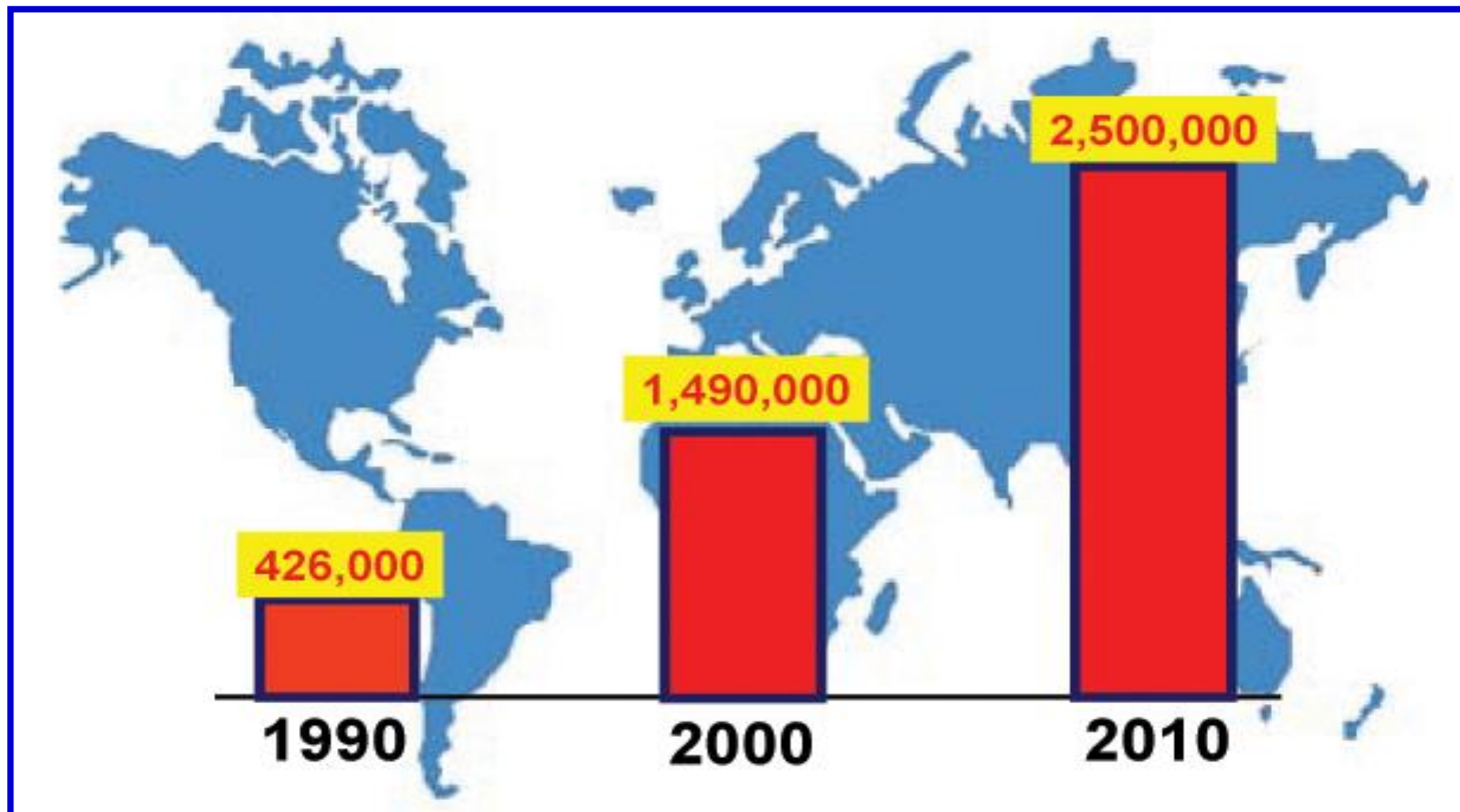


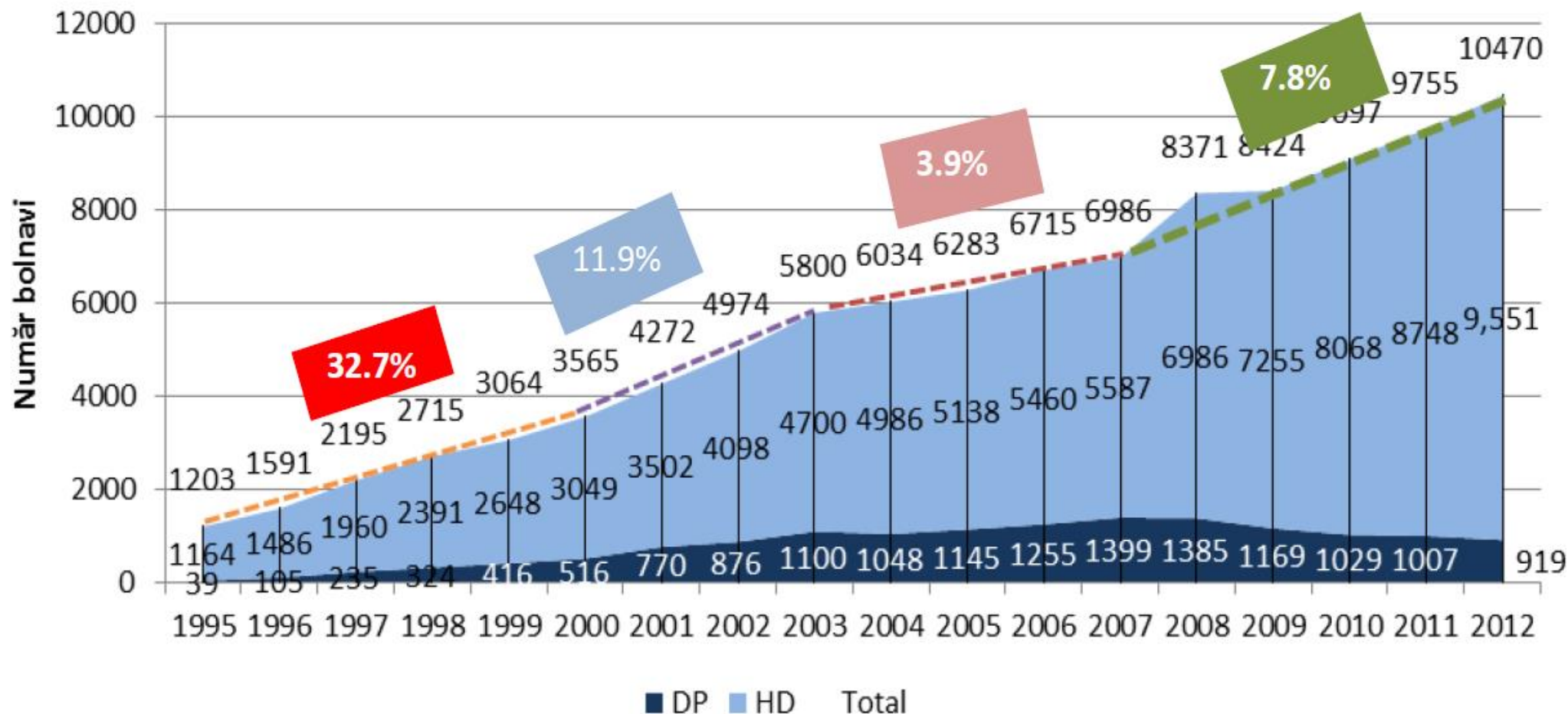
BOALA CRONICA DE RINICHI

(CHRONIC KIDNEY DISEASE)

PREVALENTA BOLNAVILOR CU IRC TRATATI PRIN DIALIZA



PREVALENCE OF RRT - ROMANIA



A high economic burden

- 5 countries (Japan, USA, Germany, Brazil, Italy) - less than 12% of world population - 58% of dialysis population
- next 10 countries – 29% of the world population – 21% of dialysis population

15 countries – 41% of the world population - 79% of dialysis population

Data based on 2001 Fresenius Medical Care global survey

“ Renal replacement therapy is so costly that there is minimal probability for the vast majority of the world’s population to take advantage from it “

A high economic burden

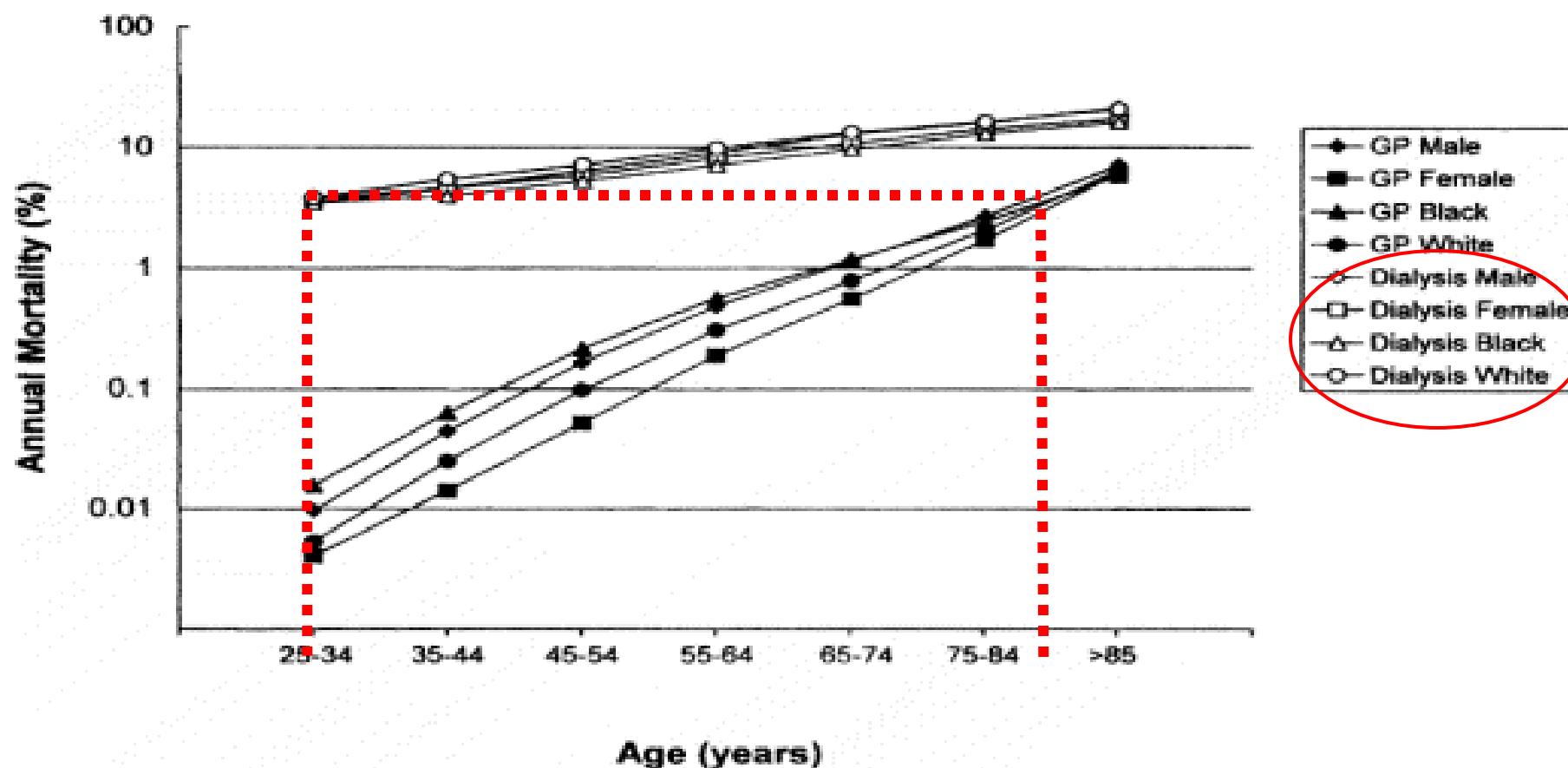
USA - USRDS

- **2010 – Estimated population 311mil. - US CENSUS BUREAU**
- **0.22% on RRT**
- **Costs/year – 28.29 bil USD**

