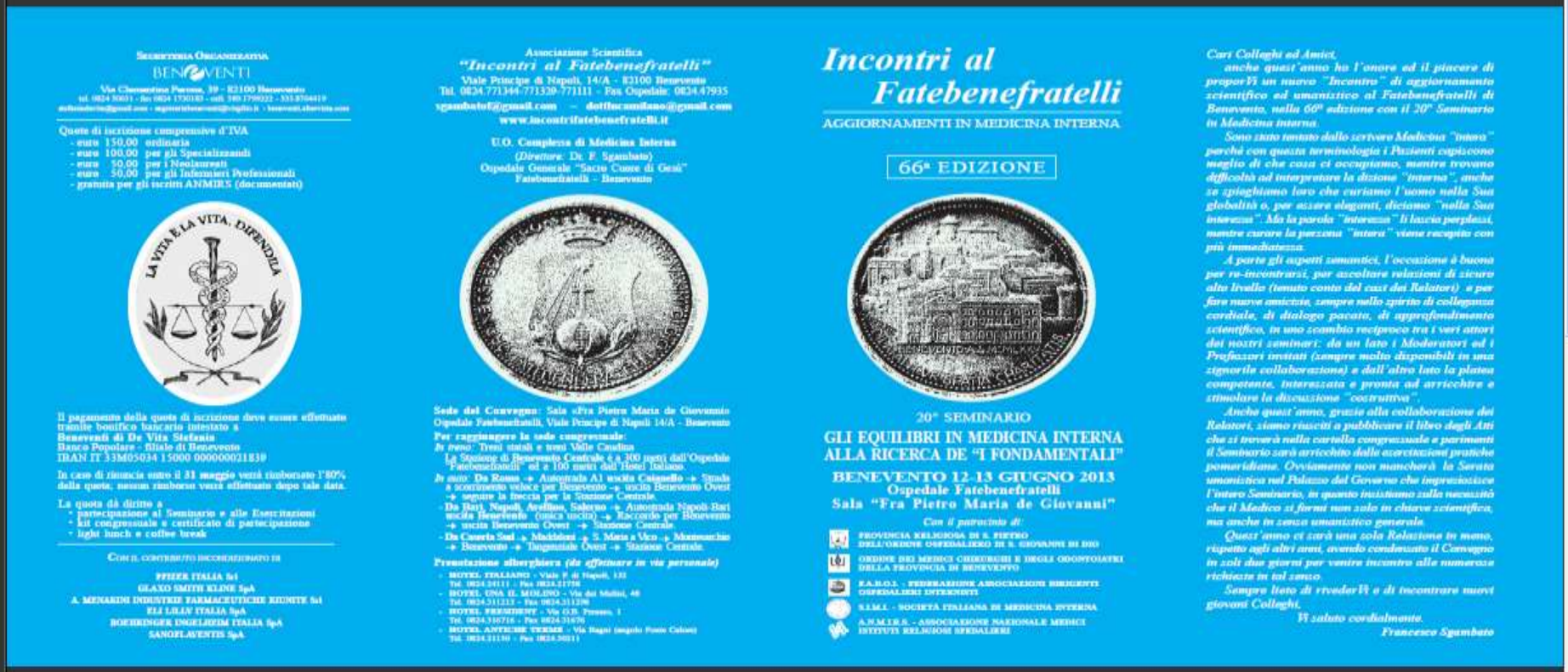


20° Seminario "Gli Equilibri in Medicina Interna :alla ricerca dei Fondamentali"

I FONDAMENTALI NEI RAPPORTI TRA FARMACI E RENE

Filippo Salvati

Direttore UOC Medicina P.O Ortona Guardiagrele ASL CHIETI

1) Il dosaggio dei farmaci in corso di insufficienza renale

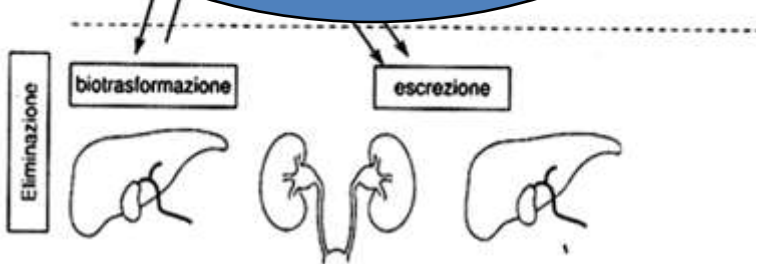
2) La nefrotossicità da farmaci

3) La nefroprotezione da farmaci

Il dosaggio dei farmaci in corso di insufficienza renale

ELIMINAZIONE

L’eliminazione di un farmaco avviene per escrezione del farmaco immodificato o dei suoi metaboliti



