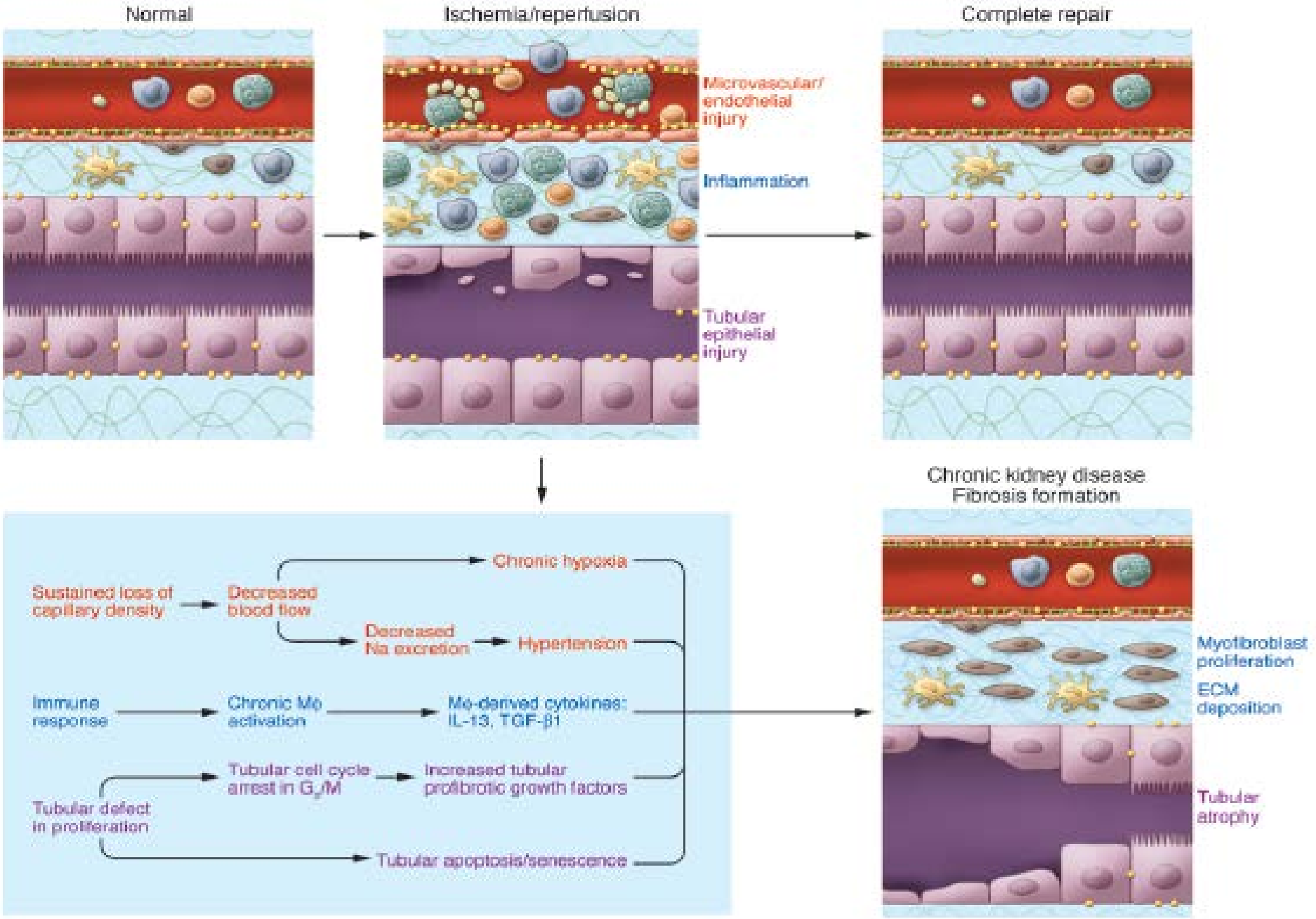
Acute Kidney Injury and Chronic Kidney Disease as Interconnected Syndromes

Lakhmir S. Chawla, M.D., Paul W. Eggers, Ph.D.,
Robert A. Star, M.D., and Paul L. Kimmel, M.D.

N ENGL J MED 371;1 NEJM.ORG JULY 3, 2014





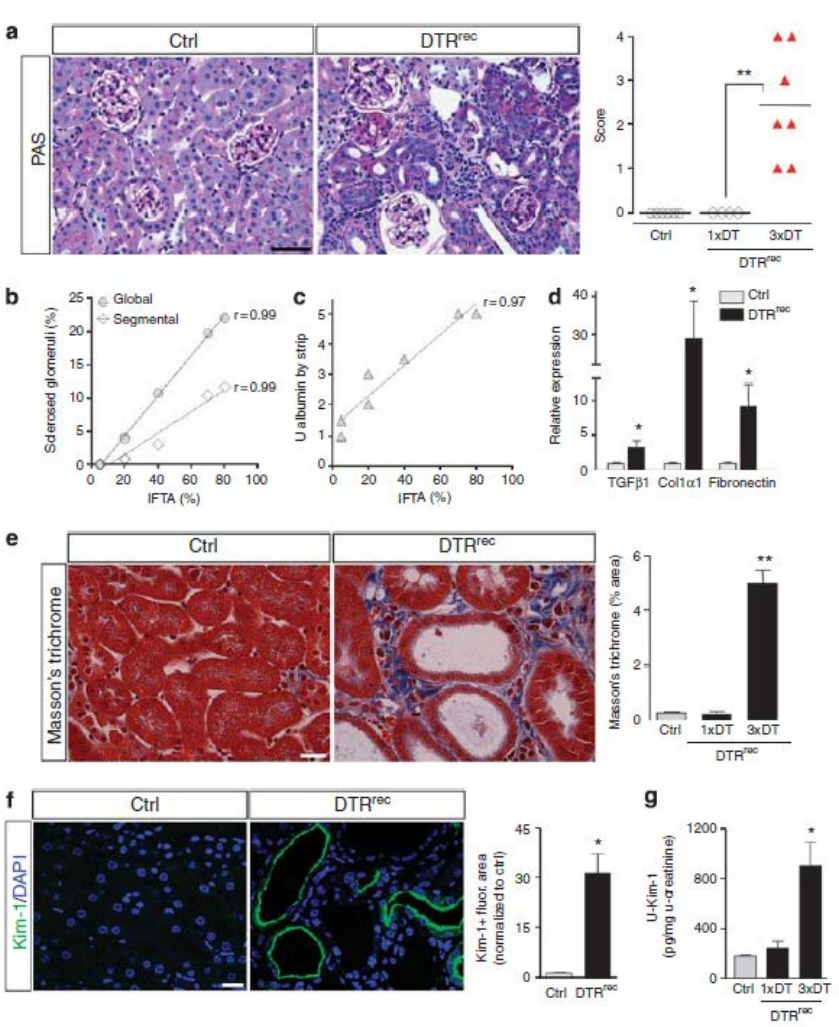


Bonventre JV. Cellular pathophysiology of ischemic acute kidney injury. *JCI*. 2011;121(11):4210-21.