INDIA – 2004 – 1.06 bilion

- **No renal registry, no RRT program**
- **No insurance program for RRT and no state founding**
- **”only 3-5% of patients needing RRT have some type of insurance program the rest are “cash and carry”**

Mortality among ESRD patients

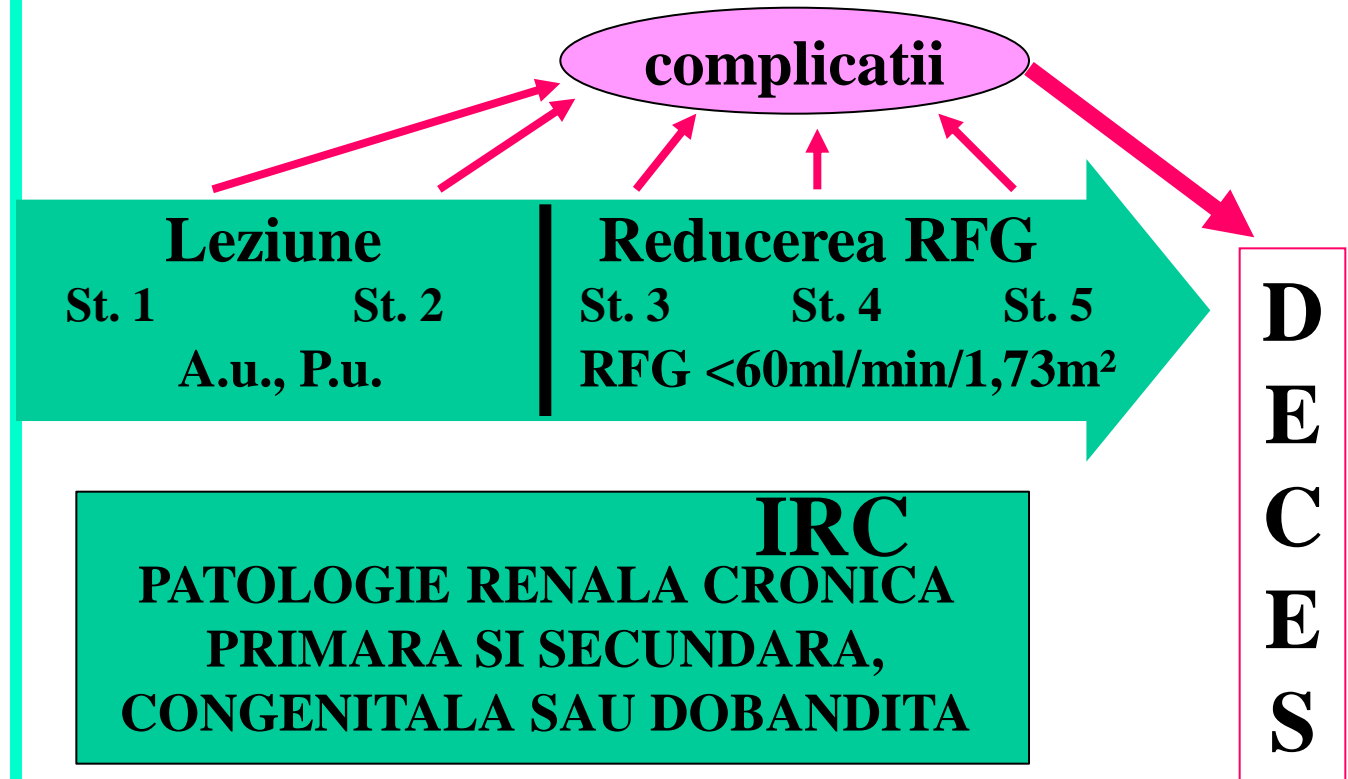


Foley AJKD 2000; 35(4 Suppl 1):S117-31.

FACTORI DE RISC

- DZ
- HTA
- Boli autoimune
- Infectii sistemice
- ITU
- Litiaza renala
- Obstructii de cai urinare
- Neoplazii
- Istoric familial de BCR
- Dupa IRA
- Reducerea masei renale
- Droguri
- Greutate mica la nastere
- Varsta inaintata
- Expunerea substante chimice si conditii de mediu
- Venit mic, educatie deficitara
- SUA – grupuri etnice

BOALA CRONICA DE RINICHI



NEFROLOGIA CLASICA

DEFINITII

BCR (independent de etiologie) se definește prin:

1. Afectare renală cu durată ≥ 3 luni

Leziunea renală se definește

- Modificări patologice sau
- Markeri de afectare renală
 - Albuminurie sau proteinurie
 - Modificări de sediment urinar
 - Imagistica

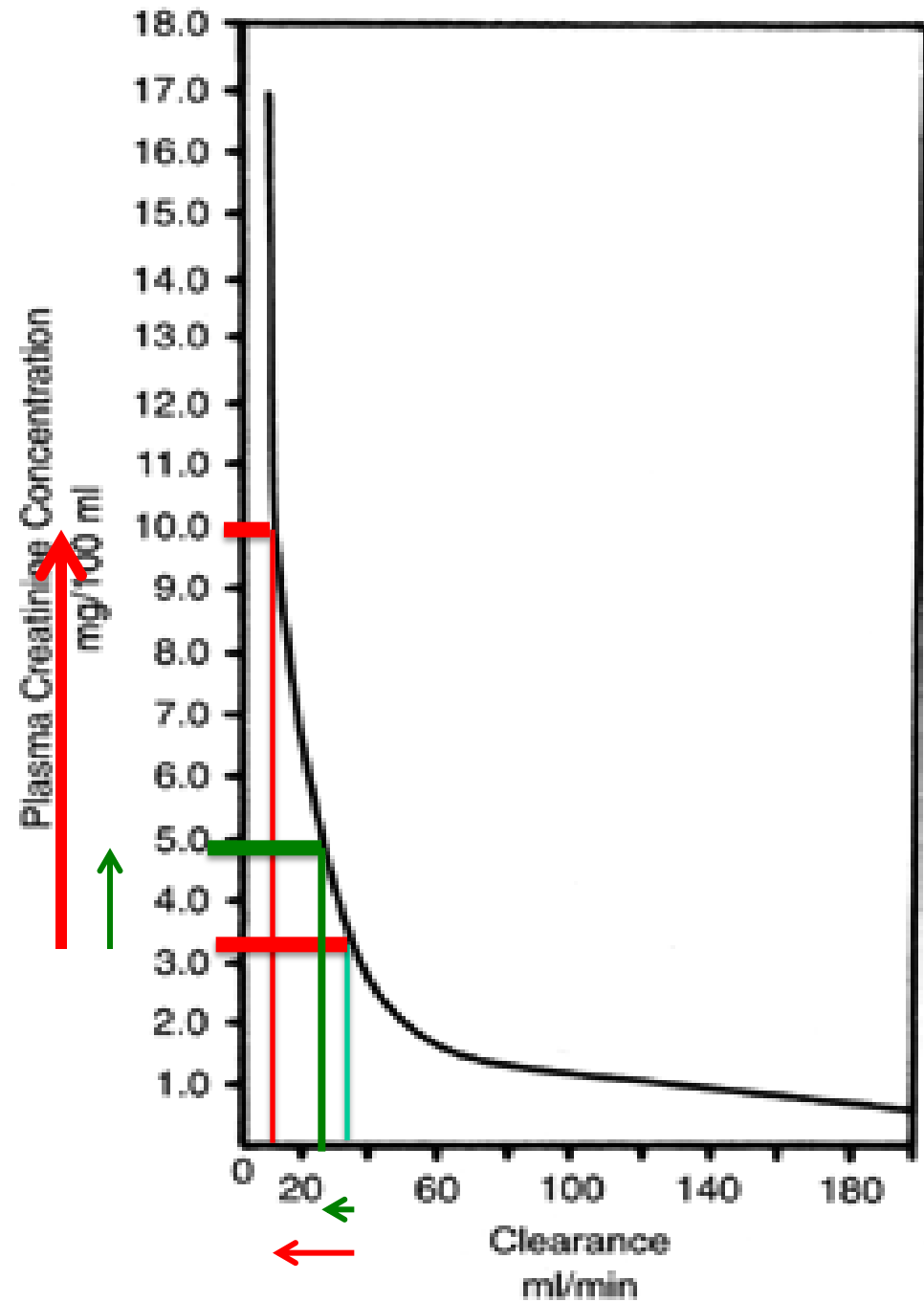
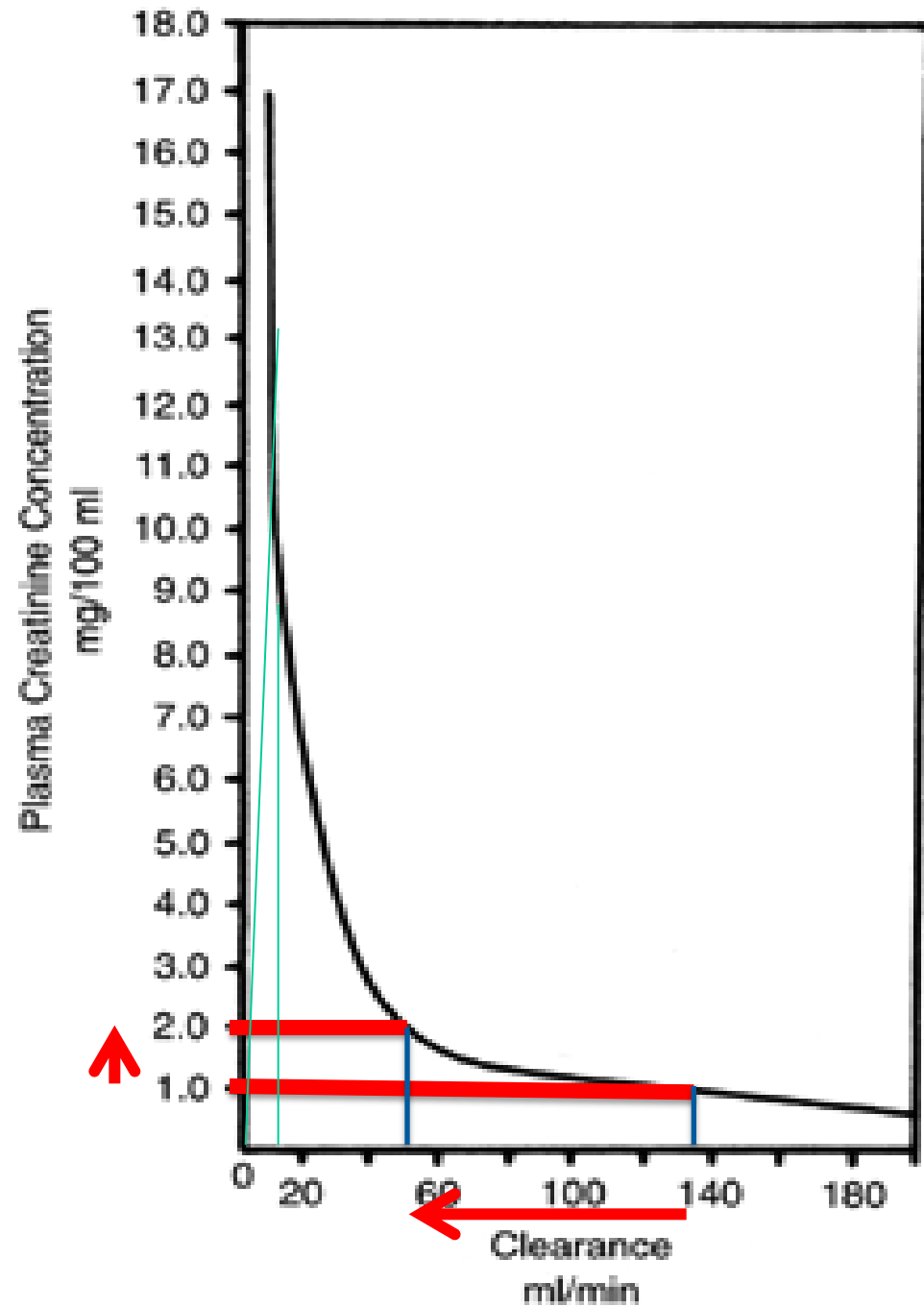
2. RFG < 60 ml/min/1,73m² cu durată ≥ 3 luni, cu sau fără markeri de leziune renală

CLASIFICARE STADIALA

STADIU	DESCRIERE	RFG ml/min/1,73m ²
1	Leziune renala cu RFG normala sau crescuta	> 90
2	Leziune renala cu usoara reducere a RFG	60 – 89
3	Moderata reducere a RFG	30 – 59
4	Reducere severa a RFG	15 – 29
5	Insuficienta renala (BCR terminala)	< 15 (sau dializa)

Proteinuria - Albuminuria

	Collecting method	Normal	Micro albuminuria	Albuminuria Proteinuria
Protein	/ 24h	< 300mg/24h Medie 50mg/24h	-	>300mg/24h
	Dipstick	< 30mg/dl	-	>30mg/dl
	First urine P/Cr	<200 mg/g	-	>200mg/g
Albumin	/ 24h	< 30mg/24h Medie 10mg/24h	30 – 300 mg/24h	>300mg/24h
	Dipstick albumin specific	<3 mg/dl	>3mg/dl	-
	First urine A/Cr	M <17mg/g F <25mg/g <30	M 17-250 F 25-355 mg/g 30-300	M > 250mg/g F > 355mg/g >300



GFR < 60 ml/min/1,73m²

VARSTA	F (Cr ser mg/dl)	M (Cr ser mg/dl)
25	1,22	1,55
35	1,12	1,45
45	1,08	1,37
55	1,06	1,29
65	1	1,25
75	0,94	1,2

Cr 2 - M, 60 years – 36ml/min/1,73m² - around 25% of the function left.