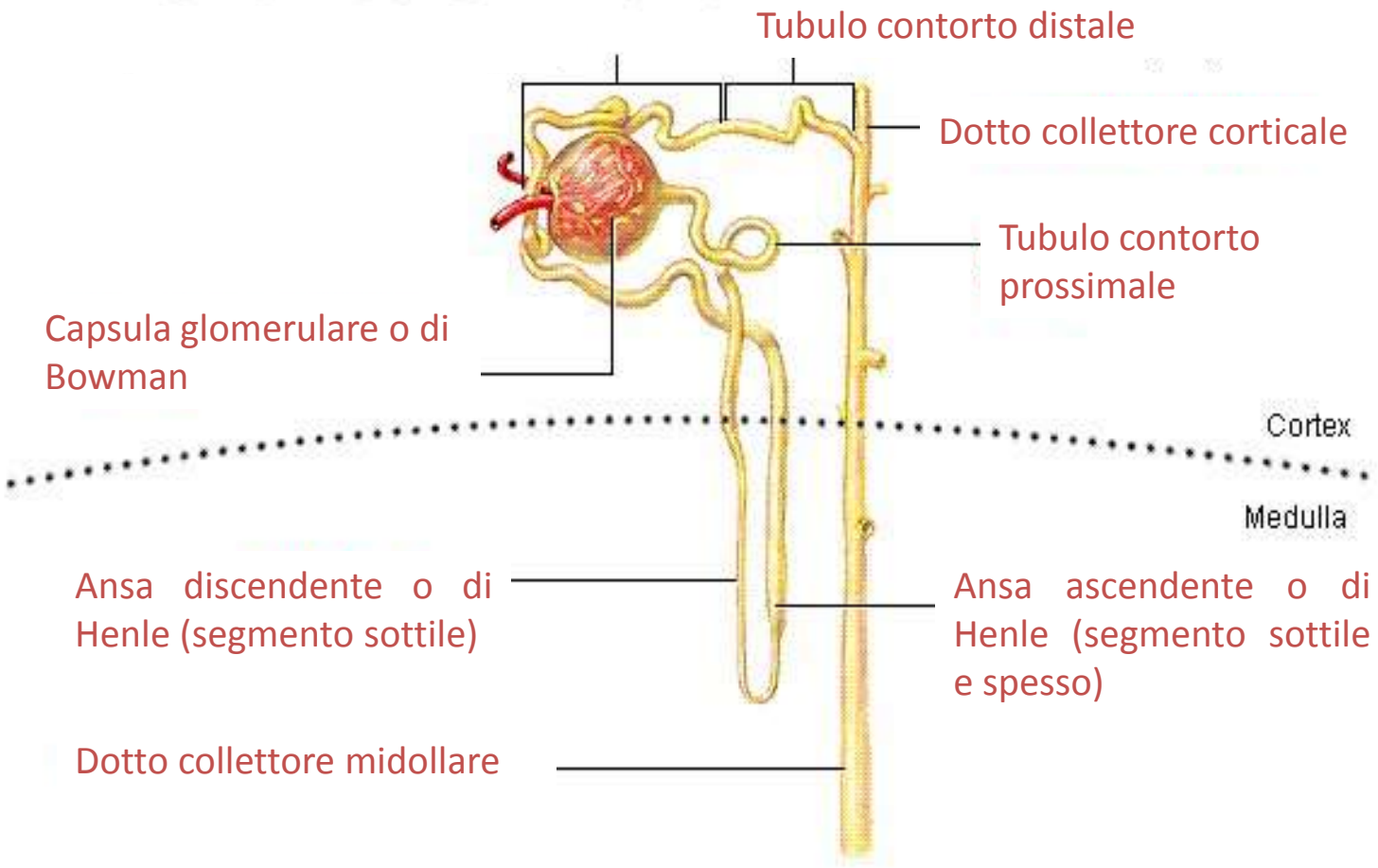
VIE DI ELIMINAZIONE DEI FARMACI

PRINCIPALI
- RENALE
- EPATICA

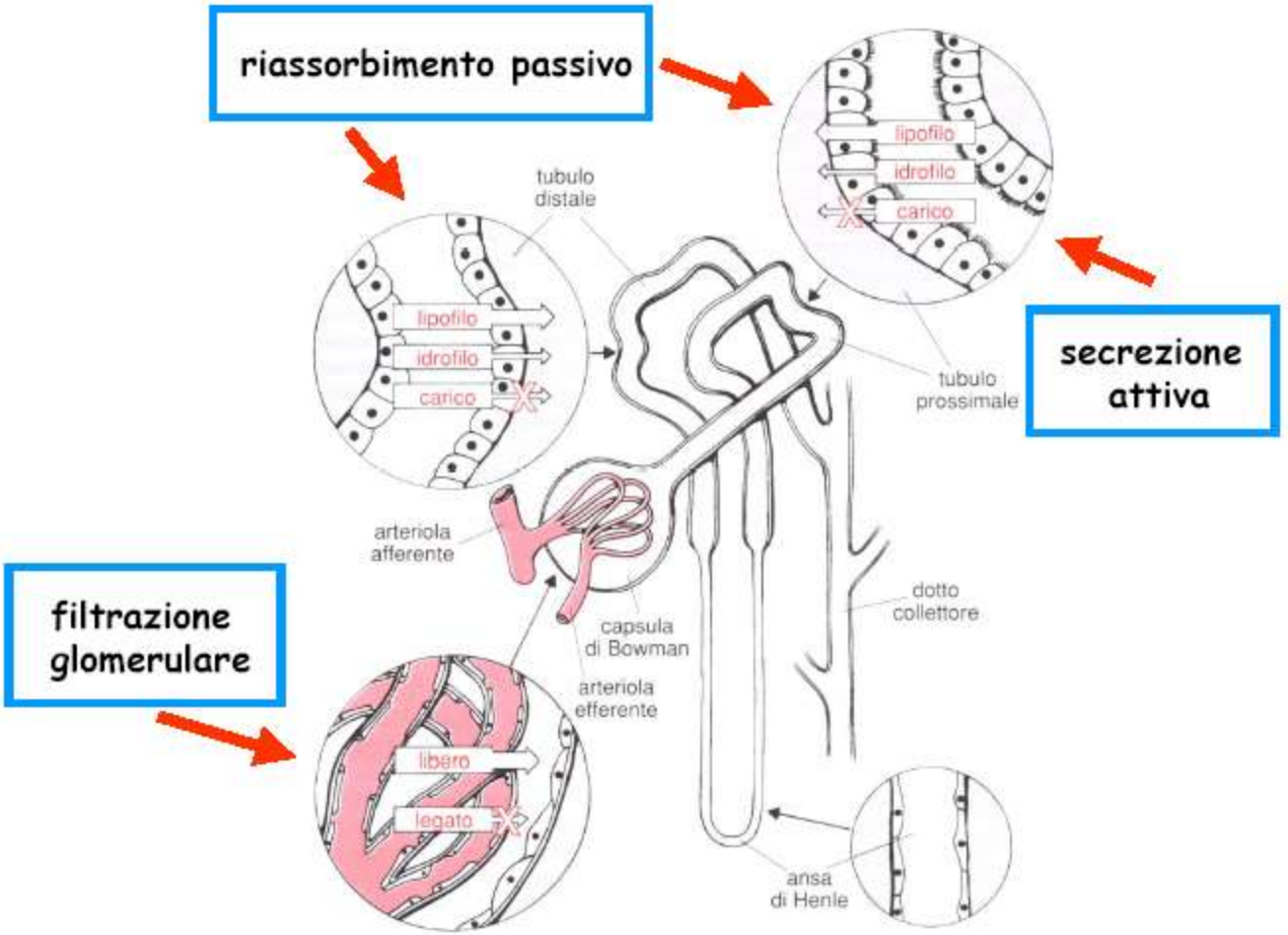
SECONDARIE
- POLMONARE
- INTESTINALE
- CUTANEA
- SALIVARE
- LACRIMALE
- CON IL LATTE

Il Nefrone

Struttura dei segmenti tubulari



Eliminazione Renale



Eliminazione renale: filtrazione glomerulare

Il 20% circa della componente acquosa del sangue viene filtrato a livello glomerulare.

I capillari glomerulari sono caratterizzati da una permeabilità particolarmente elevata.

Con l'acqua sono filtrate a livello glomerulare sostanze con PM fino a diverse migliaia di Dalton (PM < albumina).

Le proteine plasmatiche NON vengono filtrate.

I farmaci liberi o i metaboliti con basso PM vengono quindi eliminati per filtrazione glomerulare.

La quota di farmaco legata alle proteine plasmatiche NON PUO' essere eliminata con questo meccanismo.

Eliminazione dei farmaci da parte del rene.

Fattori che influenzano l'eliminazione

- età
- concentrazione plasmatica farmaco
- liposolubilità
- legame proteine
- pH urina (4,5-6,2)
- patologie
- flusso urinario
- interazione fra farmaci

Influenza del pH delle urine sull'eliminazione della metanfetamina

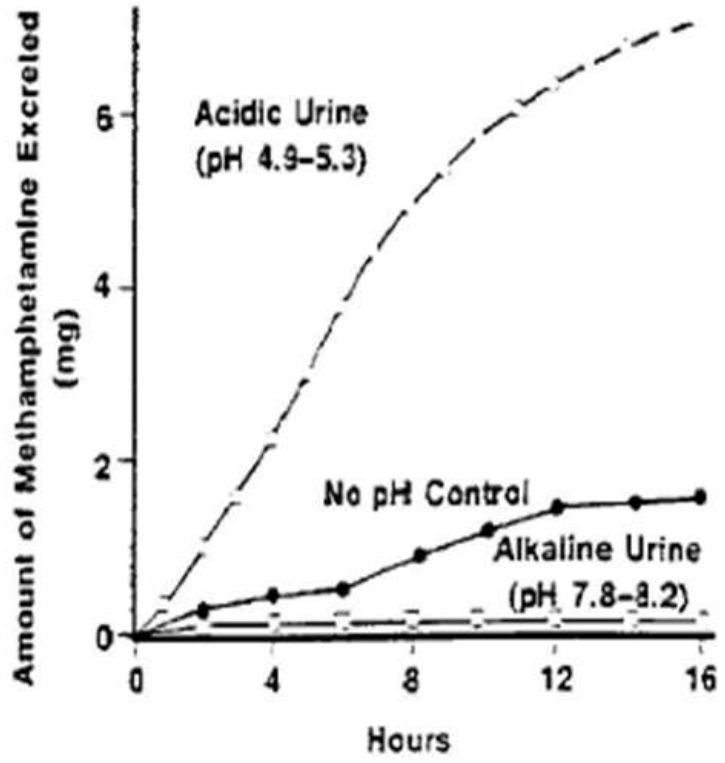
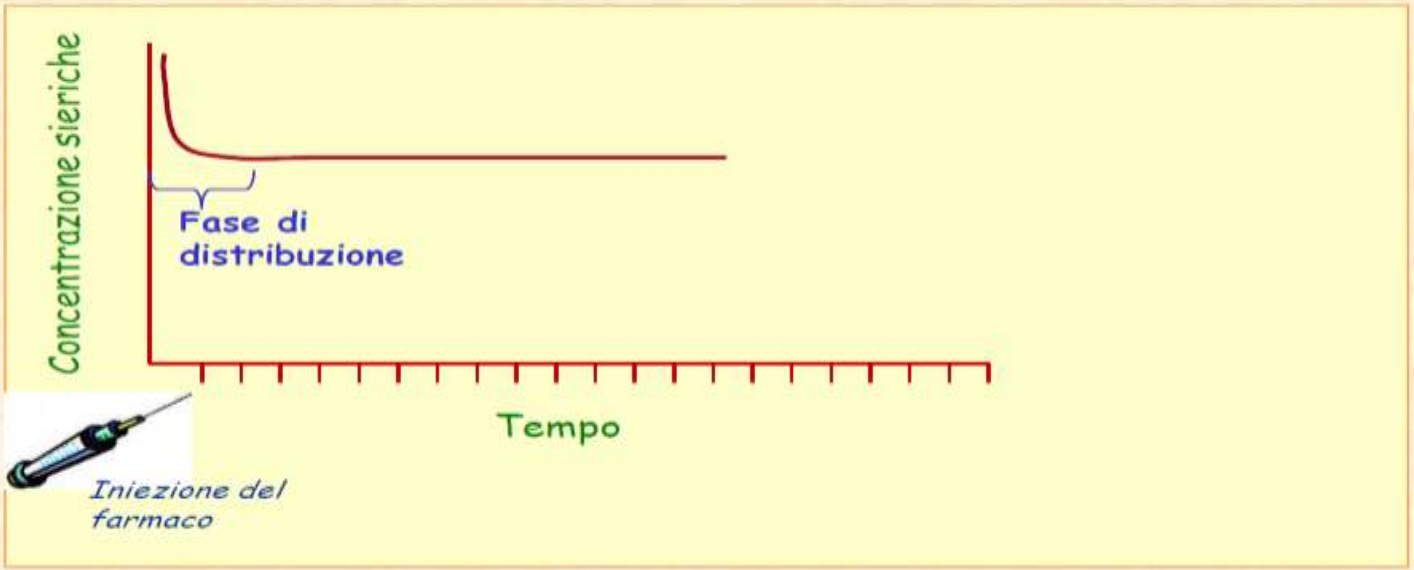