Targeted proximal tubule injury triggers interstitial fibrosis and glomerulosclerosis

Ivica Grgic[1,2,6], Gabriela Campanholle[1,6], Vanesa Bijol[3], Chang Wang[1], Venkata S. Sabbisetti[1], Takaharu Ichimura[1], Benjamin D. Humphreys[1,4] and Joseph V. Bonventre[1,4,5]

Kidney International (2012) **82**, 172–183

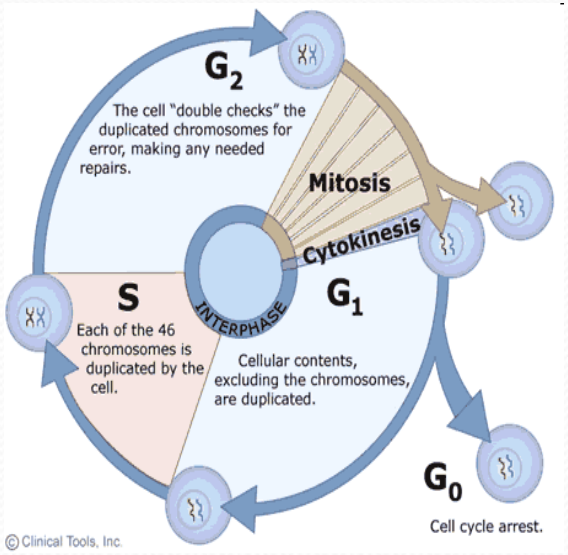


AKI: progressione verso CKD: nuovi meccanismi fisiopatologici

Epithelial cell cycle arrest in G2/M mediates kidney fibrosis after injury

Yang L, Bonventre JV et al, Nat Med 2010

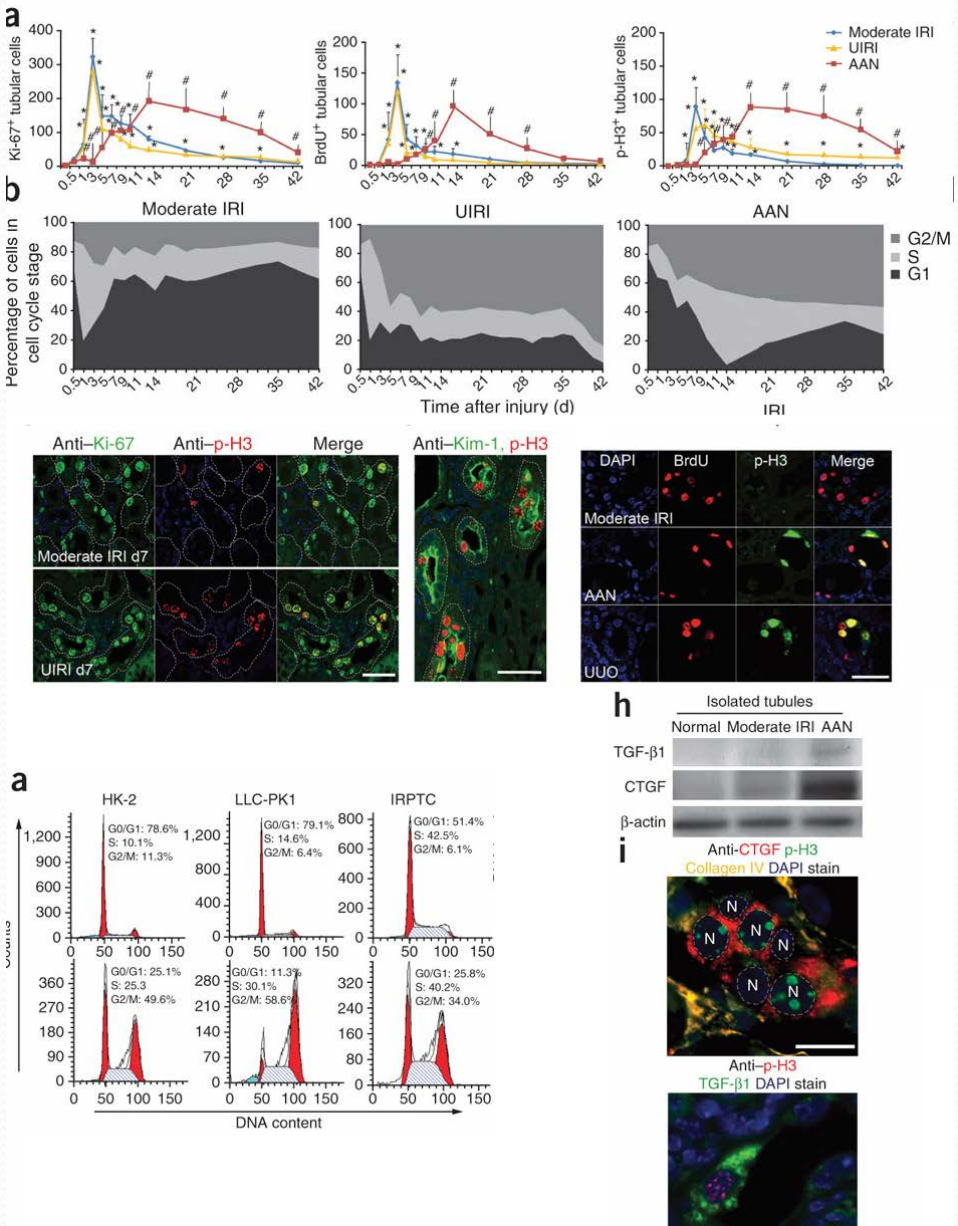
nature medicine



Arresto fase ciclo cellulare epitelio tubulare in G2/M

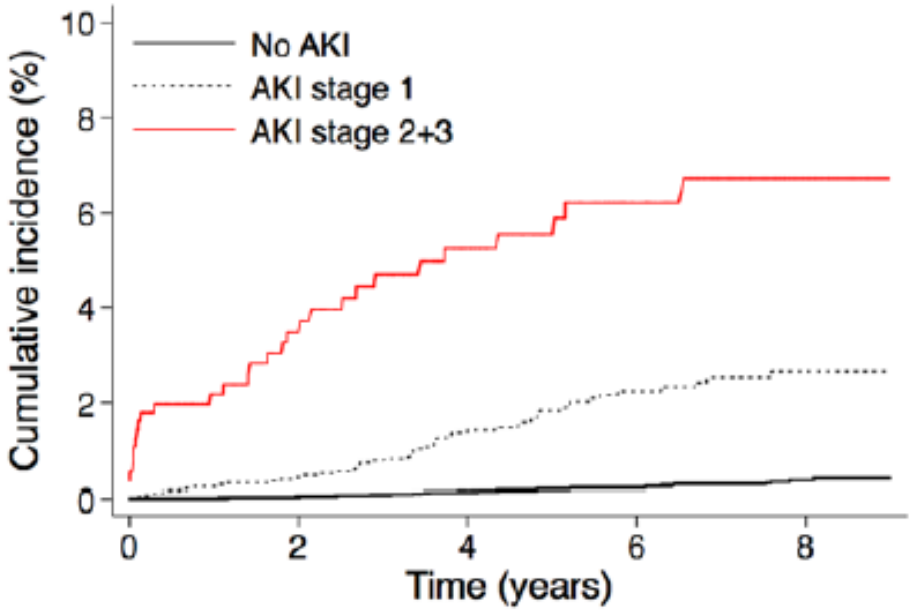
Secrezione di mediatori pro-fibrotici

Progressione CKD



Acute Kidney Injury After Coronary Artery Bypass Grafting and Long-Term Risk of End-Stage Renal Disease