R. F. G.

- **ADULTI**

- Ecuatia Cockcroft-Gault evalueaza ClCr

$\text{ClCr (ml/min)} = [(140 - \text{Varsta}) \times \text{Greutatea} / 72 \times \text{Cr ser}] \times 0,85 \text{ (daca femeie)}$

CKD Epi

Ecuatia MDRD 4 (Modification of Diet in Renal Disease Study)

$\text{RFG (ml/min/1,73m}^2\text{)} = 186 \times \text{SCr}^{-1,154} \times \text{Varsta}^{-0,203} \times 0,742 \text{ (daca femeie)} \times 1,210 \text{ (daca rasa neagra)}$

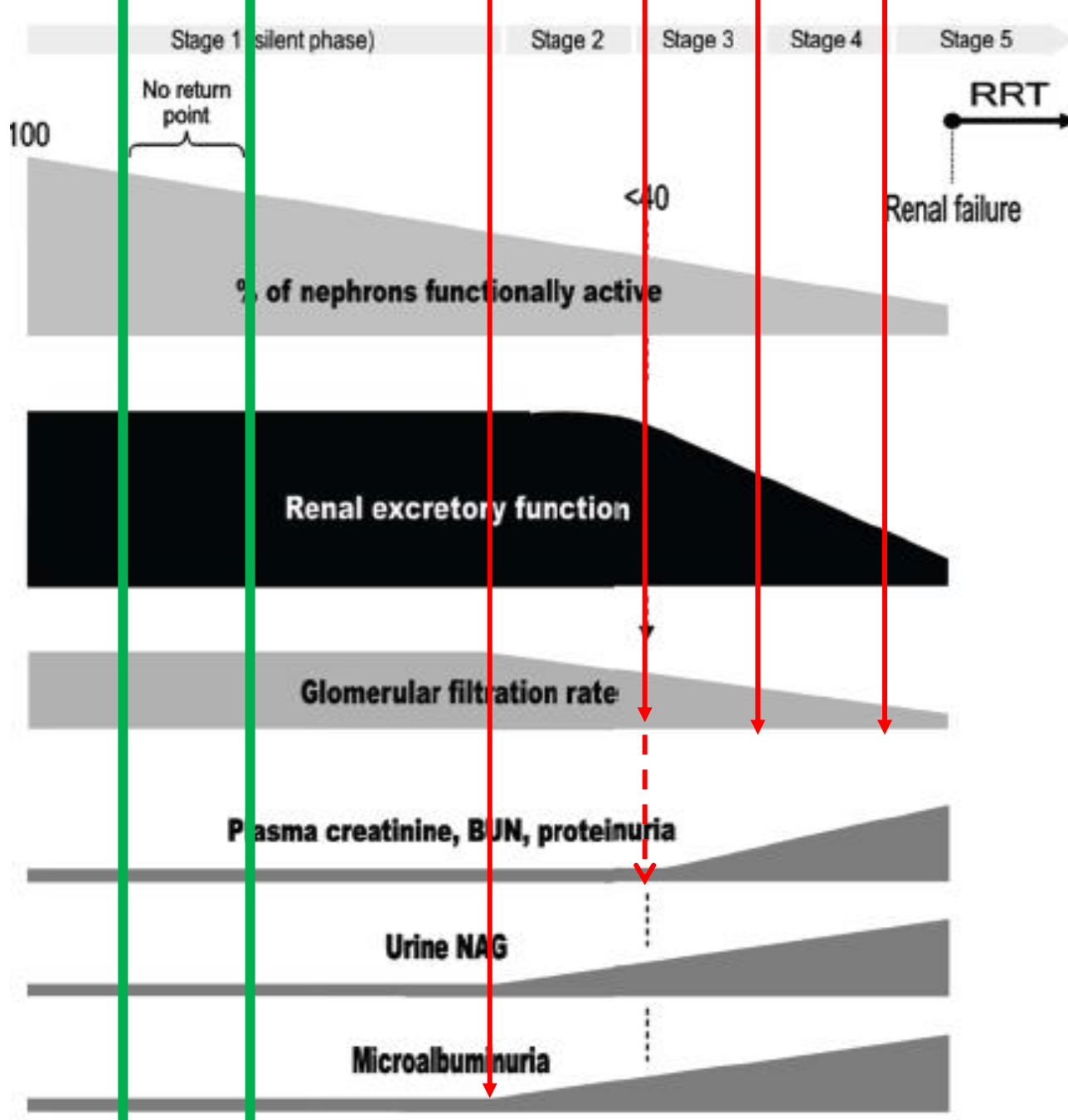
COPII

- Ecuatia Schwartz- 32 studii de validare

$\text{ClCr (ml/min)} = 0,55 \times \text{Inaltimea} / \text{Cr ser}$

- Ecuatia Counahan-Barratt – 9 studii de validare

$\text{RFG (ml/min/1,73m}^2\text{)} = 0,43 \times \text{Inaltimea} / \text{Cr ser}$

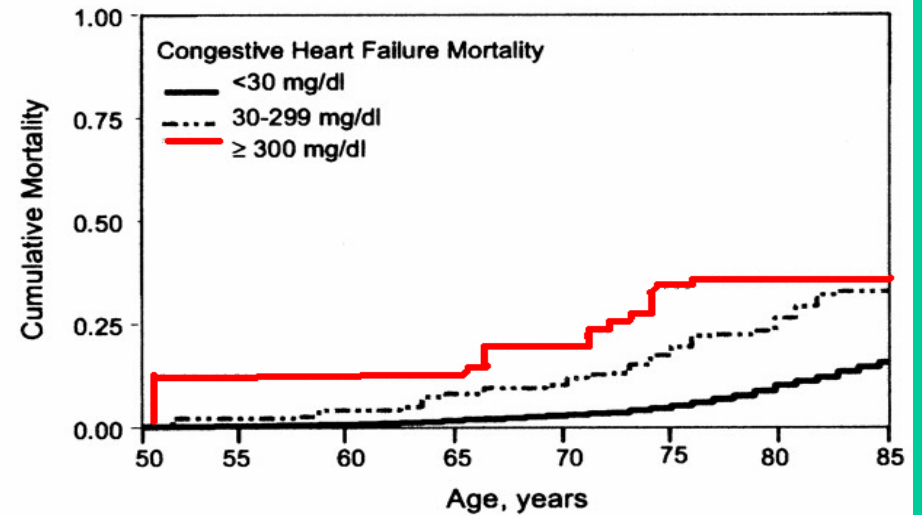
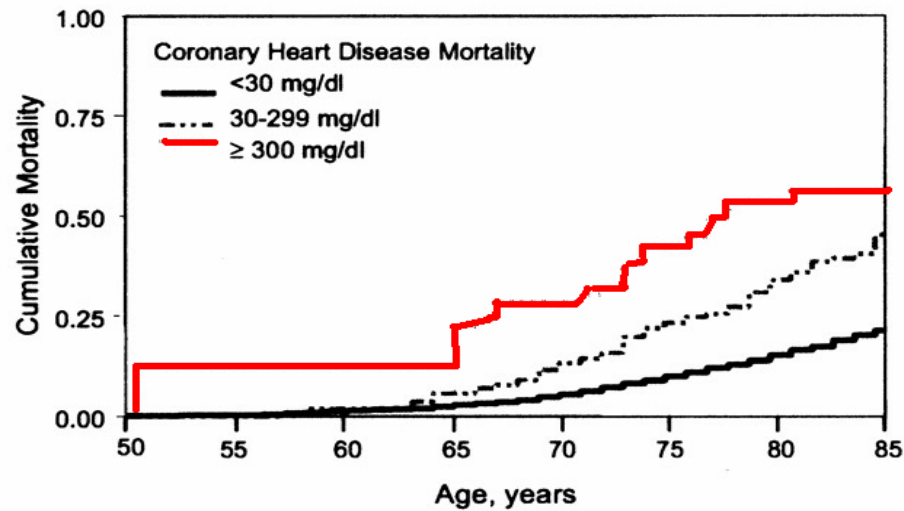
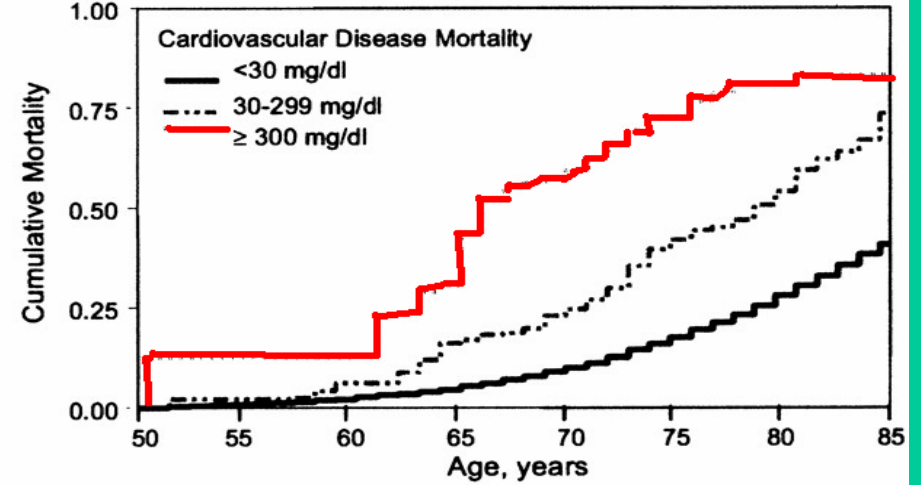
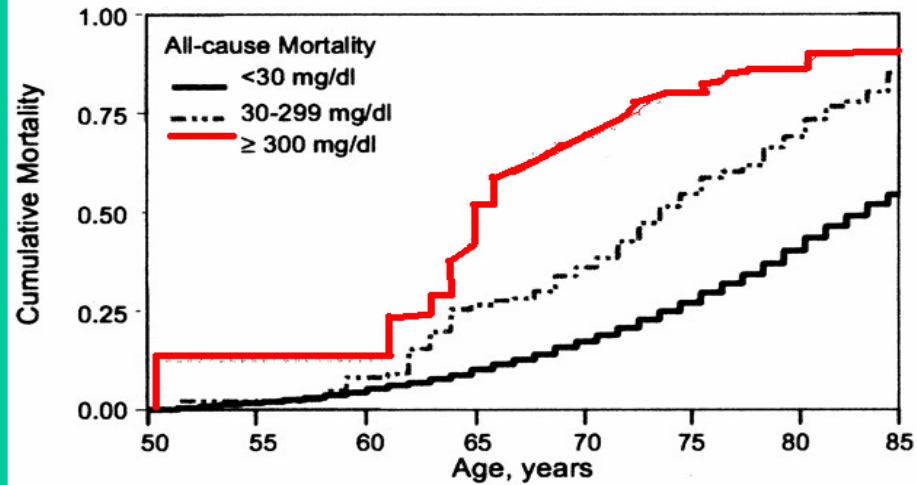


CKD markers

“Point of no return”

“*Microalbuminuria* does not indicate early renal damage, it is just the earliest indicator we have”

ALBUMINURIA



Effects of decreased GFR (on low CVD risk p.)