Fig. 11–8. The cumulative urinary excretion of methamphetamine (11 mg orally) in man varies with the urine pH. (Adapted from Beckett, A.H. and Rowland, M.: Urinary excretion kinetics of methylamphetamine in man. Nature, 206: 1260–1261, 1965.)

DETERMINAZIONE DEL Vd in ASSENZA DI ELIMINAZIONE

Concentrazioni di un farmaco nel siero dopo una singola iniezione di farmaco al tempo =0



Insufficienza renale

↓ Cl e ↑ t ½

Pharmacological management of type 2 diabetes mellitus in patients with CKD

BIGUANIDES

- **Metformin** is associated with a risk of potentially fatal lactic acidosis.
- The reported overall incidence of lactic acidosis For this reason**, NICE recommends using it with caution in patients in whom the serum creatinine exceeds 130 (xmol/l or the estimated glomerular filtration rate (eGFR) is less than 45 ml/min/1.73 m^2.**
- Doses should be lower than licensed maximum and prescribed with increased frequency of monitoring. In patients already taking metformin, **it should be discontinued if the serum creatinine exceeds 150 (xmol/l or the eGFR falls below 30 ml/min/1.73 m^2 (NICE 2009).**

INSULIN SECRETAGOGUES

- …They will therefore generally be used as the first line in the majority of patients with CKD
- The duration of action of sulphonylureas and meglitinides is variable; drugs such as tolbutamide and repaglinide are relatively short-acting (about 6–12 hours for tolbutamide, 3–6 hours for repaglinide, 4.5–7.5 hours for nateglinide) whereas chlorpropamide has a prolonged action (with a half-life over 24 hours). Additionally, while some drugs in this class are excreted in urine (e.g. glibenclamide), others undergo predomnantly hepatic metabolism and are less reliant on the kidney for excretion (less than 5% gliclazide is excreted in urine). For this reason, cautions and contraindications can vary between agents in the class and they should be considered on their individual kinetic profiles
- Insulin secretagogues are associated with an increased risk of **hypoglycaemia**. This risk **is increased in certain patient groups such as those with CKD and the elderly**.
- However, the significance varies by individual agent and **the shorter acting, hepatically cleared SUs such as gliclazide (DIAMICRON) , tolbutamide or glipizide (MINIDIAB) and also the shorter acting metaglinides such as repaglinide (NOVONORM) and nateglinide are suitable agents for patients with creatinine clearance less than 30 ml/min (Ashley & Currie 2008).**
- Conversely, longer acting **drugs such as glibenclimide (DAONIL,EUGLUCON)** and chlorpropamide **should be avoided in this patient group due to their increased propensity to hypoglycaemia**.

J Ren Care. 2012 Feb;38 Suppl 1:59-66

Pharmacological management of type 2 diabetes mellitus in patients with CKD

THIAZOLIDINEDIONES (GLITAZONES)

- **Pioglitazone, primarily excreted in faeces, may be used in patients with CKD (creatinine clearance >4 ml/min) however, up to 40% of patients with diabetes and persistent proteinuria or albuminuria, have cardiovascular disease consequently pioglitazone is contraindicated in these patients but could be still used cautiously in those patient with CKD who have no previous cardiovascular history**

ALPHA GLUCOSIDASE INHIBITORS

- **In pharmacokinetic studies of patients with renal failure (eGFR less than 25 ml/min/1.73 m^2), increased peak plasma concentrations of acarbose and areas under the concentration-time curve (of about five and six times normal, respectively) have been found (Salvatore & Giugliano 1996). The clinical significance of these effects is unknown**; however despite HbA1c reductions of up to 1% in clinical trials, this is a drug that is little used in practice as many patients find the gastrointestinal adverse effects intolerable. NICE recommend acarbose only in those patients for whom other oral anti-diabetic medications are unsuitable (NICE 2009).

DPP-4 INHIBITORS (GLIPTINS)

- **Sitagliptin (JANUVIA)** is licensed for mono, dual or triple therapy but limited clinical study experience in CKD and excretion which is calculated at 87% in urine; **mean that this can only be used safely in patients with creatinine clearance > 50 ml/min** (Merck Sharp & Dohme Limited [MSD] 2011).
  In patients with creatinine clearance between 5 and 49 ml/min, the dose of saxagliptin should be reduced to 2.5 mg daily and patients should be monitored for any deterioration in renal function and for episodes of hypoglycaemia. Saxagliptin is not recommended for patients with end-stage renal disease (ESRD) requiring haemodialysis (Bristol Myers Squibb-AstraZeneca [BMS/AZ] 2011).
- **Vildagliptin (GALVUS)** is licensed only as a dual therapy with either met-formin, a SU or a thiazolidinedione. Vildagliptin is 85% renally excreted and **is not licensed in patients with creatinine clearance less than 50 ml/min** (Novartis 2011).

J Ren Care. 2012 Feb;38 Suppl 1:59-66

Pharmacological management of type 2 diabetes mellitus in patients with CKD

INCRETIN MIMETICS

- **Exenatide (BYETTA)** is predominantly eliminated by glomerular filtration.
  It can be used without dose adjustment in patients with a creatinine clearance over 50 ml/min.
  Doses should be escated with caution from 5 to 10 micrograms in patients with creatinine clearance of 30–50 ml/min due to the kinetic profile and also rare reports from post-marketing surveillance which have shown development or worsening or CKD.
  These reports, which may increase the risk of hypoglycaemic episodes, particularly when used in combination with an SU, may occur more frequently in patients taking other agents known to impair renal function, such as ACE inhibitors. If new or worsening CKD occurs, the incretin mimetic and other possible causative agents should be stopped and impairment is usually reversible with supportive care.
- **Liraglutide (VICTOZA) is cautioned for use in patients with creatinine clearance of 30–60 ml/min and contraindicated if less than 30 ml/min**.
  The newly licensed once weekly exenatide injection is not recommended for use in patients with a creatinine clearance less than 50 ml/min and is absolutely contraindicated if the creatinine clearance is less than 30 ml/min (Eli Lilly 2011).