Linda Rydén, MD; Ulrik Sartipy, MD, PhD; Marie Evans, MD, PhD; Martin J. Holzmann, MD, PhD



Number at risk					
No AKI	25609	20105	13755	7326	1371
AKI stage 1	3159	2399	1723	925	214
AKI stage 2+3	562	383	269	149	28

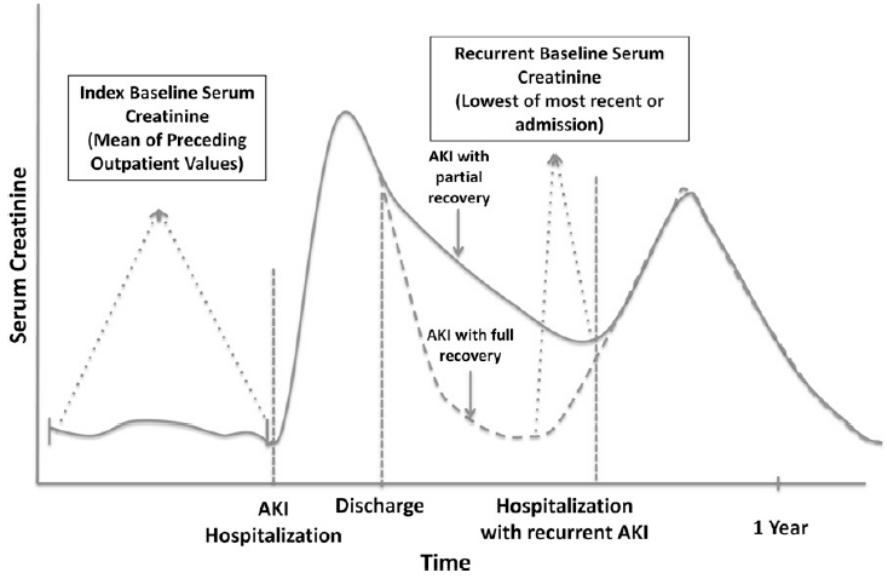
Figure 2. Cumulative incidence of end-stage renal disease according to the Acute Kidney Injury Network (AKIN) classification of acute kidney injury (AKI) in 29330 patients who underwent primary isolated coronary artery bypass grafting in Sweden between 2000 and 2008.

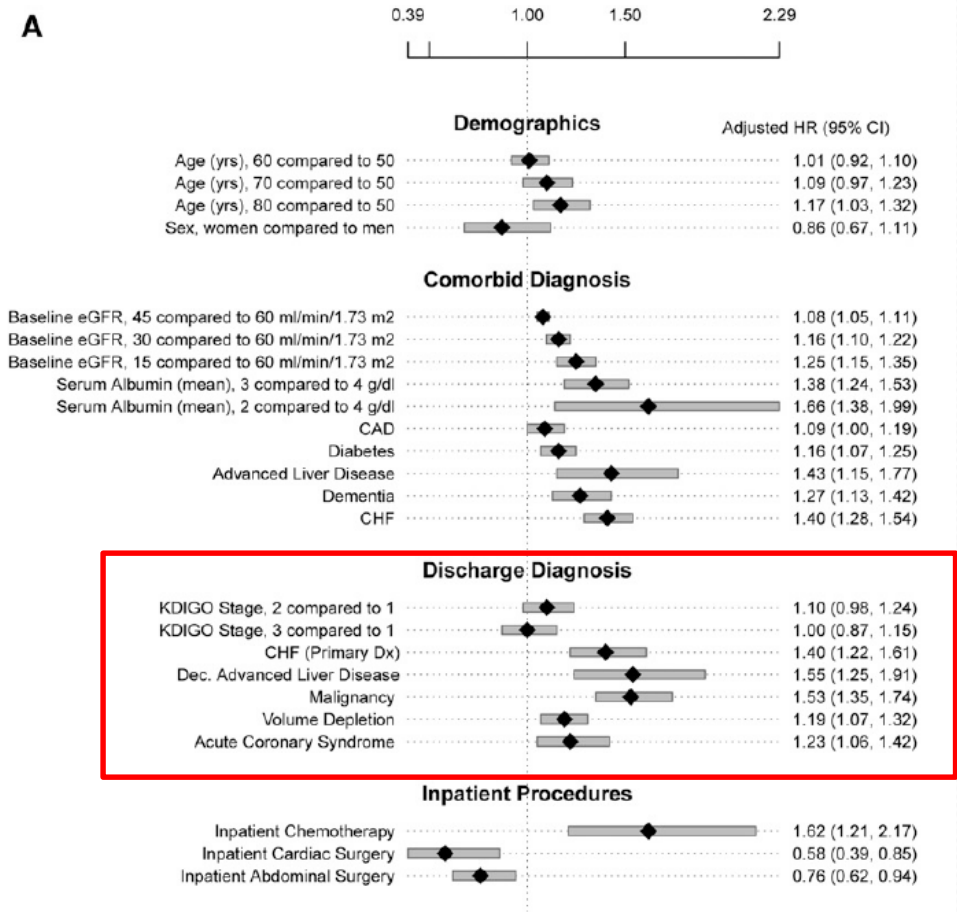
(*Circulation*. 2014;130:2005-2011.)

Predictors of Recurrent AKI

Edward D. Siew,*†‡ Sharidan K. Parr,†‡ Khaled Abdel-Kader,†‡ Svetlana K. Eden,§ Josh F. Peterson,‖ Nisha Bansal,¶ Adriana M. Hung,*†‡ James Fly,* Ted Speroff,*§** T. Alp Ikizler,*†‡ and Michael E. Matheny*§**††

J Am Soc Nephrol 27: ●●●–●●●, 2015. doi: 10.1681/ASN.2014121218





- 11683 hospitalization for AKI: 2954(25%) hospitalization for recurrent AKI within 12 months (median 64 days)