ARIC (Atherosclerosis Risk in Communities Study)

CHS (Cardiovascular Health Study)

FHS (Framingham Heart Study)

BCR 7.35%

Offspring (Framingham Offspring Study)

	GFR 15 – 59 (% events)	GFR > 60 (% events)
MI / FATAL CAD	10.1	5.3
STROKE	7.5	2.8
ALL-CAUSE MORTALITY	23.0	8.1
COMPOSITE	30.1	13.2

WOSCOPS, CARE, LIPID Trials n=19737

High risk patients

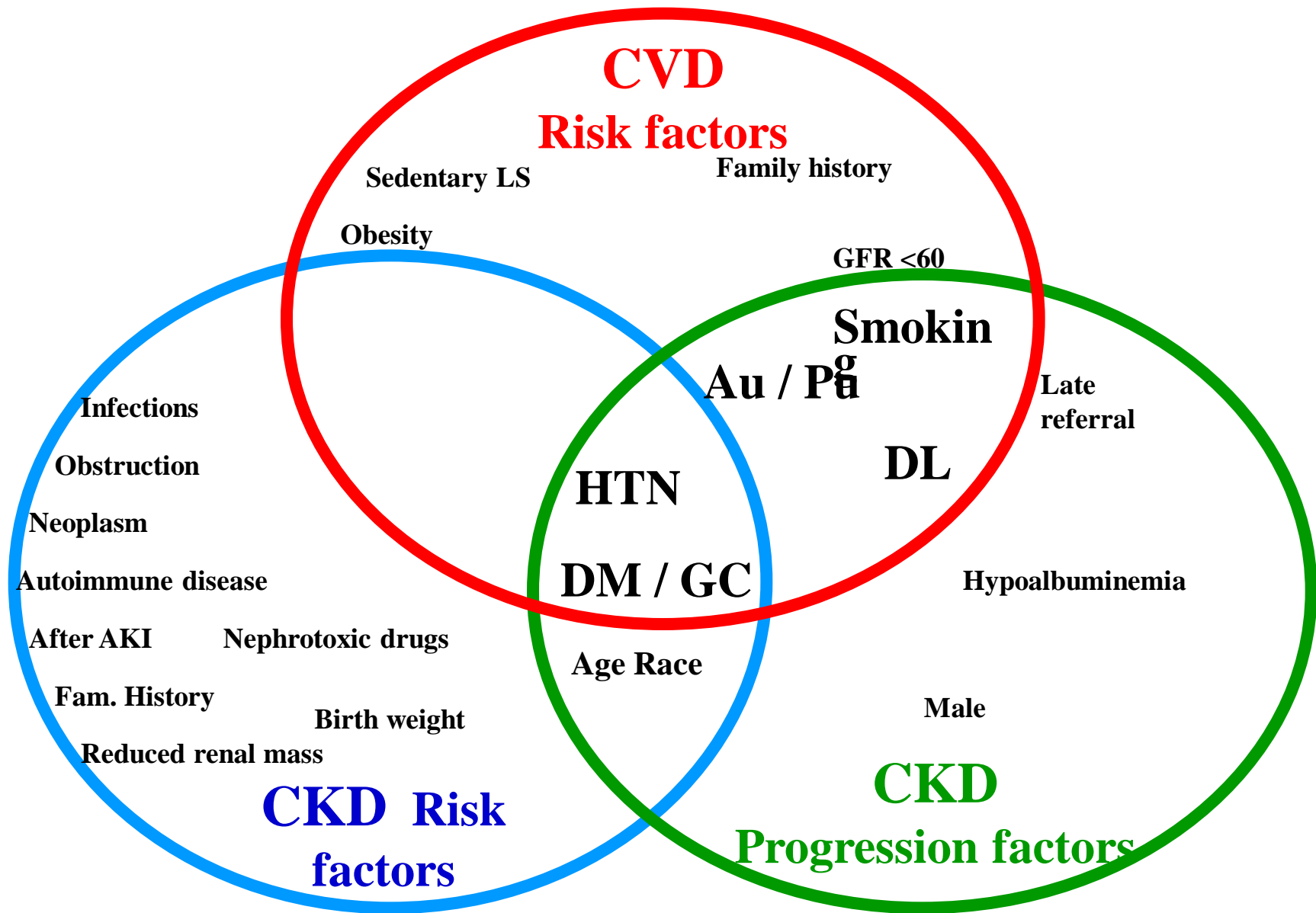
BCR 32.90%

	No CKD No DM	CKD No DM	No CKD DM	CKD DM
<i>N</i>	14,194	4099	873	571
Outcome Events (rate)				
CAD death, nonfatal MI CABG, PTCA, or stroke	16.7	21.2	25.2	31.7
All-cause mortality	6.4	10.3	11.6	18.5
CAD death or nonfatal MI CABG or PTCA	8.9	13.3	14.8	20.1
Stroke	7.4	7.5	8.6	10.0
	2.2	3.6	5.8	7.5

Stadiu 1	Stadiu 2	Stadiu 3	Stadiu 4	Stadiu 5	TOTAL	
3.3%	3%	4.4%	0.2%	0.2%	11%	NHANES III
5,7%	5,4%	5,4%	0,2%	0,2%	16,8%	SUA 98-04
3.1%	4%	10.9%	0.3%	0.02%	18.3%	AUSDIAB
5.3%	15.4%	4.2%	0.17%	0.04	25.1%	UK
					11,7%	Romania

> 27000 cazuri RFG < 90ml/min/1,73m2 - urmarire 5 ani

	Progresie IRCT	Mortalitate
BCR st 2	1,1%	19,5%
BCR st 3	1,3%	24,3%
BCR st 4	19,9%	45,7%



ETIOLOGIE

ORICE BOALA CRONICA DE RINICHI care distruge
progresiv populatia de nefroni

REGISTRUL NATIONAL ROMAN (acum 15 ani)

1. GLOMERULONEFRITE CRONICE

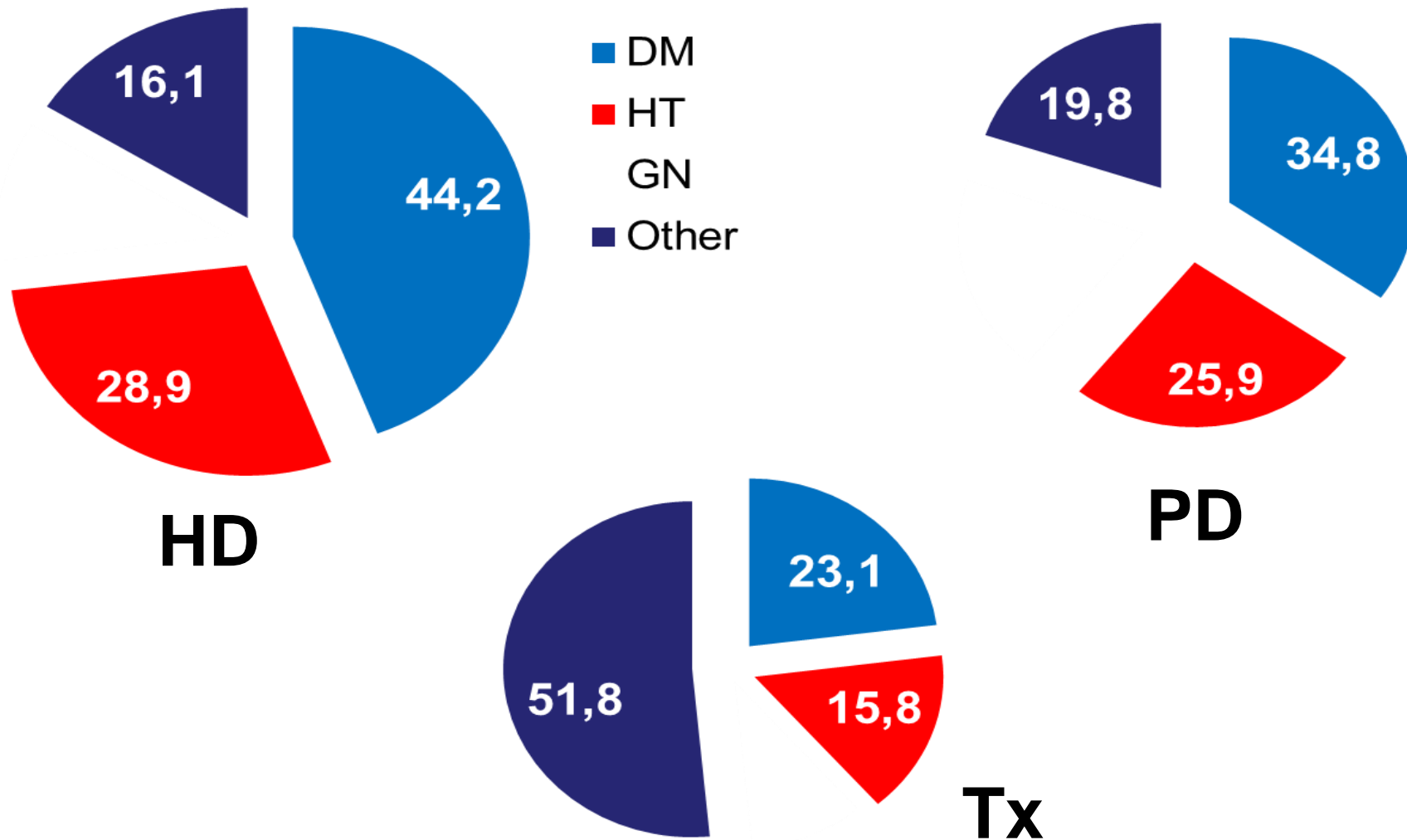
2. NEFROPATII TUBULO-INTERSTITIALE

3. BOLI CHISTICE RENALE

4. NEFROPATIA DIABETICA

Boala renală primară (Pacienti incidenti)	2007	2008	2009	2010	2011	2012
Nefropatii glomerulare (%)	17,1	16,2	13,5	13,9	13,6	1,37
Nefropatii interstițiale (%)	12,4	11,5	11,4	11,2	11,3	11,3
Ereditare-congenitale (%)	5,7	5,8	5,1	4,6	5,3	6,6
Diabet (%)	11,7	19,9	18,7	13,3	14,8	15,7
Boli vasculare renale (%)	6,5	11,8	6,2	6,3	14,5	15,4
Altele (%)	15,5	9,4	6,4	7,4	5,5	6,4
Necunoscute (%)	31.1	25.4	38.7	43.3	35	30.9

Etiology of ESKD on RRT - USRDS 2014



1. FUNCTIA EXCRETORIE

- alterarea capacitatii maxime de concentrare
- alterarea capacitatii maxime de diluare
- modificari ale echilibrului hidro-electrolitic
- modificari ale echilibrului acido-bazic - ACIDOZA
- Alterarea capacitatii de epurare - AUTOINTOXICATIE