INSULIN

- **… there are no specific recommendations on dose adjustment in renally impaired patients** who will be managed similarly under specialist care;
- however, it should be remembered that renal elimination accounts for up to half of the clearance of insulin and therefore **patients with acute changes to their renal function will require increased monitoring of blood glucose levels and are likely to need insulin dose reductions.**

J Ren Care. 2012 Feb;38 Suppl 1:59-66

ANTICOAGULANTI E IRC

La clearance renale è il più importante mezzo di eliminazione di molti anticoagulanti ,come le eparine a basso peso molecolare,il fondaparinux l'idraparinux,gli inibitori diretti della trombina ximelagratan e dabigatran , l'inibitore diretto del fattore Xa rivaroxiban .

Con ridotta clearance della creatinina questi farmaci possono accumularsi e aumentare il rischio emorragico

E’ stata dimostrata una assenza di accumulo di dalteparina e tinzaparina nella IRC,mentre ciò si verifica per la enoxaparina,motivo per cui la dose terapeutica di questo farmaco va modificata in corso di IRC (dimezzata) per valori di creatinina clearance<30 ml/min.

Una revisione della letteratura (12 studi)

ha documentato un incremento di emorragie maggiori in pazienti con IRC e Creat. Clearance <30 ml/min trattati con EBPM ,ma dati robusti erano solo per enoxaparina (a dose dimezzata dimostrava un rischio emorragico analogo ai pazienti senza IRC).

Controindicazioni alla profilassi farmacologica del TEV in pazienti acuti medici

- Bleeding (active and uncontrollable)
- Hypersensitivity to UFH or LMWH
- Heparin-induced thrombocytopenia
- Coagulopathy
- Spinal tap or epidural anesthesia within 12 hours
- Hemorrhagic stroke
- Other relative or absolute exclusion criteria for pharmacological thromboprophylaxis which place a patient at high risk for bleeding, including uncontrolled hypertension, some surgical procedures, and significant renal insufficiency (creatinine clearance <30ml/min)*

*Patients should be assessed on a case by case basis in terms of benefit versus risk and with reference to product labeling.
LMWH, low-molecular-weight heparin; UFH, unfractionated heparin.

LMWH - pazienti con clearance creatinina 30-50 ml/min nessuna riduzione
< 30ml/min enoxaparina 2000 UI/die

Cohen AT Thromb Haemost 2005; 94: 750
Siddiqui MAA Drugs 2005; 66: 1025

La terapia anticoagulante orale con dicumarolici non ha una controindicazione assoluta nei pazienti con IRC, ma ovviamente richiede uno stretto monitoraggio clinico e laboratoristico del paziente soprattutto nella IRC severa grave.

Per quanto riguarda ultimi farmaci anticoagulanti immessi nel mercato o in fase di utilizzazione clinica a breve termine non vi sono in letteratura dati sicuri per molti di essi circa il loro utilizzo nei pazienti con IRC.

Purtuttavia possiamo al momento affermare che il dabigatran (eliminato totalmente dalle urine) non deve essere assolutamente somministrato ai pazienti con IRC di qualsiasi grado, mentre lo ximelagratan è stato ritirato dal mercato per severi problemi di tossicità epatica.

Il fondaparinux non deve essere usato in pazienti con clearance della creatinina<20 ml/min,tra 20 e 30 ml/min il dosaggio va ridotto a 1,5 mg/die , tra 30 e 50 a 1,5 mg/die per la profilassi a breve termine .

Il rivaroxiban viene eliminato al 66% attraverso le urine e pertanto deve essere usato con assoluta cautela nei pazienti con IRC.

L'inibitore diretto del Fattore Xa apixaban ha una duplice via di somministrazione (25% per via urinaria,il resto con le feci);il suo uso nella IRC (possibile) va strettamente monitorizzato.

Possiamo riportare inoltre le dosi da utilizzare in caso di ridotta funzione renale per altri anticoagulanti e antiaggreganti in fase di studio o di imminente immissione nel mercato, sempre con la raccomandazione di uno strettissimo controllo clinico e di un loro utilizzo in caso di stretta necessità laddove non sia possibile utilizzare farmaci storicamente più sicuri e di provata sicurezza ed efficacia.

La desirudina richiede riduzione del dosaggio a 1/6 in caso di clearance della creatinina < 20 ml/min,il lamifaban a 1/10,il lotrafiban a 1/2, il tirofiban a 1/2.

Il sulotroban va ridotto a 1/2 per clearance >50 ml/min, a 1/5 se < 50 ml/min, a 1/20 se < 20 ml/min.

CLEARANCE RENALE

Volume di plasma che viene depurato dal farmaco nell'unità di tempo

$$\text{CLEARANCE (ml/min)} = \frac{U \times V}{P}$$

U = Concentrazione del farmaco nell'urina
V = Volume urina in 1 min.
P = Concentrazione del farmaco nel plasma

>650ml/min sostanza che viene tutta filtrata e secreta (meccanismo attivo tubulare) (acido p-aminoippurico; l'escrezione renale del PAI è circa del 100%)
<130ml/min: sostanza filtrata, ma parzialmente riassorbita a livello tubulare
=130 ml/min: sostanza filtrata, no secreta, no riassorbita

Cl = 0 farmaco non escreto, ma completamente riassorbito (glucosio)

NON BASTA LA CREATININA

Creatinina
…ma …basta solo usare la Creatininemia?

40 Kg 52 ml/min

1 mg/dl

30 anni

$$\frac{(140\text{-}30 \text{ anni}) \times 90 \text{ Kg}}{72}$$

137 ml/min

!!

Formula di Cocroft = $\frac{(140\text{- Età}) \times \text{Peso corporeo}}{72 \times \text{Creatininemia}}$

nelle donne moltiplicare x 0.85

formula MDRD : Creatinina, età, sesso e razza

Se la funzione renale è normale...

... è meglio usare la formula di Cockcroft-Gault

$BC_{rc} = (140\text{-età}) \times Peso / P_{cr} \times 72$ x (0,85 se femmina)

Se la funzione renale è alterata…

… MDRD ha la migliore attendibilità

Table 48. Abbreviated MDRD Study Equation

$$\text{Estimated } GFR \text{ (ml/min/1.73m}^2\text{)}$$
$$= 186 \times (S_{Cr})^{-1.154} \times (Age)^{-0.203} \times (0.742 \text{ if female}) \times (1.210 \text{ if African-American})$$
$$= \exp(5.228 - 1.154 \times \ln(S_{Cr}) - 0.203 \times \ln(Age) - (0.299 \text{ if female}) + (0.192 \text{ if African-American}))$$

For explanation, see text and references 17,18.

Nefrotossicità da farmaci

Pseudo – renal failure

Steroids, tetracycline→ ↑BUN (hypercatabolic effect)

Trimethoprim. cimetidine, probenecid, triamterene, amiloride, spironolactone →↑Scr (competitive with creatinine for tublar secretion)

Ascorbic acid, cefoxitin, cephalothin, cefazolin, cefotaxime, flucytosine, levodopa, methyldopa→ interfere enzymatic measurement of creatinine by Jeffe' method

Manifestations of drug-induced renal disorders

- **Acute renal failure**
- **Chronic renal failure**
- **Nephrotic syndrome (Acute/Chronic)**
- **Fluid and Electrolyte disturbances**
- **Acid-base disorders**

- **Most episodes of drug-induced renal disorders are reversible**

→discontinue drug → renal fn. return to baseline.