JACC Vol. 52, No. 19, 2008
November 4, 2008:1527–39

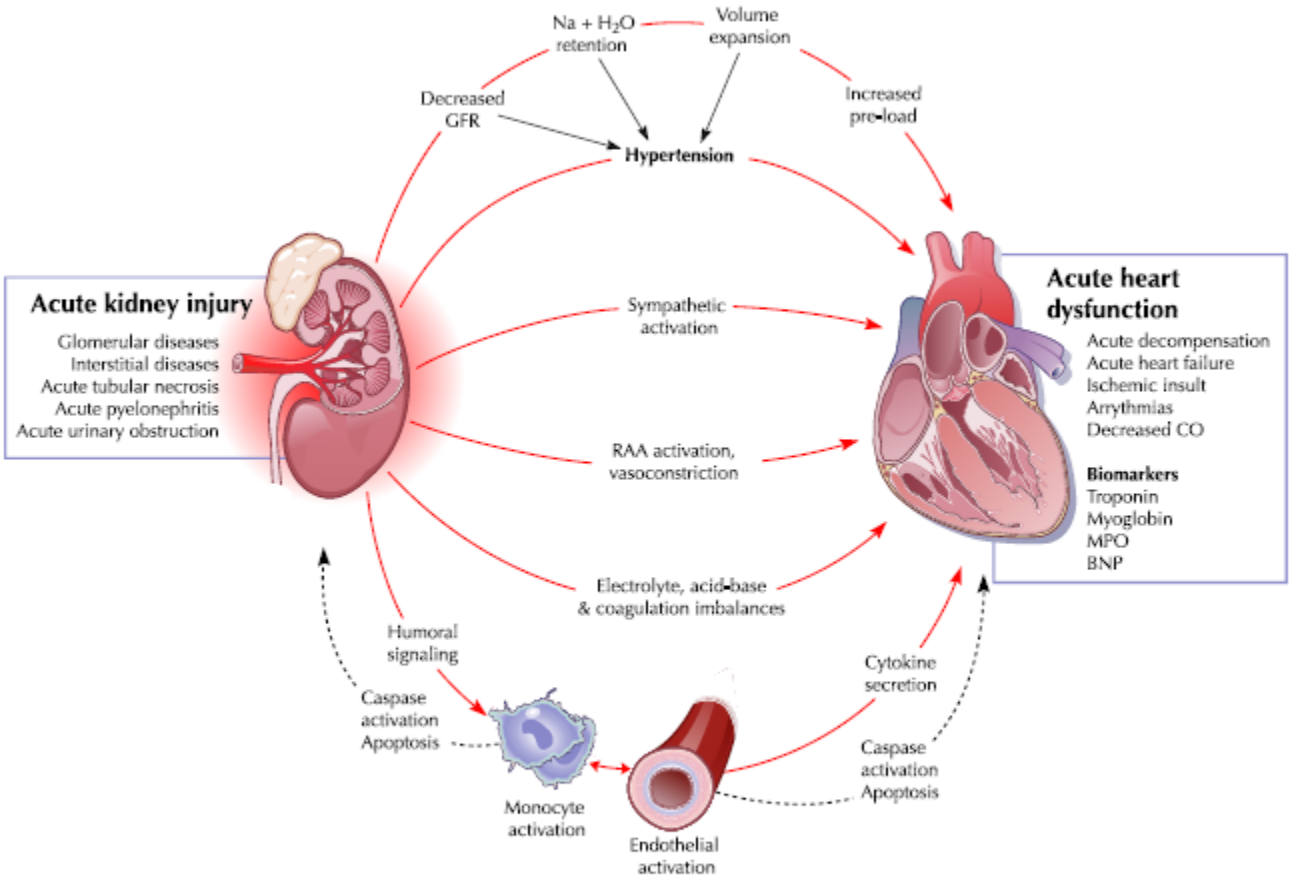


Figure 3 CRS Type 3

Pathophysiological interactions between heart and kidney in type 3 CRS or "acute renocardiac syndrome" (abrupt worsening of renal function, e.g., acute kidney failure or glomerulonephritis) causing acute cardiac disorder (e.g., heart failure, arrhythmia, pulmonary edema). MPO = myeloperoxidase; other abbreviations as in Figure 1. Figure illustration by Rob Flewell.

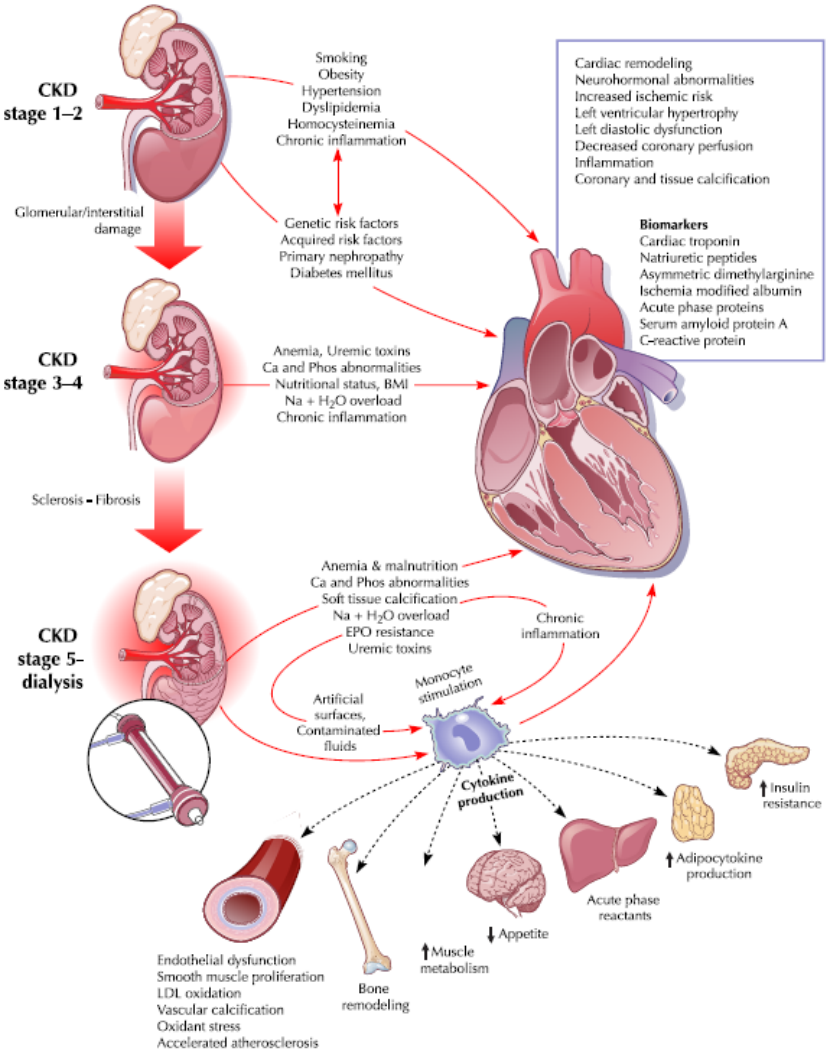


Figure 4 CRS Type 4

Pathophysiological interactions between heart and kidney in type 4 cardiorenal syndrome (CRS) or "chronic renocardiac syndrome" (chronic kidney disease [CKD], e.g., chronic glomerular disease, contributing to decreased cardiac function, cardiac hypertrophy, or increased risk of adverse cardiovascular events). BMI = body mass index; EPO = erythropoietin; LDL = low-density lipoprotein. Figure illustration by Rob Flewell.