2. FUNCTIA DE SINTEZA

- eritropoietina - ANEMIE RENALA
- 1,25,(OH)₂ colecalciferol

Totalitatea simptomelor generate de alterarile de functii =

SINDROMUL UREMIC

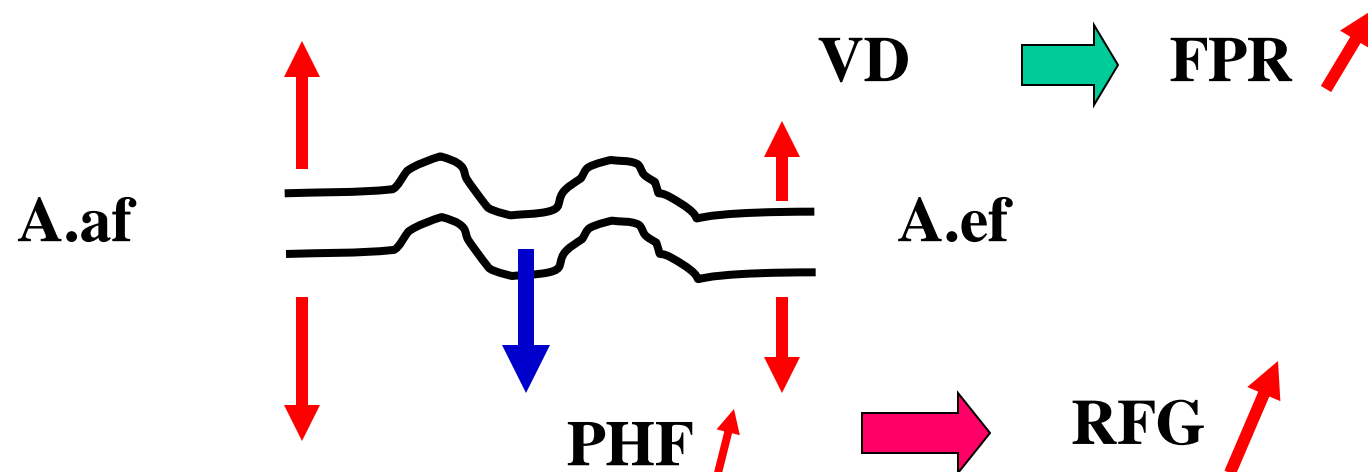
PATOGENIE

Teoria clasica (glom-tub)

ADAPTAREA RINICHILOR LA REDUCEREA POPULATIEI DE NEFRONI

MODELE EXPERIMENTALE

- reducerea populatiei de nefroni cu 75% creste RFG si FPR de 2,5x
fenomen hemodinamic



ADAPTARE GLOMERULARA

- **Morfologica**
 - **crestere in dimensiune a glomerulului**
 - **dilatare capilara**
 - **proliferare si hipertrofia componentelor celulare**
- **Functionala**
 - **Creste fluxul plasmatic renal**
 - **Creste rata filtrarii glomerulare**
 - **Creste presiunea hidrostatica de filtrare**

ADAPTARE TUBULARA

Functionala

- mentinerea echilibrului glomerulo-tubular
- cresterea RFG → cresterea secretiei si reabsorbției

Morfologica

- TCP creste - diametru 15% - lungime 35%
- TCD creste - diametru 10% - lungime 17%

Mecanism hormonal ? - apare si pe rinichiul denervat

Favorizat de

- varsta tanara
- STH si H.Tiroidieni (ablatia chirurgicala nu blocheaza HT)
- regimul normoprotidic

FORMAREA URINII

TEORIA NEFRONULUI RESTANT A LUI BRICKER

- In afectiunile glomerulare
 - distructie glomerulara ➡ atrofia tubului corespunzator
- In afectiuni tubulo-interstitiale
 - distructia tubulara ➡ atrofia glomerulului corespunzator

FUNCTIA RENALA ASIGURATA DE NEFRONII INTACTI

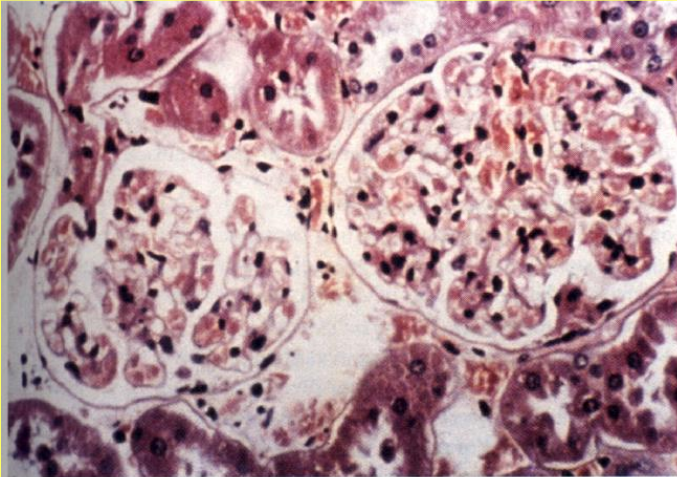
Pierdereea functiei nefronilor restanti

Clinic – RFG < 60 → progresie nereversibila spre uremie

MECANISMELE PROGRESIEI IRC

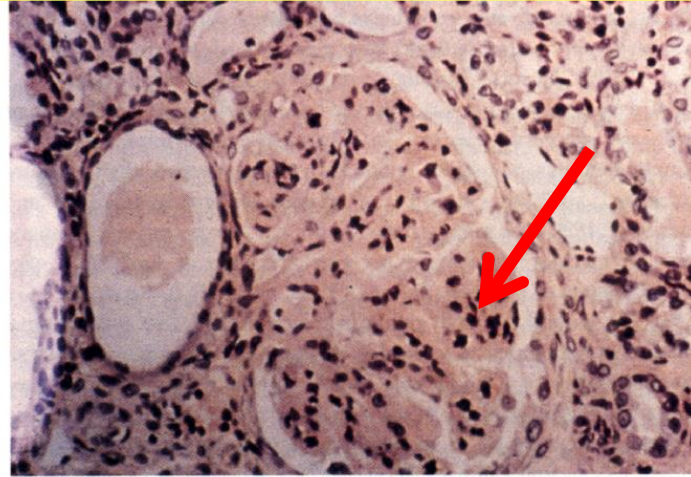
- Glomeruloscleroza**
- Scleroza tubulo-interstitiala**
- Scleroza vasculara**

**Glomerul
normal**



(a)

**Proliferare
mezangiala**

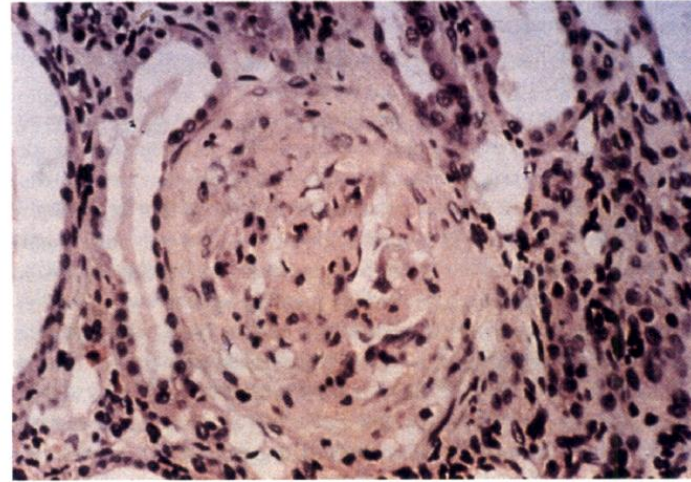


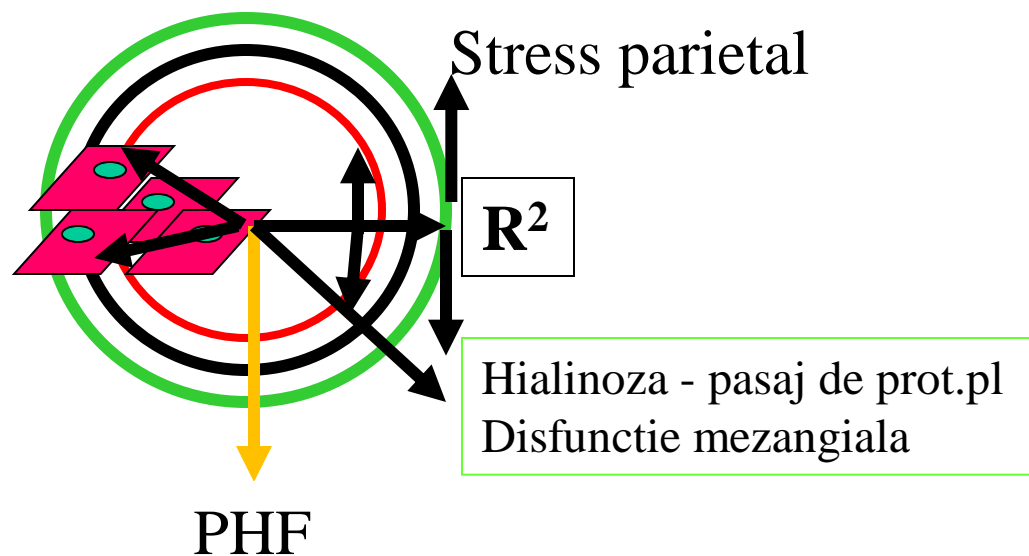
(b)

**Scleroza
segmentala**



**Scleroza
globala**





►► **Adaptare hemodinamica**
(Brenner si Hostetter)

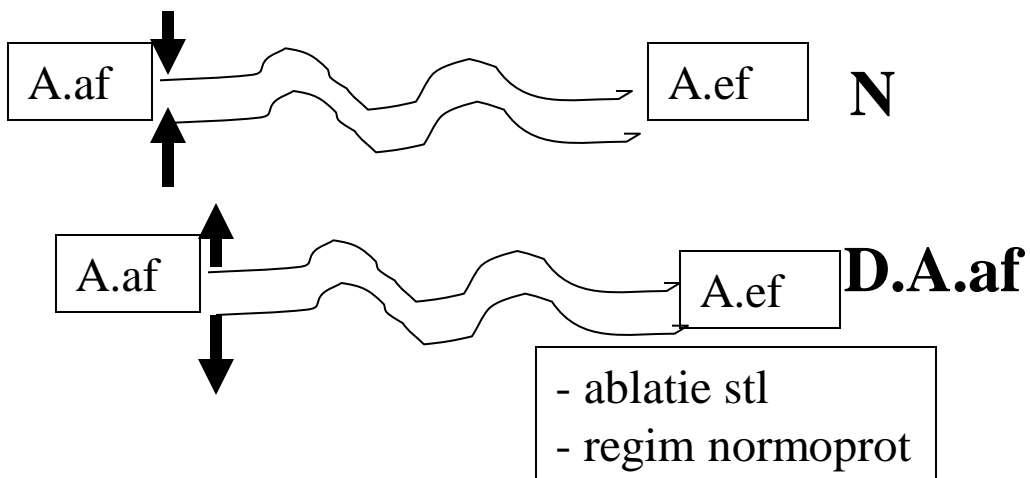
►► **Hipertrofia glomerulara**
(Ichikawa si Fogo)

►► **Proteinuria**
(Remuzzi si Bertani)

►► **Hipertensiunea sistemică**
(El Nahas)

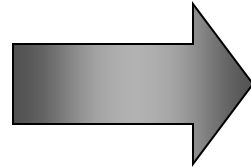
►► **Rolul lipidelor**
(Moorhead)

Incarcare mezangiala → LDL → Efect citotoxic
Activare



C. ENDOTELIALA

- ✍ Anticoagulant
- ✍ Vasoactiv
- ✍ Antiinflamator
- ✍ Antiproliferativ

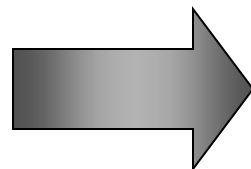


**STIMULI
MECANICI,
IMUNI,
METABO -
LICI**

C. MEZANGIALA

- ✍ Contractile
- ✍ Fagocitare
- ✍ Metabolice

C. EPITELIALA



✍ Histologic

- tumefiere, modificari de suprafata, detasare de MBG

✍ Functional

- pierderea prop. A.C.
- expresia de m.de adeziune **ICAM-1**
- activare - citochine (FC, Pro.inf, Che.tact)