- **Chronic renal injury (due to medication) → Chronic tubulointerstitial inflammation, pallillaly necrosis or prolonged proteinuria**

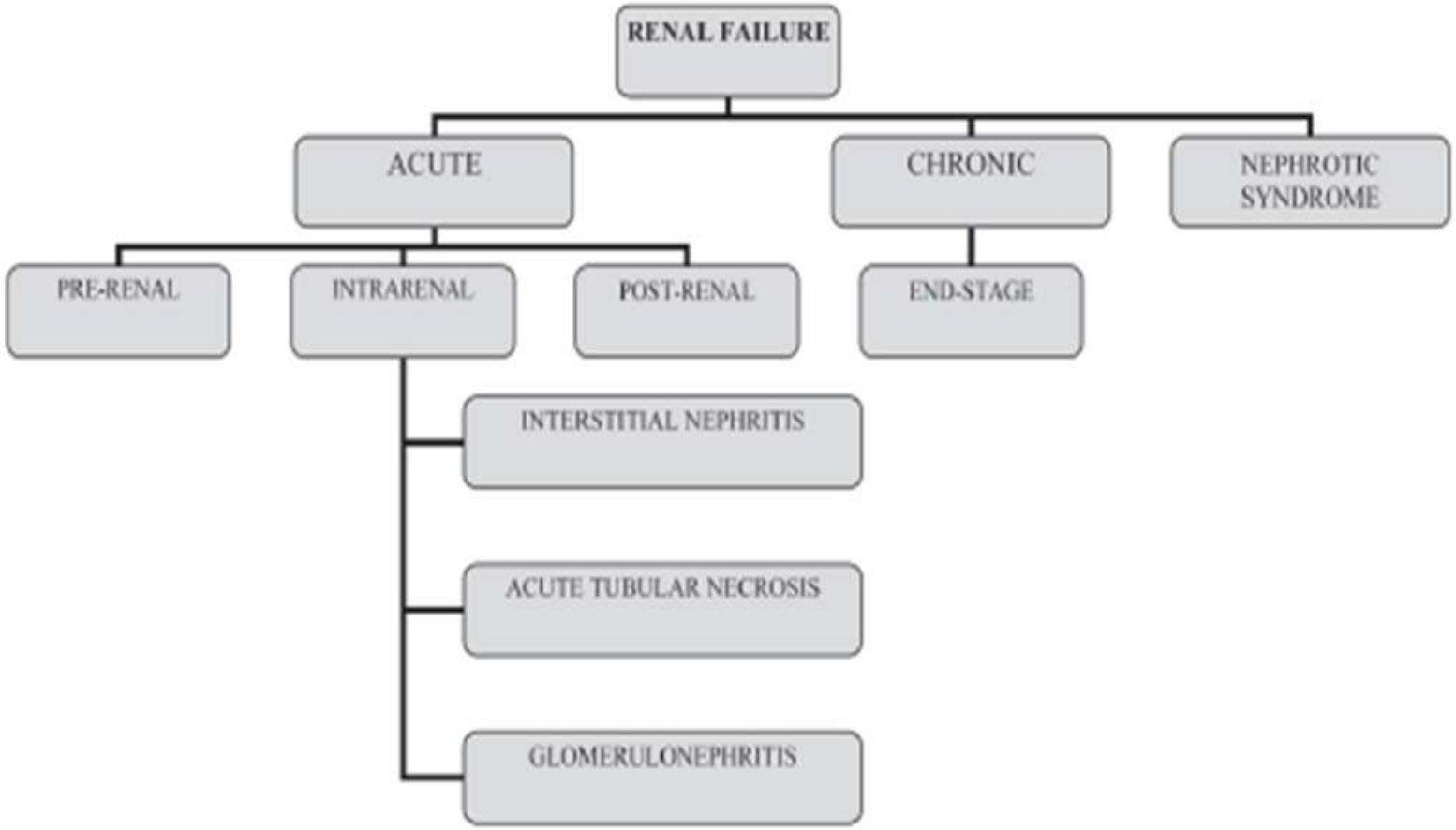


FIGURE 3. CLASSIFICATION OF DRUG-INDUCED RENAL FAILURE

Based on time frame (acute or chronic). Sub-classification of acute renal failure based on cause (pre-renal, intrarenal or post-renal). Nephrotic syndrome occurs with glomerular damage and the excessive loss of protein in the urine.

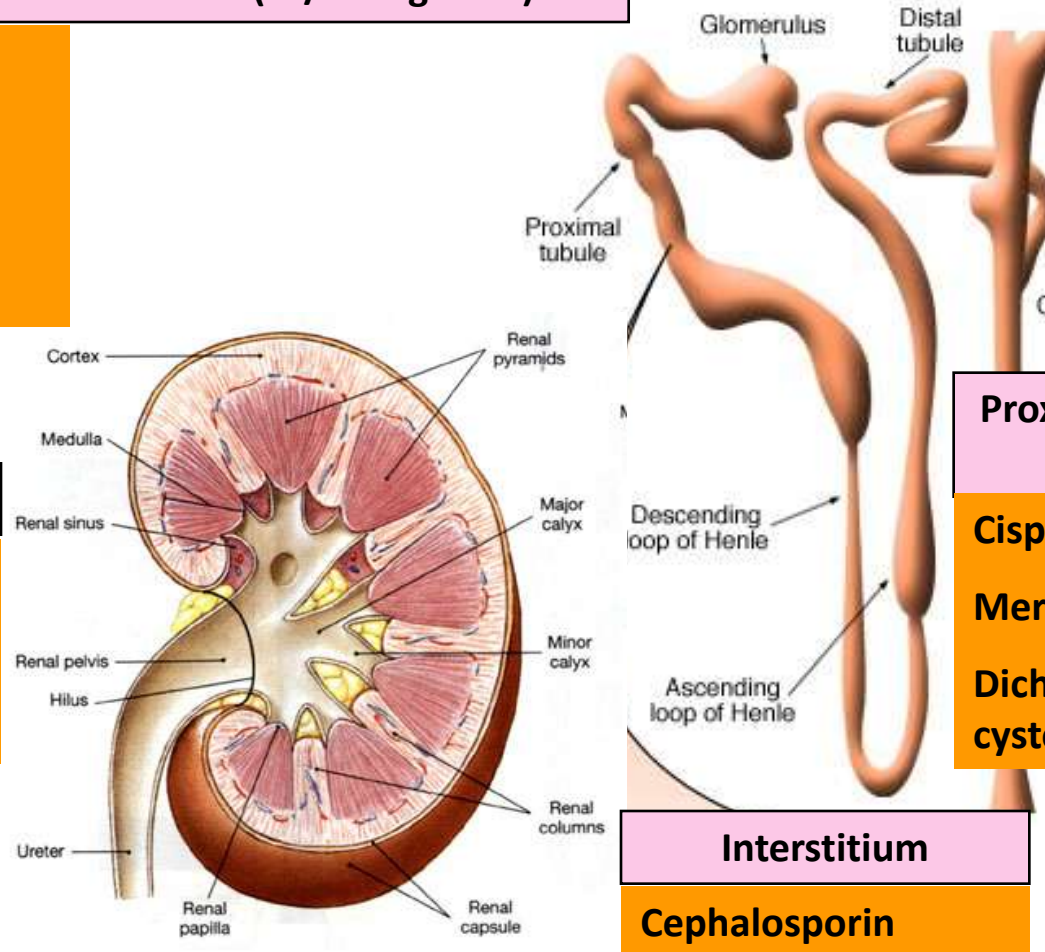
Drug-induce renal structural-functional changes

Proximal convoluted tubule (s1/s2 segment)

- Aminoglycoside
- Cephaloridine
- Cadmium Cl
- K dichromate

Glomeruli

- Interferon-α
- Gold
- Penicillamine



Proximal straigt tubule (s3 segment)