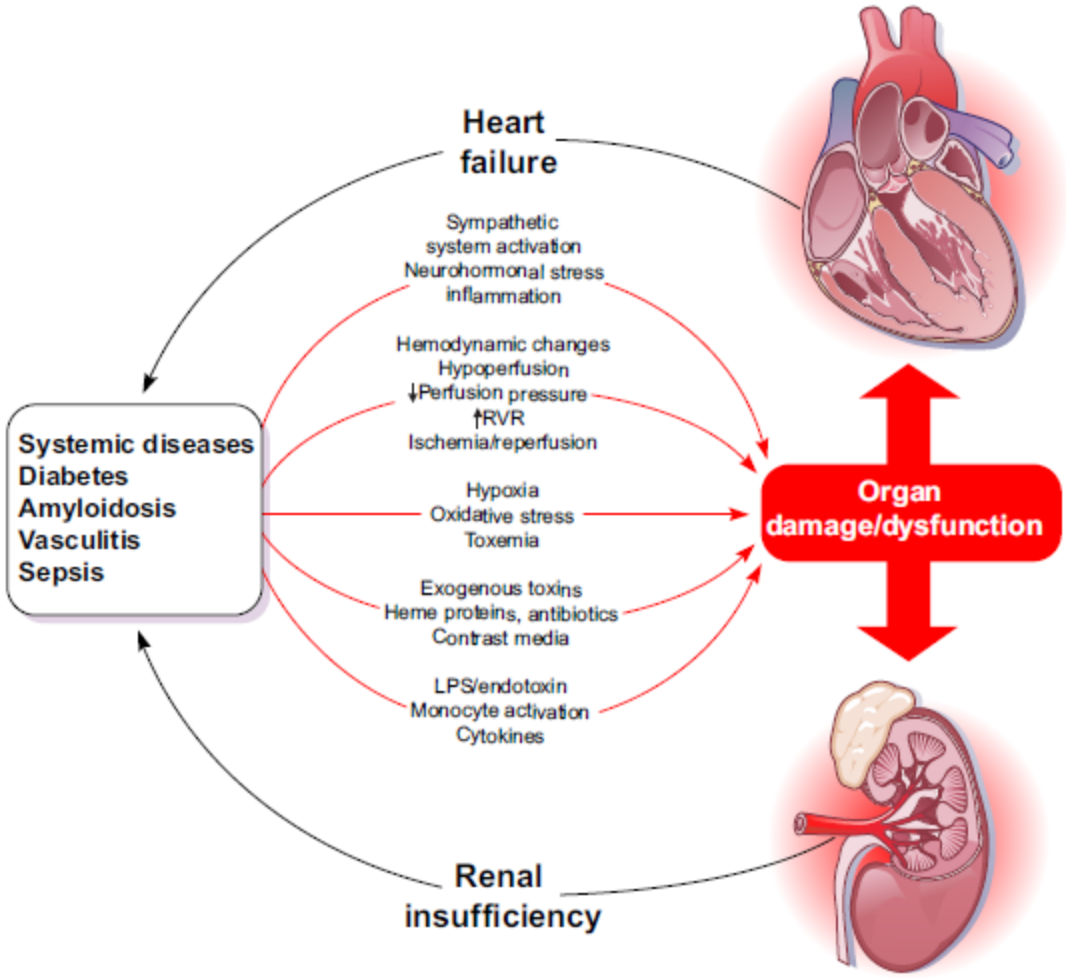
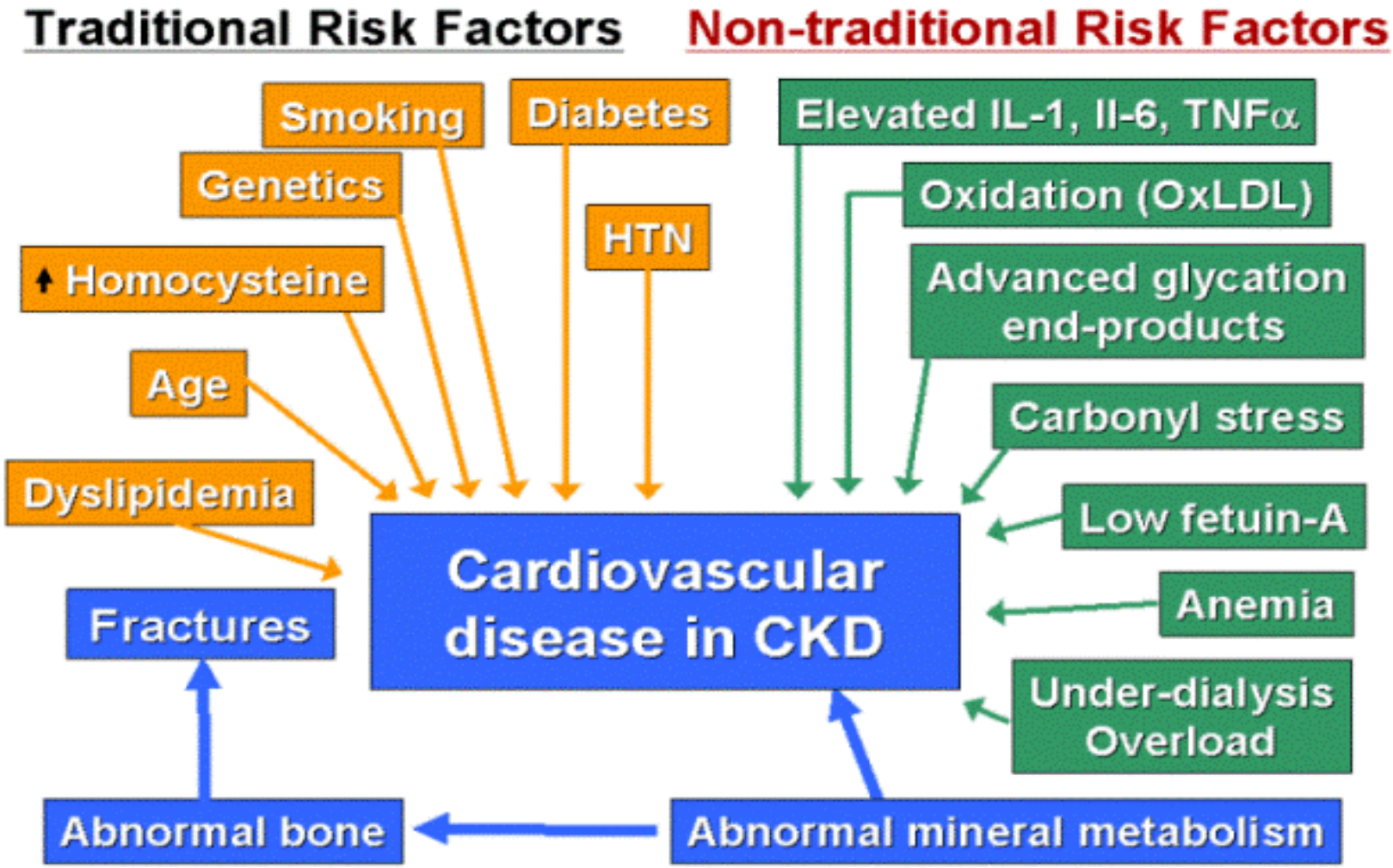
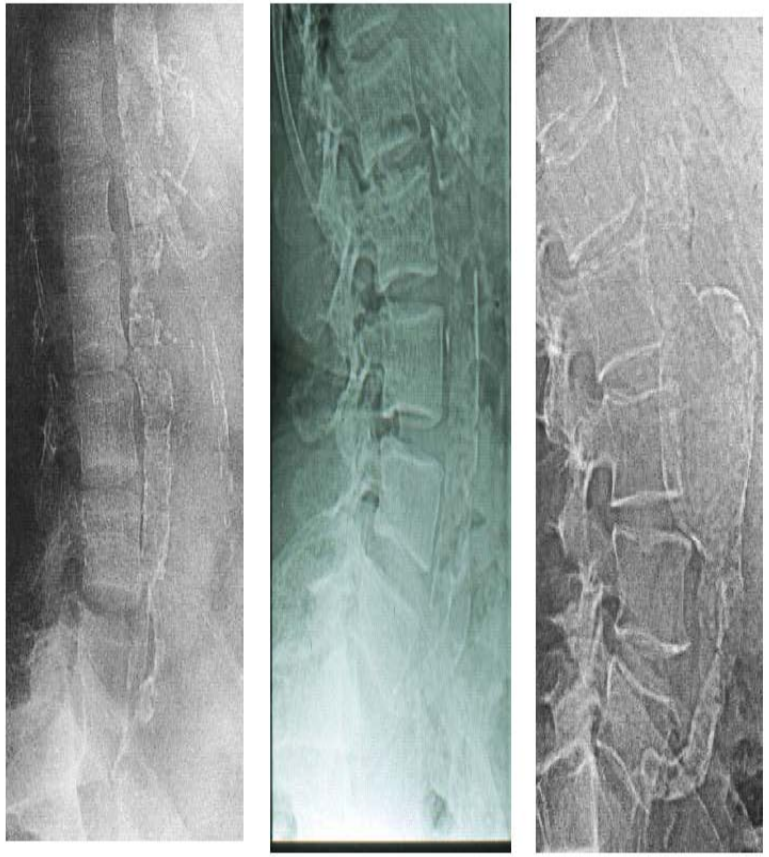