✍ Histologic

- mezangioliza, proliferare, expansiune, scleroza

✍ Functional

- acumulari mezangiale de macromolecule
- activare - citochine (PDGF, bFGF, TGF β ,etc)
- disfunctie mezangiala

✍ Histologic: fuziune, applatizari, retractii

- ✍ Functional: activare (citochine, complement , depletie de GAG, sinteza de fibronectina, etc)

Teoria retrograda (tub-glom)



- **Excess deposition of extra cell matrix components**
collagen I, III, V, VII, XV, fibronectin;
- normal components of TBM**
collagen IV and laminin;
- de novo synthesized proteins** -
tenascin, fibronectin isoforms, laminin chains, SPARC,
thrombospondin, decorin and biglycan
- **Alteration of renal collagenase activity**
- **Collapse of the kidney parenchyma**

immune
chemical
biomechanical

Triggering agents

Glomerular vascular damage

Activation of TEC

Activation of NF- κ B and Release PAI-1, IL-1, IL-6, MCP1/CCL2, RANTES/CCL5, and TNF α

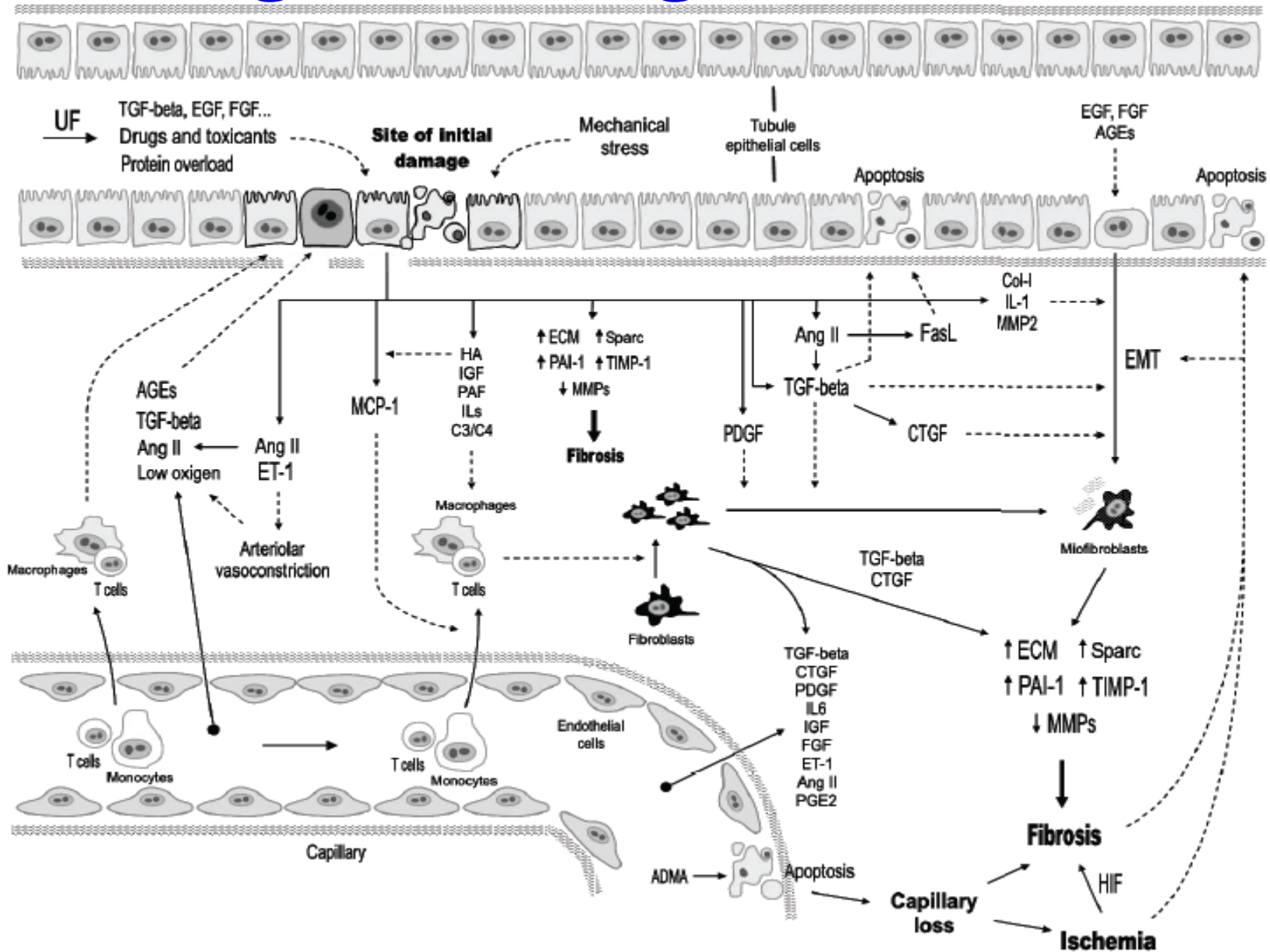
Infiltration of the TI comp by dendritic cells, lymphocytes, macrophages, mast cells

Teoria retrograda (tub-glom)

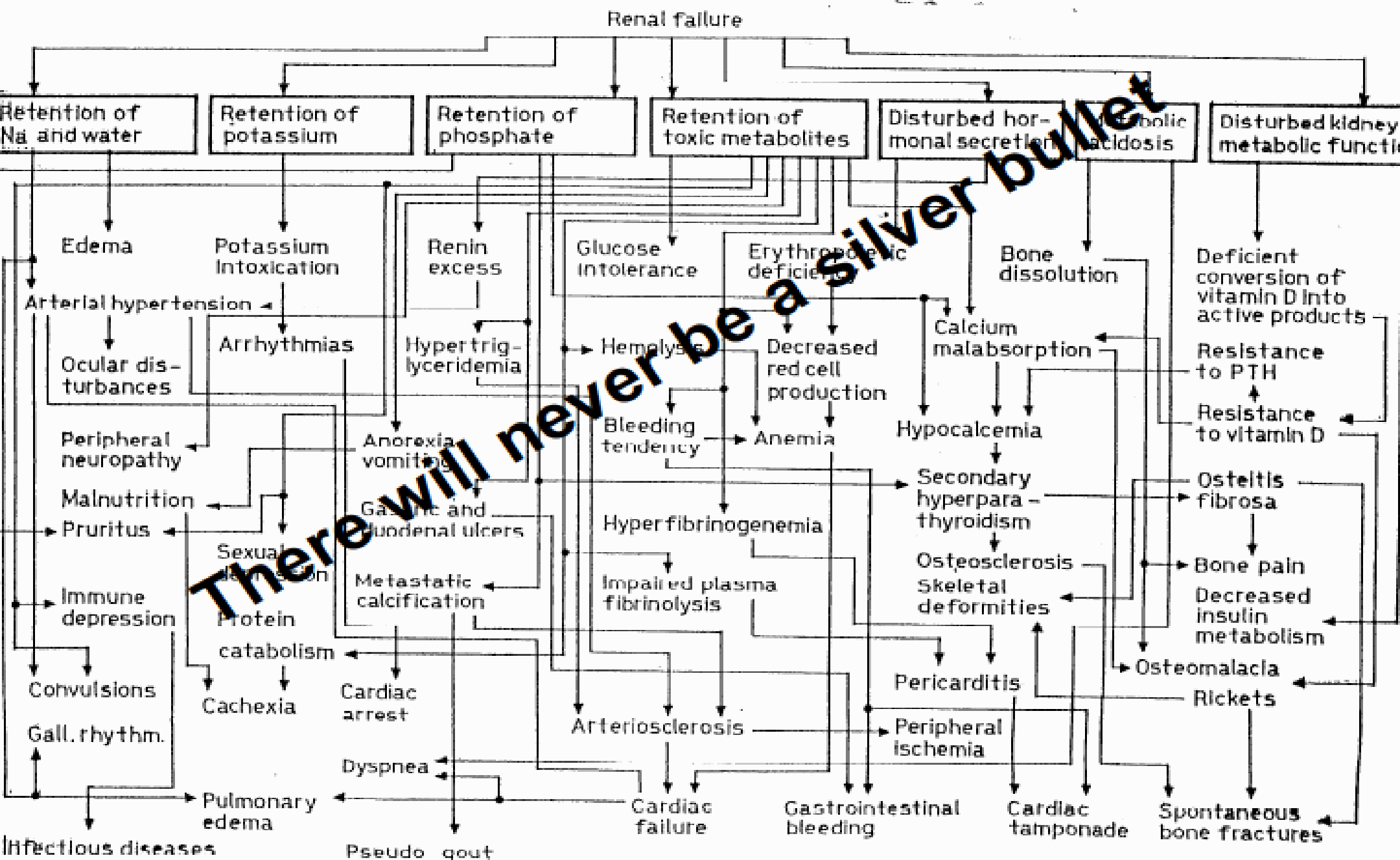
Tub

Int

Cap.



Simplified flow schedule of uremia and its complications



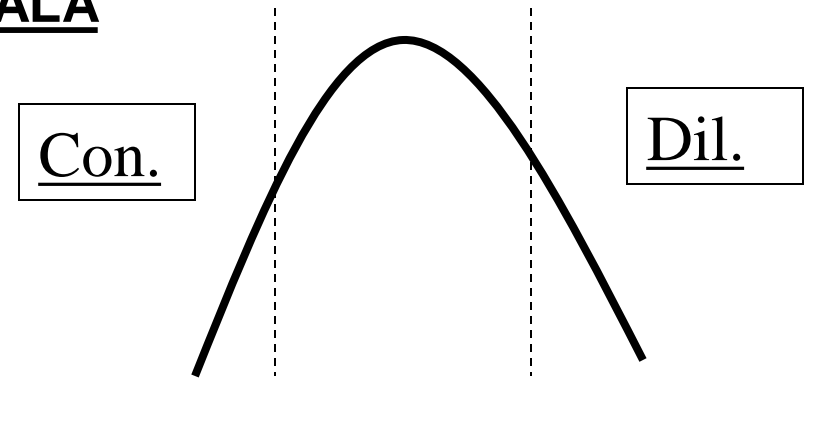
ALTERAREA FUNCTIEI EXCRETORII

ALTERAREA CAPACITATII DE CONCENTRARE MAXIMALA

- normal – 1200 – 1300 mOsm/l
- IRC – supraincarcarea cu fluide a nefronilor restanti
 - efectul diuretic al ureei
- Semne clinice – **poliuria, nicturia, densitate urinara scazuta – 1010 – 1011 (izostenuria)**

ALTERAREA CAPACITATII DE DILUTIE MAXIMALA

- normal – 40 – 50 mOsm/l
- IRC – scaderea severa a RFG
 - incarcarea cu fluide



Tendinta la dezechilibre hidrice

ALTERAREA FUNCTIEI EXCRETORII

ECHILIBRUL Na

- Echilibrul Na este pastrat pana in forme avansate de IRC prin cresterea excretiei fractionate a Na
- Bolnavul cu IRC este un pierzator de sare – sinteza crescuta de FNaA
 - Retentie de Na – aport crescut
 - Hiponatremia – dieta cu aport mic de Na, diuretice

ECHILIBRUL K

- Echilibrul k este pastrat pana in forme avansate de IRC prin cresterea excretiei fractionate a K. Hiperpotasemie uzual apare la diureze < 1000ml/24h
 - **Hipo K emia – pierderi extrarenale, dieta hipo K, abuz de diuretice**
 - slabiciune musculara, aritmii, ECG – T negativ, ST deprimat, QT alungit
 - **Hiper K emia – dieta hiper K, transfuzii, infectii**
 - **Usoara ($K = 5.5 - 6.5 \text{ mEq/l}$) - ECG normal**
 - **Moderata ($K = 6.5 - 7.5 \text{ mEq/l}$) – ECG – unde T inalte si ascutite**
 - **Severa ($K = >7.5 \text{ mEq/l}$) – ECG – absenta undei P, QRS largit, aritmii ventriculare**