- Cisplatin
- Mercuric Cl
- Dichlorovinyl-L-cysteine

Renal vessel

- NSAIDs
- ACE Inhibitor
- Cyclosporin A

Interstitium

- Cephalosporin
- Cadmium
- NSAIDs

Pappillae

- Phenacetin

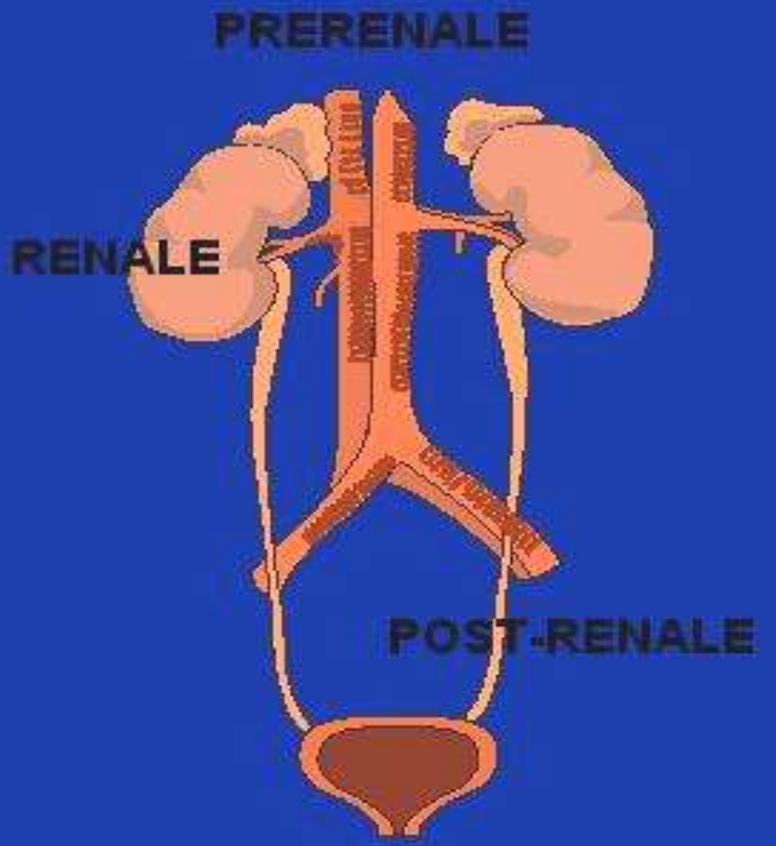
TABLE 1. DRUG CLASSES ASSOCIATED WITH RENAL FAILURE/DYSFUNCTION

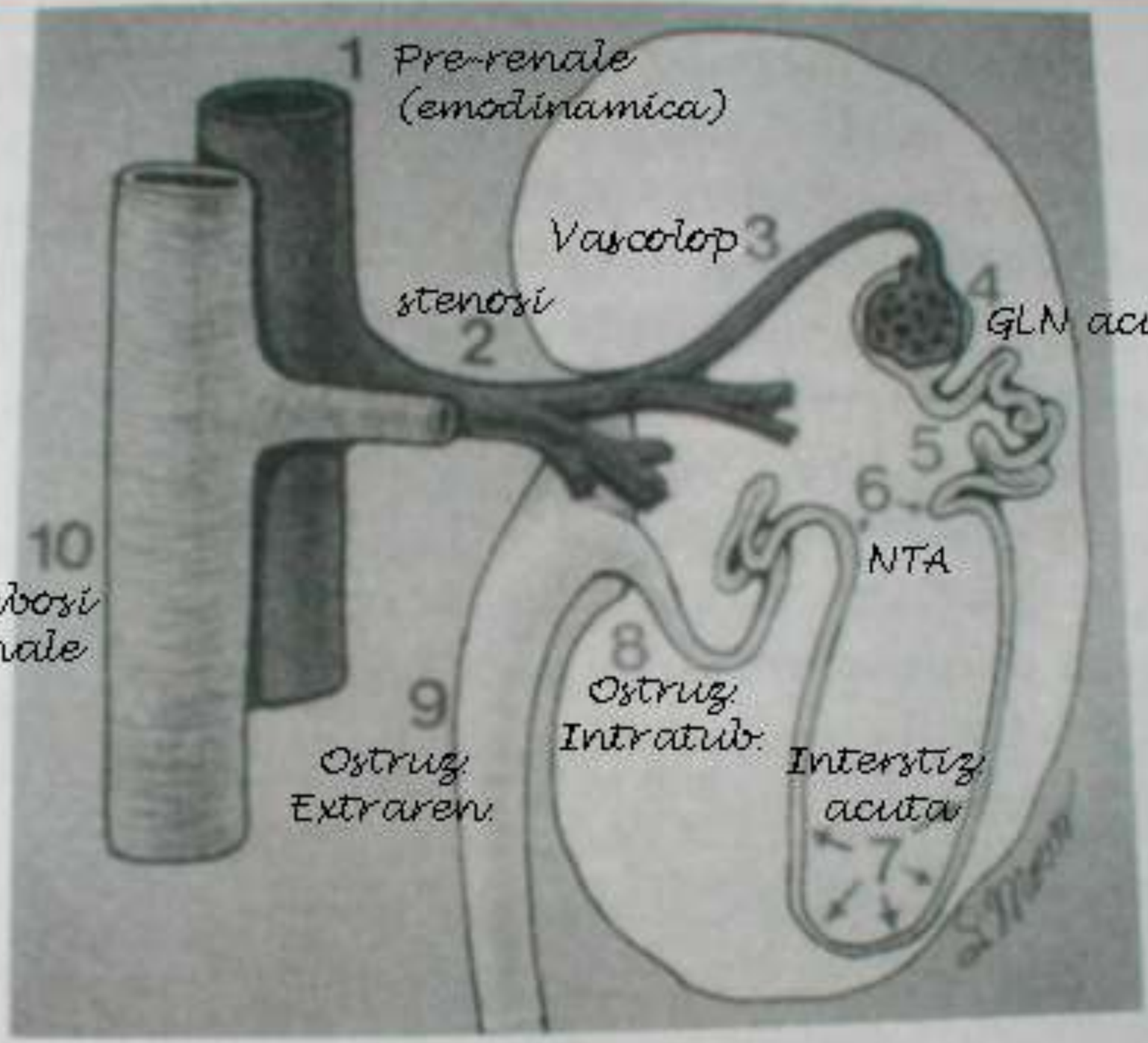
Antibiotics
Analgesics
Anticonvulsants
Antivirals
Amphotericin B
Antineoplastics
Antihypertensives
Drugs of abuse
Diagnostic agents
Herbal supplements
HMG-CoA reductase inhibitors
Immune globulin
H_2-antagonists
Lithium
Proton pump inhibitors
Others

Insufficienza renale acuta

- Complica il 5% di tutti i ricoveri
- 30% dei ricoveri in terapia intensiva

- **IRA pre-renale** (70% dei casi/50% in ospedale)
- **IRA renale o intrinseca** (25% dei casi)
- **IRA post-renale** (5% dei casi)




1 Pre-renale
(emodinamica)
Vascolop 3
stenosi
2
4
GLN acuta
5
6
NTA
10
Trombosi
V.renale
8
Ostruz.
Intratub.
9
Ostruz.
Extraren.
Interstiz.
acuta
7

RIFLE criteria for diagnosis of acute kidney injury

		Increase in serum creatinine	Urine output
R	Risk of renal injury	1,5 x baseline	<0.5 mL/kg per h for >6 h
I	Injury to the kidney	2 x baseline	<0.5 mL/kg per h for >12 h
F	Failure of kidney function	3 x baseline	<0.5 mL/kg per h for >24 h
		or	Or
		Serum creatinine ≥ 4 mg/dL with an absolute increase of >0.5 mg/dL	Anuria for >12 h
L	Loss of kidney function	Persistent renal failure for > 4 weeks	
E	End stage disease	Persistent renal failure for > 3 months	

Palevsky PM, Nephrology Self-Assessment Program;(5)March 2006

PRERENAL CAUSES

- CHF
- Excessive dehydration due to fluid loss
- Diuretics
- Sepsis
- Combination of these causes