Figure 5 CRS Type 5

Pathophysiological interactions between heart and kidney in type 5 cardiorenal syndrome (CRS) or "secondary CRS" (systemic condition, e.g., diabetes mellitus, sepsis, causing both cardiac and renal dysfunction). LPS = lipopolysaccharide (endotoxin); RVR = renal vascular resistance. Figure illustration by Rob Flewell.


Traditional Risk Factors
Non-traditional Risk Factors
Smoking
Diabetes
Genetics
HTN
Homocysteine
Age
Dyslipidemia
Fractures
Elevated IL-1, Il-6, TNFα
Oxidation (OxLDL)
Advanced glycation end-products
Carbonyl stress
Low fetuin-A
Anemia
Under-dialysis Overload
Cardiovascular disease in CKD
Abnormal bone
Abnormal mineral metabolism

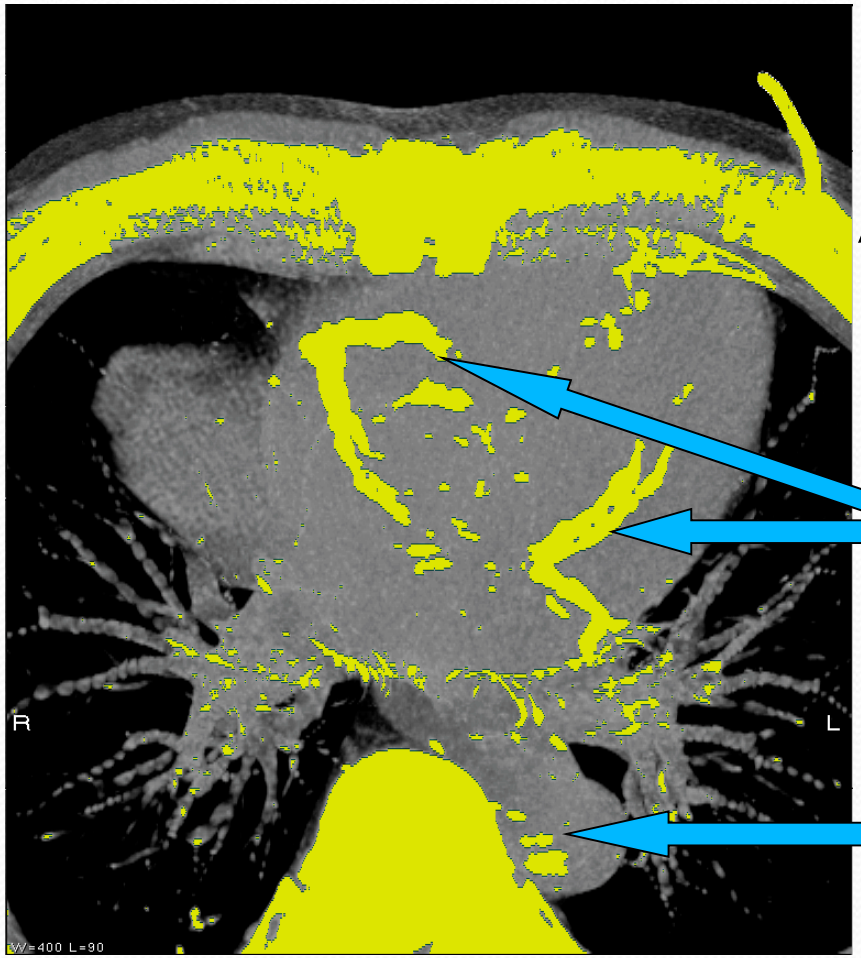
CALCIFICAZIONI VASCOLARI



Calcificazioni vascolari aortiche

30-70% dei pazienti con CKD (*Sigrist M et al, NDT 2006*)
15% dei pazienti pediatrici con CKD (*Civilibal M et al, Ped Nephrol 2006*)

CALCIFICAZIONI CORONARICHE



osso

Depositi vascolari di calcio

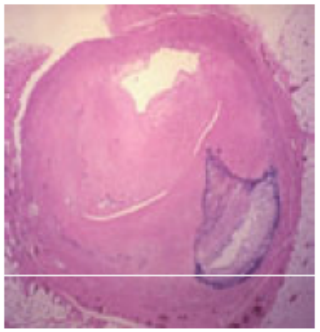
osso

La Electron Beam Computed Tomography (EBCT) permette di visualizzare le lesioni aterosclerotiche calcifiche.

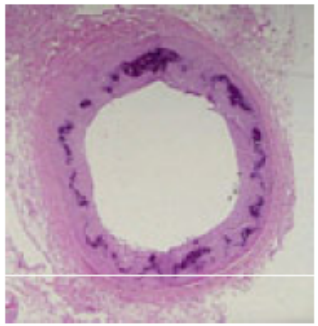
Types of Vascular Calcification in CKD

Atherosclerosis

Patchy lesions
- related to lipids
- older persons
- elastic and muscular arteries



Uremic arteriolopathy:

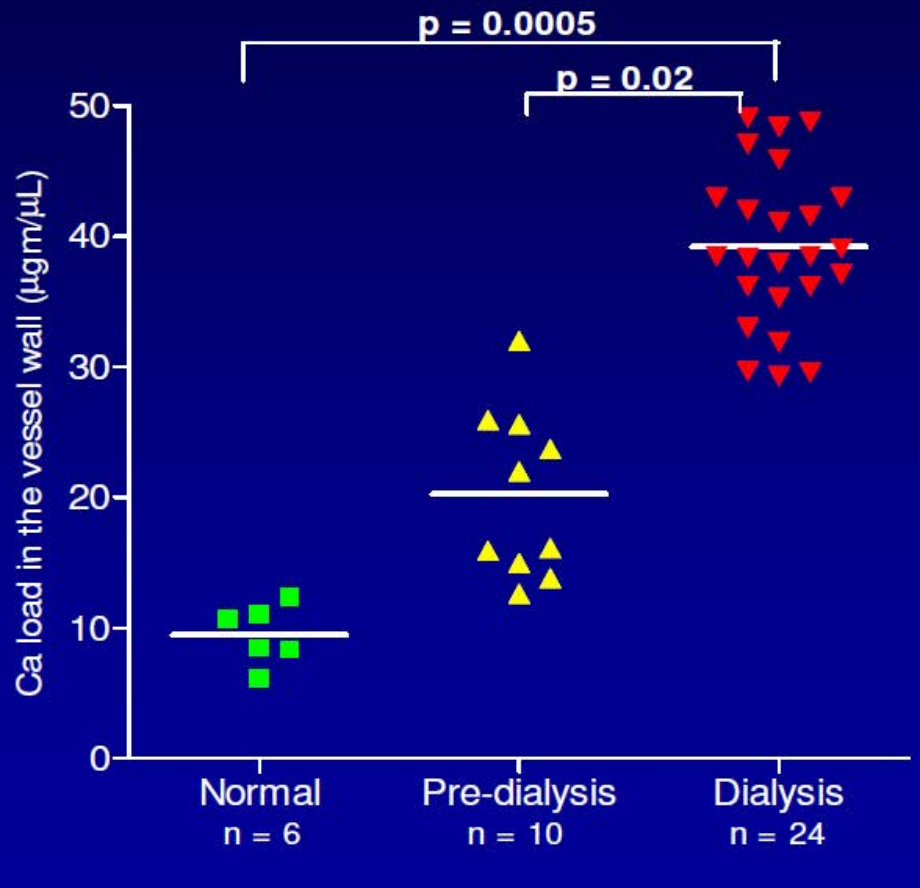


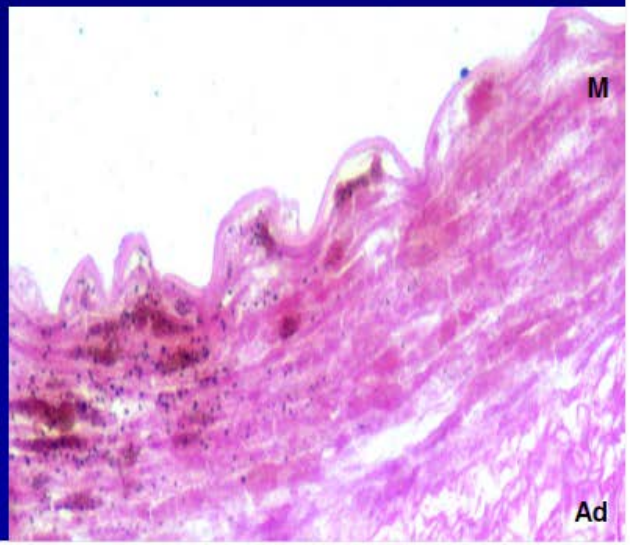
linear lesions
- disturbances in mineral metabolism
- young and old persons
- CKD, DM
- muscular arteries

Atherosclerosis
↓
Atherosclerotic atherosclerotic plaque
↓
arterial stenotic lesion
↓
ischaemia

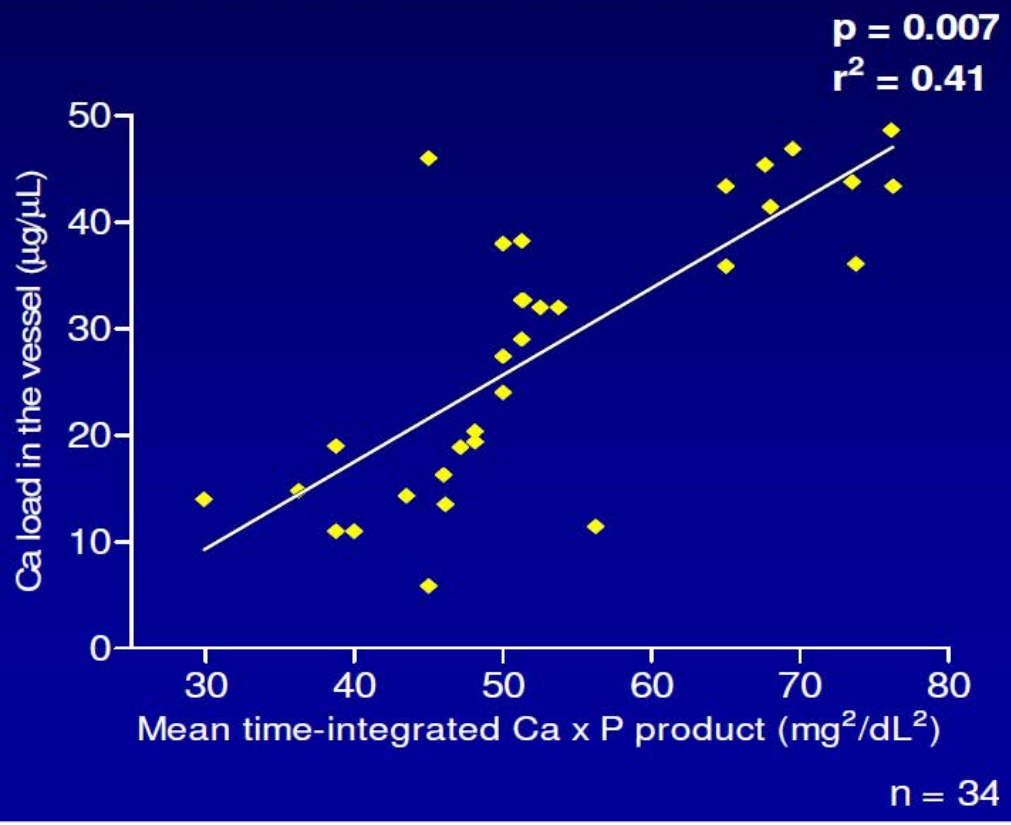
Atheriolosclerosis
↓
Modification of arterial wall properties
↓
↑ arterial stiffness (↑ PWV; ↑PP)
↓
↑Afterload • LVH
Coronary perfusion • Angor