ALTERAREA FUNCTIEI EXCRETORII

ACIDOZA METABOLICA

Excretie normala de H^+ 1 – 4 mEq/kg/zi

- Cauze – insuficienta eliminare a ionilor amoniu
 - alterarea reabsorbtiei de bicarbonat
 - alterarea acidifierii distale
- Semne clinice
 - $pH < 7.38$
 - $PaCO_2 < 35\text{mmHg}$
 - Bicarbonat plasmatic $< 20 \text{ mEq/l}$
 - Baze exces $< - 3\text{mMol/l}$
 - Respiratie Kussmaul

ALTERAREA FUNCTIEI EXCRETORII

SCADEREA ELIMINARII PRODUSILOR DE DEGRADARE METABOLICA DIN METABOLISMUL PROTEINELOR

(Retentie azotata + Autointoxicare cu toxine uremice)

- **AZOTEMIA (RETENTIA AZOTATA)**

- Uree, Creatinina crescute

- Toxine uremice - > 400 (methyl guanidine, acid hippuric, pyrimidines, amine aromate, indols, phenols, parathormone, calcitonine, etc

MODIFICAREA TRANSPORTULUI TRANSMEMBRANAR DE IONI

- **alterarea functionarii pompei Na / K ATPase dependenta datorita toxinelor uremice i**
 - **creste concentratia IC de Na – incarcare celulara cu apa, scaderea reabsorbtiei tubulare de Na, cresterea excitabilitatii neuromusculare, cresterea rezistentelor vasculare periferice**

METABOLISMUL GLUCIDIC

- **Cresterea insulinemiei datorita eliminarilor renale scazute**
- **Cresterea rezistentei periferice la insulina**
- **Cresterea nivelelor serice de glucagon**

INSTABILITATEA ECHILIBRULUI GLICEMIC

METABOLISMUL LIPIDIC

- **Scaderea catabolismului lipoproteinelor**
- **Scaderea activitatii lipoprotein lipazei si a lipazelor hepatice**
- **Cresterea sintezei de trigliceride datorita aportului crescut de glucide**
 - **Aproape toti bolnavii cu IRC dezvoltă dislipidemii aterogene similare cu cele intalnite in DZ**

METABOLISM PROTEIC

- **Hipercatabolism proteic**
- **Modificari ale AA plasmatici si intracelulari**

HIPOPROTEINEMIE cu HIPOALBUMINEMIE

SINDROMUL UREMIC

**Totalitatea semnelor clinice si biologice din fazele avansate ale BCR.
Instalarea acestor semne are loc treptat, pe masura reducerii functiei renale**

APARATUL RESPIRATOR

- **EDEMUL PULMONAR UREMIC**
 - hiperhidratare, IVS, cresterea permeabilitatii capilare
 - RX – “Fluid lung”
- **PNEUMONITA UREMICA** – membrane alveolare bogate in fibrina, depozite interstitiale de fibrina
- **CALCIFICARI PULMONARE** – datorate hiperparatiroidismului
- **PLEUREZIA**

APARAT CARDIOVASCULAR

- **HIPERTENSIUNEA**

- **Forme usoare de BCR 50-60%, Forme severe de BCR - > 80% din bolnavi**
- **Retentie hidrosalina, hiperreninemie, alte cauze**

- **BOALA CORONARIANA ISCHEMICA**

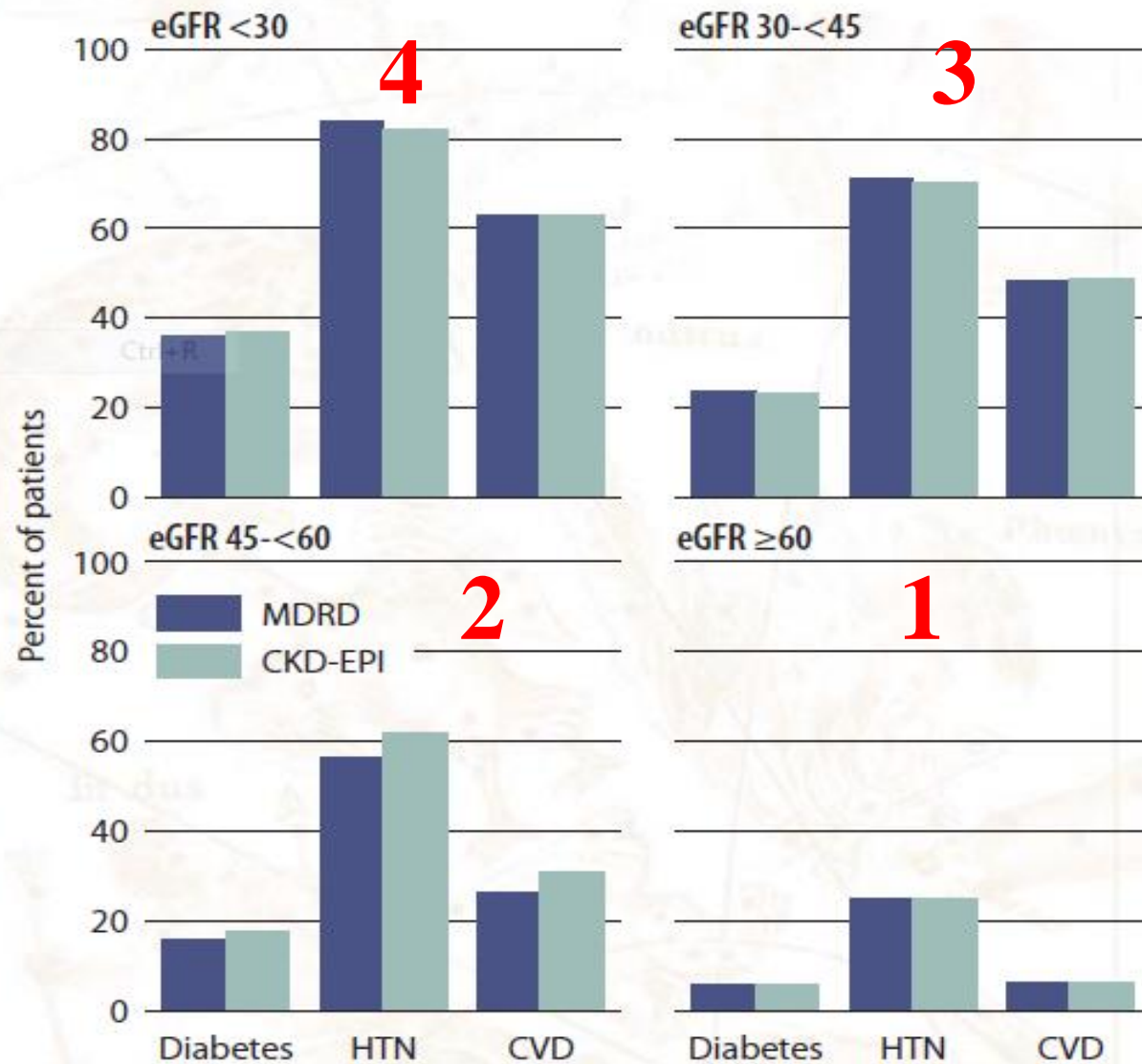
- **ateroscleroza accelerata – factori de risc multipli**
- **Clinic – debut precoce, evolutie accelerata, frecventa mare a afectarii bi si trivascularare**

- **CARDIOMIOPATIA UREMICA**

- **Leziuni nespecifice – fibroza interstitiala, calcificari miocardice, miocitoliza**
- **Clinic – tulburari de ritm si conducere, ICC, moarte subita**
- **ECO – HVS in absenta HTA, scaderea functiei diastolice**

- **PERICARDITA**

Prevalence of comorbidities in NHANES 1999–2006 participants, by risk factor, expanded eGFR categories, & method used to estimate GFR



APARAT DIGESTIV

- **STOMATITA UREMICA**
- **ESOFAGITA EROZIVA**
- **GASTRITA EROZIVA**
- **INTESTIN SUBTIRE** – absorbtie alterata a glucozei, AA, etc
- **FICAT - Hepatita**

MODIFICARI ENDOCRINE

- **Hormoni cu nivel plasmatic crescut: PTH, glucagon, STH, prolactin, calcitonin, FSH, aldosteron, gastrin**
- **Hormoni cu nivel plasmatic scazut: Erythropoietin, adrenal steroids, T4, 1,25(OH)2D3**
- **Interactiune deficitara hormon-receptor: Insulina, glucagon, PTH**

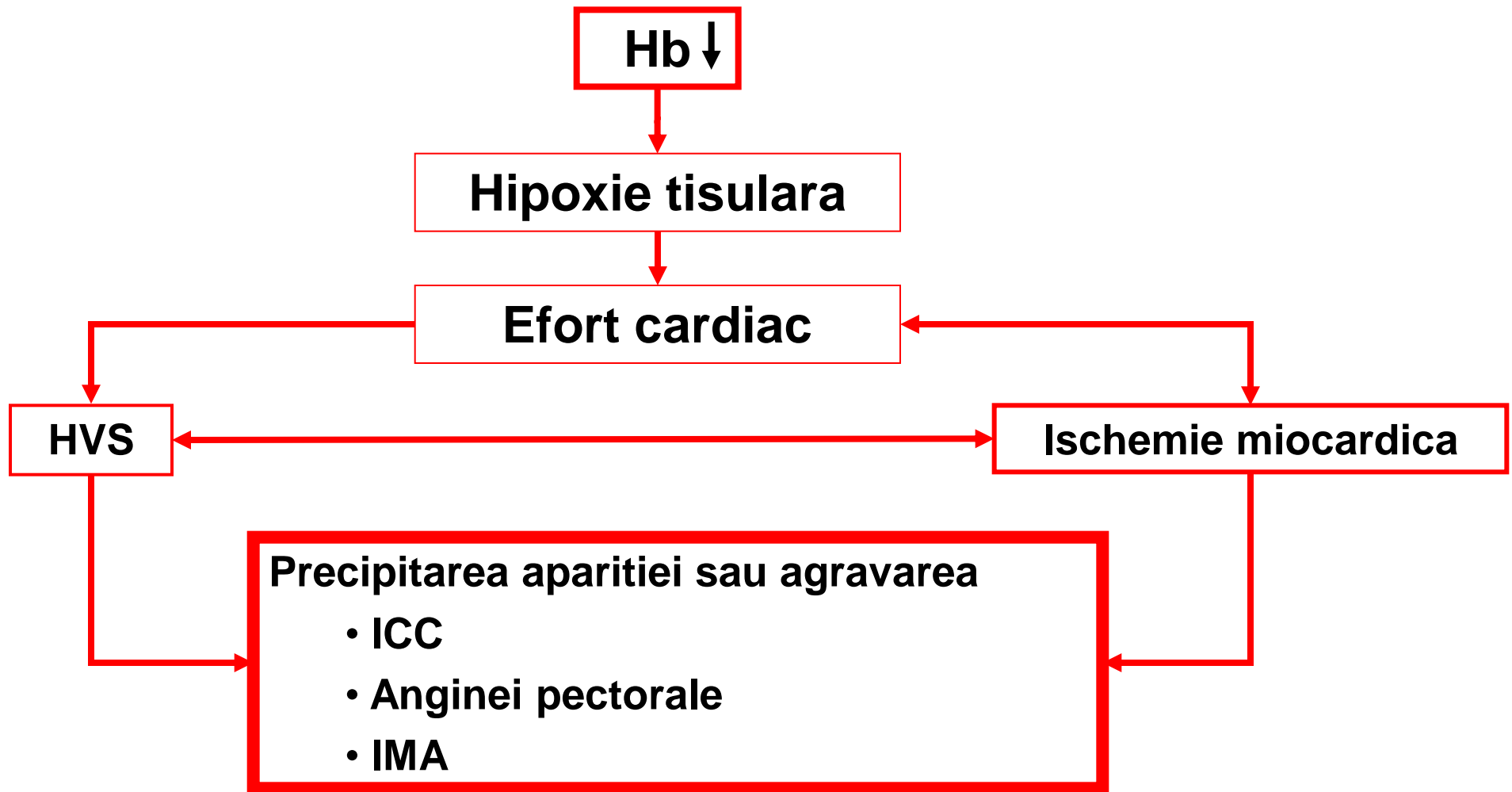
MODIFICARI HEMATOLOGICE

- **ANEMIA RENALA**

- **Modificari clinice – N N N, nivelul depinde de nivelul restant de eritropoietina**
- **Mecanisme – Anemie hemolitica moderata + deficit de eritropoietina**
 - **Deficit de Fe**
 - **deficit de folati**
 - **Infectii, malnutritie**
 - **HD**