Hemodynamically mediated renal failure

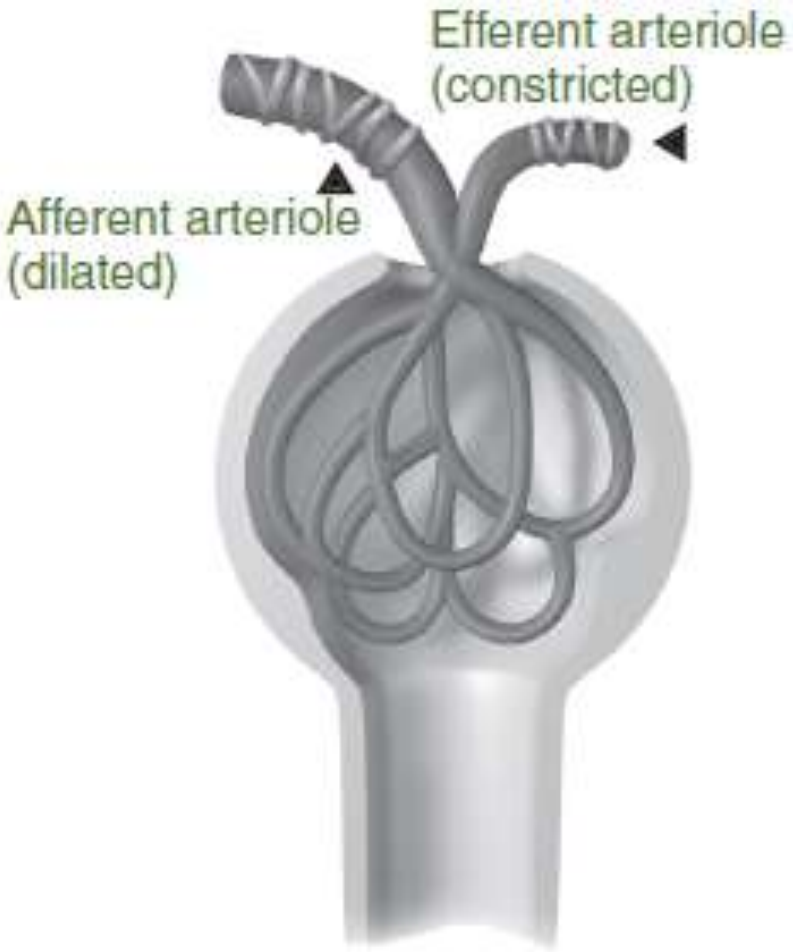
- Decrease total renal blood flow
- Vasoconstriction of glomerular afferent arterioles
- Vasodilation of glomerular efferent arterioles
- Increase Vascular permeability
- Increase collioid oncotic pressure and blood viscocity

Pre-renal causes

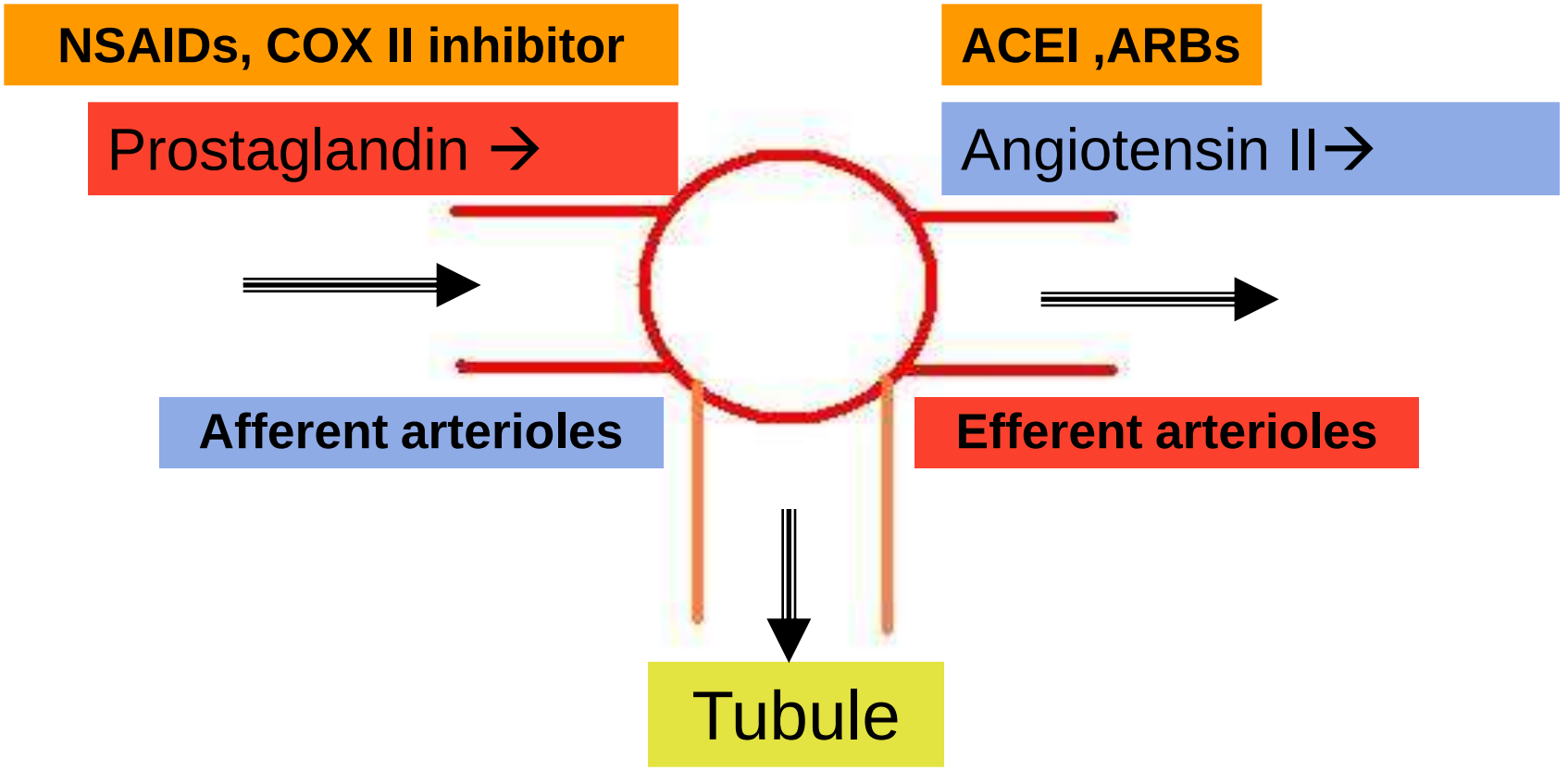
- Vasoconstriction
- Amphotericin, noradrenaline and immunosuppressive agents such as tacrolimus and ciclosporin
- Contrast agents
- Iodinated contrast media, in particular, have been shown to inhibit the synthesis of nitric oxide in renal artery smooth muscle

Hemodynamically mediated renal failure

- Diuretic, alone or combination with other antihypertensives
- ACEI & ARBs
- NSAIDs & COX inhibitor
- CyclosporinZreduce GFR in adose dependent and reversible manner)
- Tacrolimus, triamterene, propanolol, OKT3,dextran, epoietin


Efferent arteriole
(constricted)
Afferent arteriole
(dilated)

When the rate perfusion decrease, the renal bed autoregulates



REGOLAZIONE DELLA MICROCIRCOLAZIONE RENALE

Pressione glomerulare normale

"riduzione del "pre-load"
Ipertensione sistemica
e normotensione glomerulare

"riduzione del "post-load"
ACE inibitori

"aumento del post-load"
Normotensione sistemica e
ipertensione glomerulare
(diete iperproteiche