Ca accumulation begins pre-dialysis



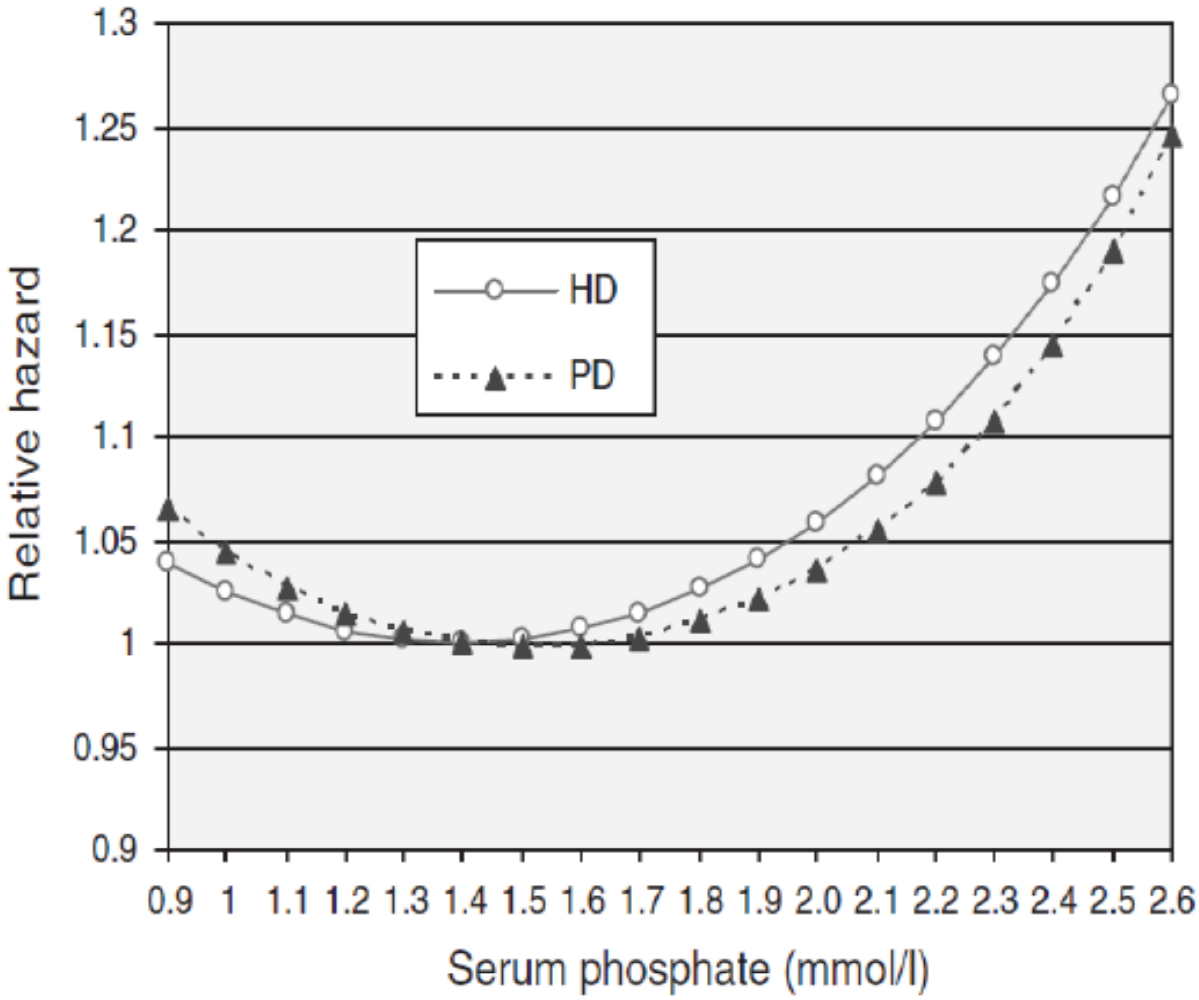


The vessel Ca load correlates with the serum Ca x P product



Fosforemia e rischio relativo di morte nei pazienti dializzati. UK Renal Registry

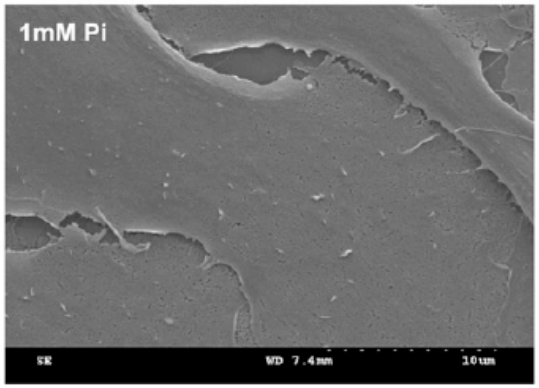
"…In patients with CKD stages 3-5D, we suggest limiting dietary phosphate intake in the treatment of hyperphosphatemia alone or in combination with other treatments…"

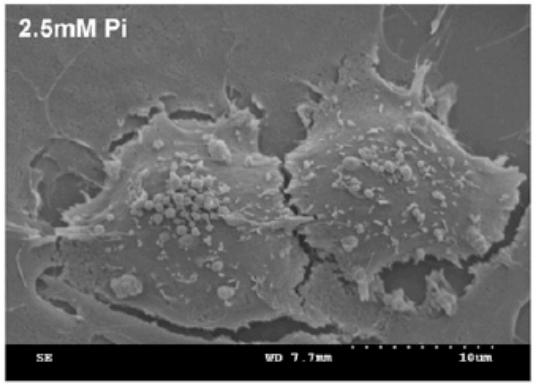


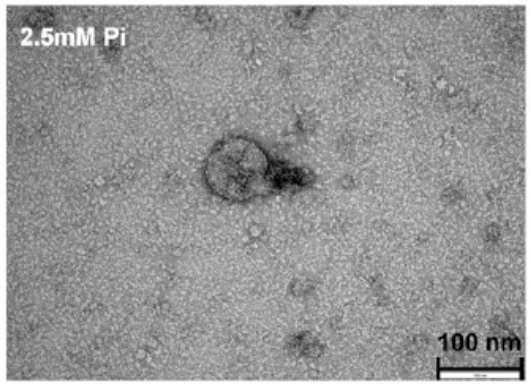
Hyperphosphatemia, Phosphoprotein Phosphatases, and Microparticle Release in Vascular Endothelial Cells

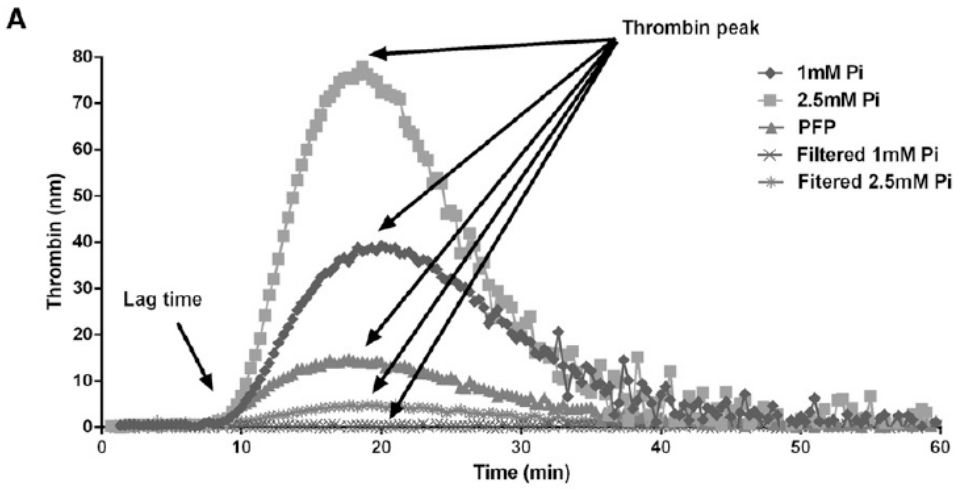
Nima Abbasian,* James O. Burton,*† Karl E. Herbert,‡§ Barbara-Emily Tregunna,* Jeremy R. Brown,*† Maryam Ghaderi-Najafabadi,‡§ Nigel J. Brunskill,*† Alison H. Goodall,‡§ and Alan Bevington*

J Am Soc Nephrol 26: 2152–2162, 2015. doi: 10.1681/ASN.2014070642









CONCLUSIONI

- **IRC e albuminuria sono fattori indipendenti per lo sviluppo di malattia cardiovascolare**
- **L'interazione tra cuore e rene è critica per l'outcome del paziente**
- **Singoli eventi di AKI possono condizionare la progressione della CKD**