- **TULBURARI DE COAGULARE**

- **Cauze - alterari: P, disfunctie endoteliala, interactiunii P-P – toxine uremice**
- **Manifestari – sindrom hemoragipar**



MODIFICARI IMUNITARE

- **Imunitate nespecifica**
 - **neutrofilie cu alterari ale capacitatii chemotactice, scaderea proprietatilor fagocitare si ale activitatii antibacteriene**
- **Imunitate specifica celulara si umorala**
 - **Limfopenie cu exces de TS si deficit de TS**
 - **Raspuns diminuat la tuberculina**
 - **Supravietuire prelungita a grefei cutanate**
 - **Raspuns deprimat al L la mitogeni**
 - **Scaderea LB**
 - **Alterarea sintezei de anticorpi**

TULBURARILE METABOLISMULUI MINERAL SI OSOS ASOCIATE BCR (TMO-BCR)

Definitie a TMO - BCR

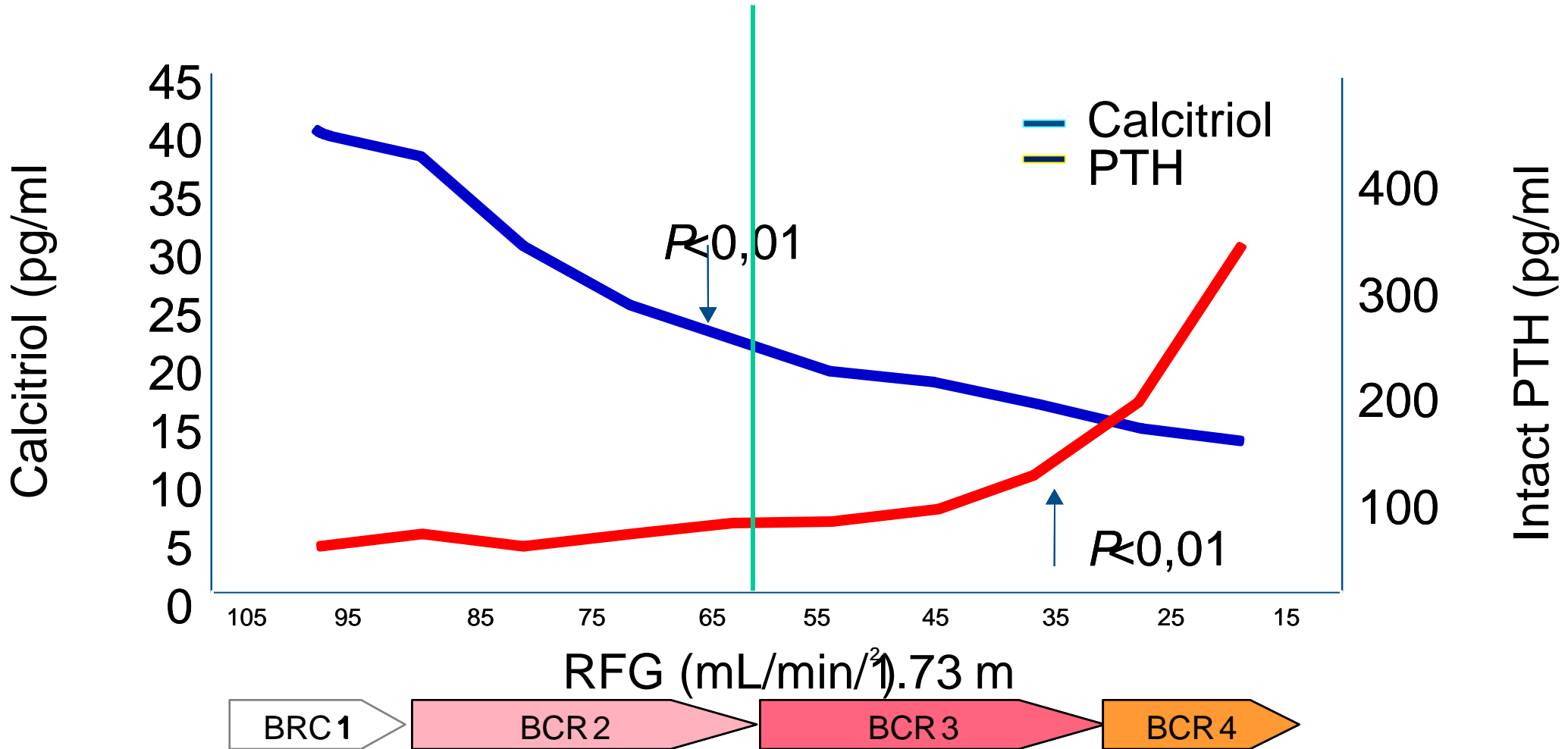
Tulburare sistematica a metabolismului mineral si osos datorat BCR manifestat prin oricare din urmatoarele:

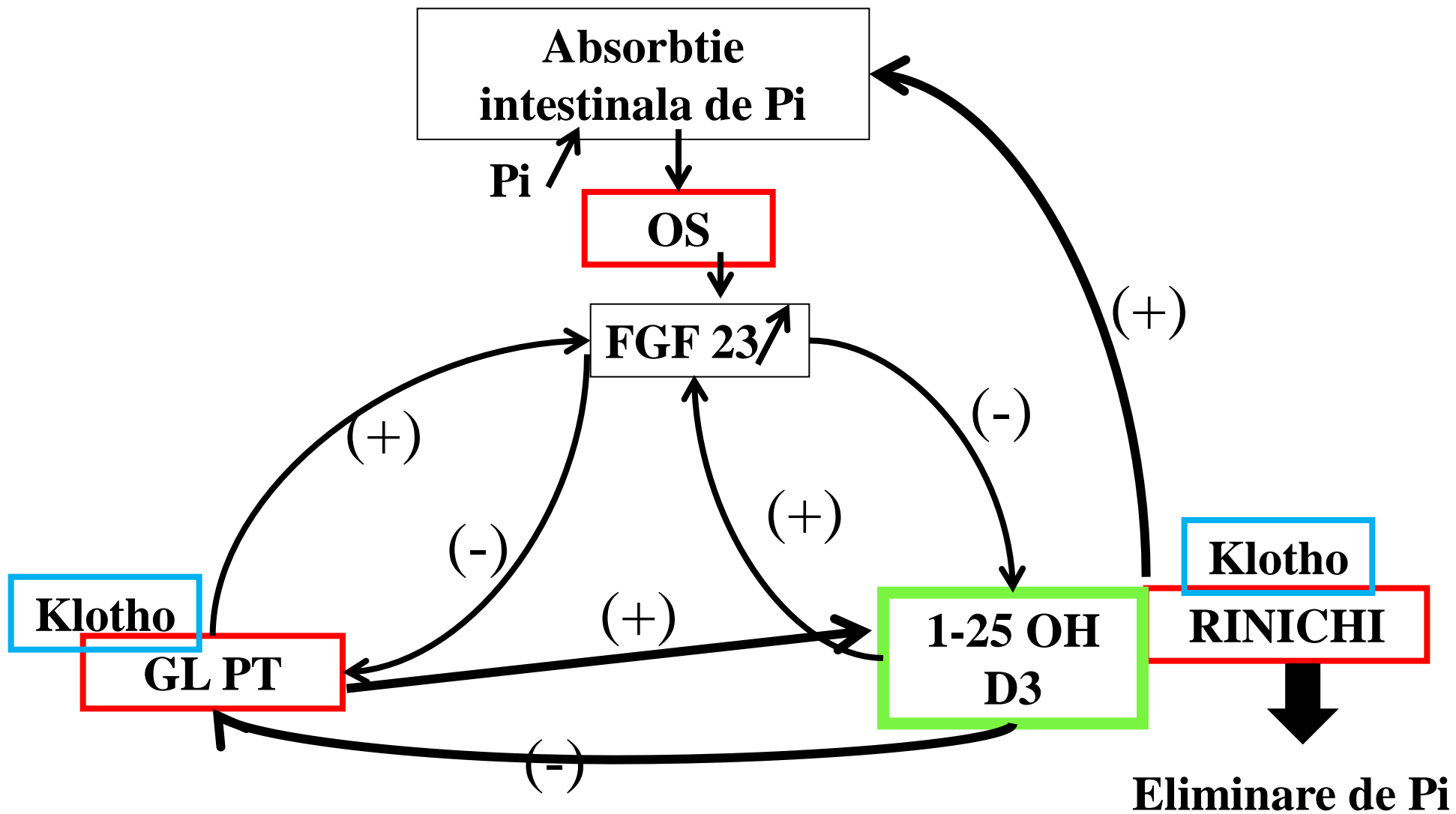
- **Anomalii ale metabolismului Ca, PO₄, PTH, si vitamina D.**
- **Anomalii ale turnover-ului mineralizarii, volumului, cresterii oaselor**
- **Calcificari vasculare si ale tesuturilor moi.**

Osteodistrofia renala

- **Alterarea morfologiei osoase indusa de BCR.**
- **Este o manifestare a TMO-BCR evaluata prin histomorfometrie a punctiei osoase.**

PTH SI VITAMINA D SERICA IN BOALA CRONICA DE RINICHI (BCR)





MODIFICARI NEUROLOGICE

- **SNC**
 - **Encefalopatie uremica**
- **SN PERIFERIC**
 - **Polineuropatie periferica, simetrica, mixta senzitivo-motorie**
 - **Restless leg syndrome**
 - **Burning foot syndrome**
 - **Parestezii “in ciorap”**
 - **Atrofii musculare, mioclonii, paralizii**
- **SN AUTONOM**
 - **Hipotensiune posturala, Hipotensiunea de dializa**
 - **Alterarea sudoratiei,**
 - **Nistagmus**

ALTE

- **MODIFICARI REUMATOLOGICE** : miopatii, bursite, rupturi ligamentare spontane, artrite
- **MODIFICARI OCULARE** : calcificari conjunctivale si corneene, scaderea secretiei lacrimale – “Ochiul rosu uremic”
- **MODIFICARI DERMATOLOGICE**
 - **Hiperpigmentare cutanata**
 - **Calcificari cutanate**
 - **Prurit**

TRATAMENT CONSERVATOR

SCOP

- 1. Scaderea ratei de degradare a functiei renale**
- 2. Tratamentul episoadelor de LAR/BCR**
- 3. Prevenirea aparitiei sindromului uremic – la costuri acceptabile**

1.Scaderea ratei de degradare a functiei renale

Controlul HTA – Scaderea proteinuriei

Tinta < 140/90, (<130/80), DZ <140/80

- IEC sau BRA
- Reducerea proteinuriei/albuminuriei

Controlul Glicemiei - HbA1c < 7%

Tratamentul dislipidemiei – Statine

In faza avansate :Corectarea anemiei si TMO-BCR

REGIM IGIENO-DIETETIC

- **Regim hiposodat in functie de pierderi**
- **Aport redus de proteine**
 - **Cr 1-2mg/dl – 0,8g/kg/zi**
 - **Cr > 2mg/dl – 0,6g/kg/zi**
- **Aport caloric – 30-35kcal/kg/zi**
- **Aport hidric – diureza+ perspiratie – diureza tinta 1500-2000ml/zi**

2.Tratamentul episoadelor de LAR/BCR

- **OBSTRUCTII**
- **INFECTII**
- **CORECTAREA ACIDOZEI, REECHILIBRARE H-E**
- **OPRIREA ADMINISTRARII NEFROTOXICELOR**
- **CONTROL STRICT AL HTA, GLICEMIEI, DISLIPIDEMIEI**

- **HD**

- **DPCA**

sau

- **TRANSPLANT RENAL**

Epidemiology and burden of chronic diseases