Un trio pericoloso

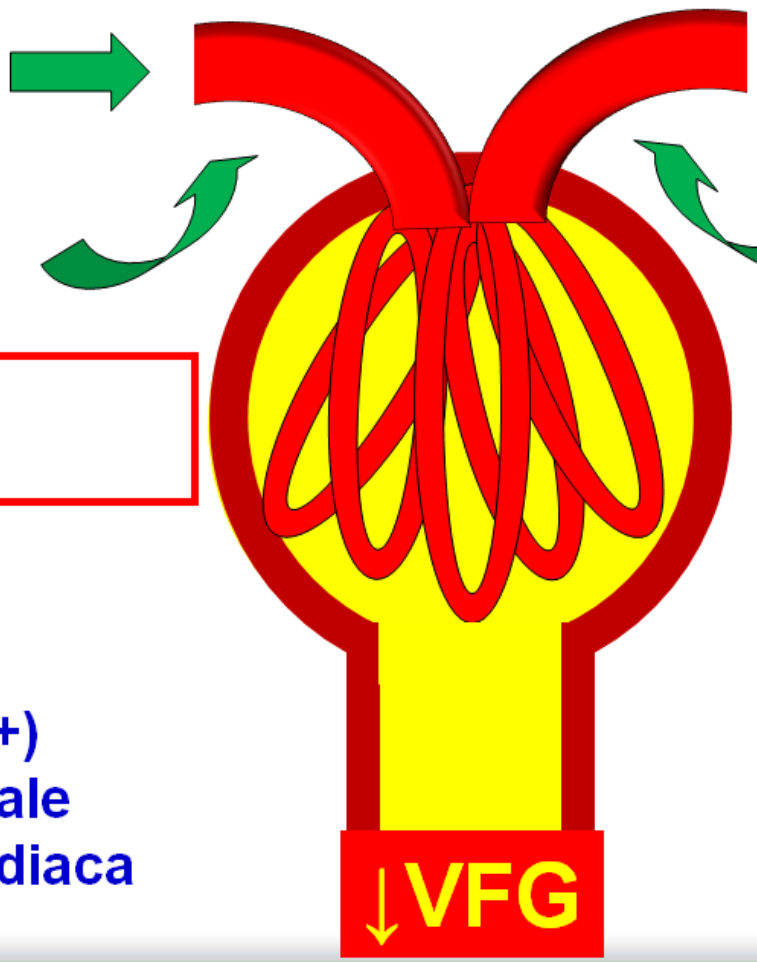
UN TRIO PERICOLOSO !

- ACE-INIBITORI e SARTANI
- DIURETICI
- FANS

LA TRIPLICE "BATOSTA"
riduzione funzionale renale acuta da farmaci

Diuretici

Riduzione volemia



ACE inibitori
Sartani

↓Tono arteriola efferente

↑Tono arteriola afferente

FANS*
(inclusi COX 2 inib.)

↓VFG

Fattori precipitanti:
- **Età avanzata (75+)**
- **Insufficienza renale**
- **Insufficienza cardiaca**

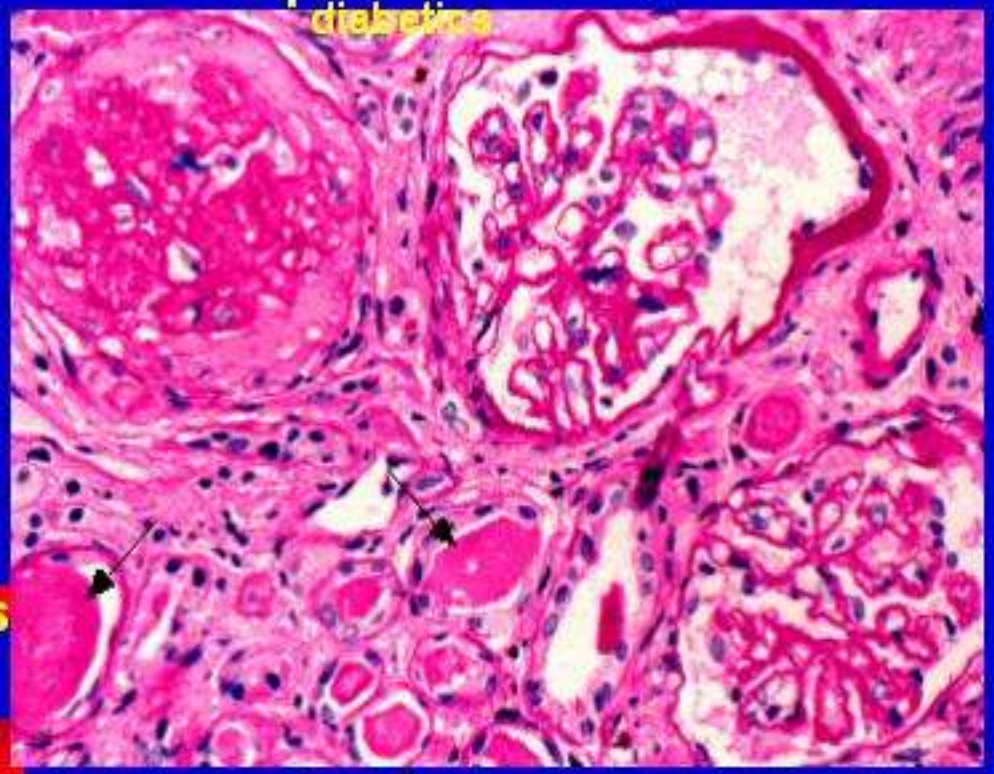
* spesso assunti spontaneamente

Risk Group RAS/Prostaglandin dependent

- Nephrosclerosis
- Bilateral renal artery stenosis renal stenosis artery
- Hypovolumia
- Heart failure
- Chronic kidney disease

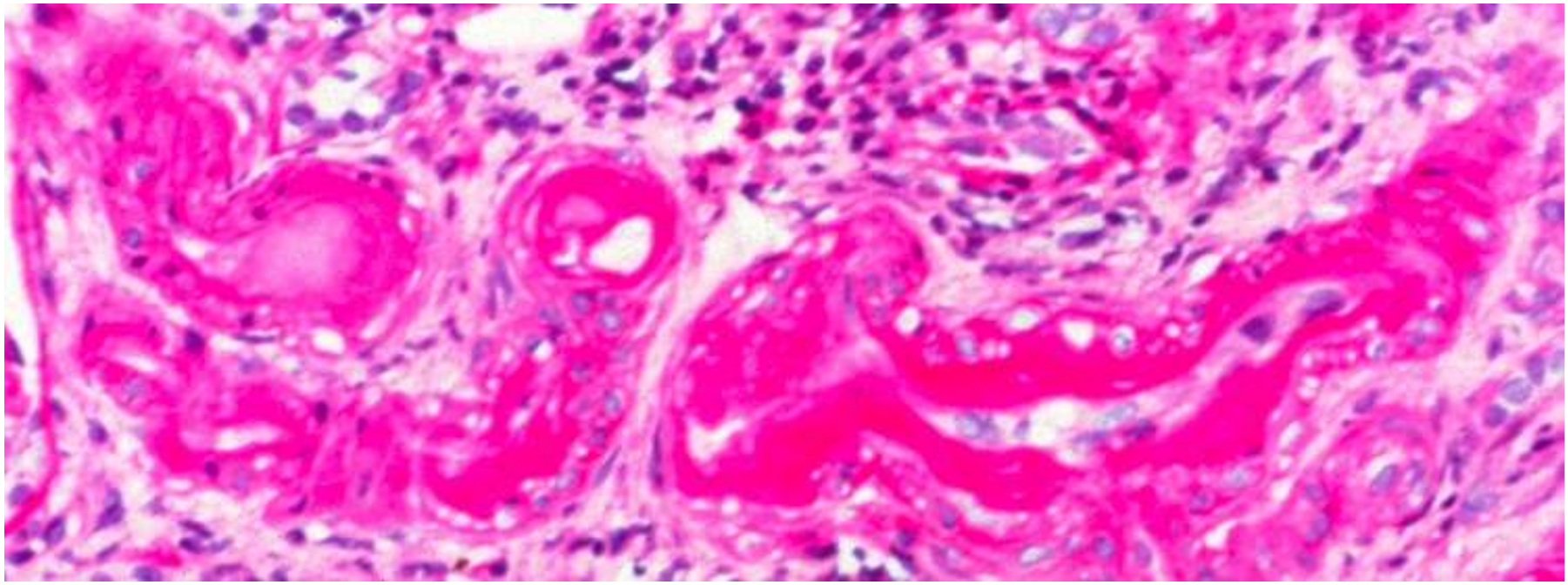
Hypertension, smoking,
Hyperlipidemia

Nephrosclerosis is the most common histologic alteration in diabetics

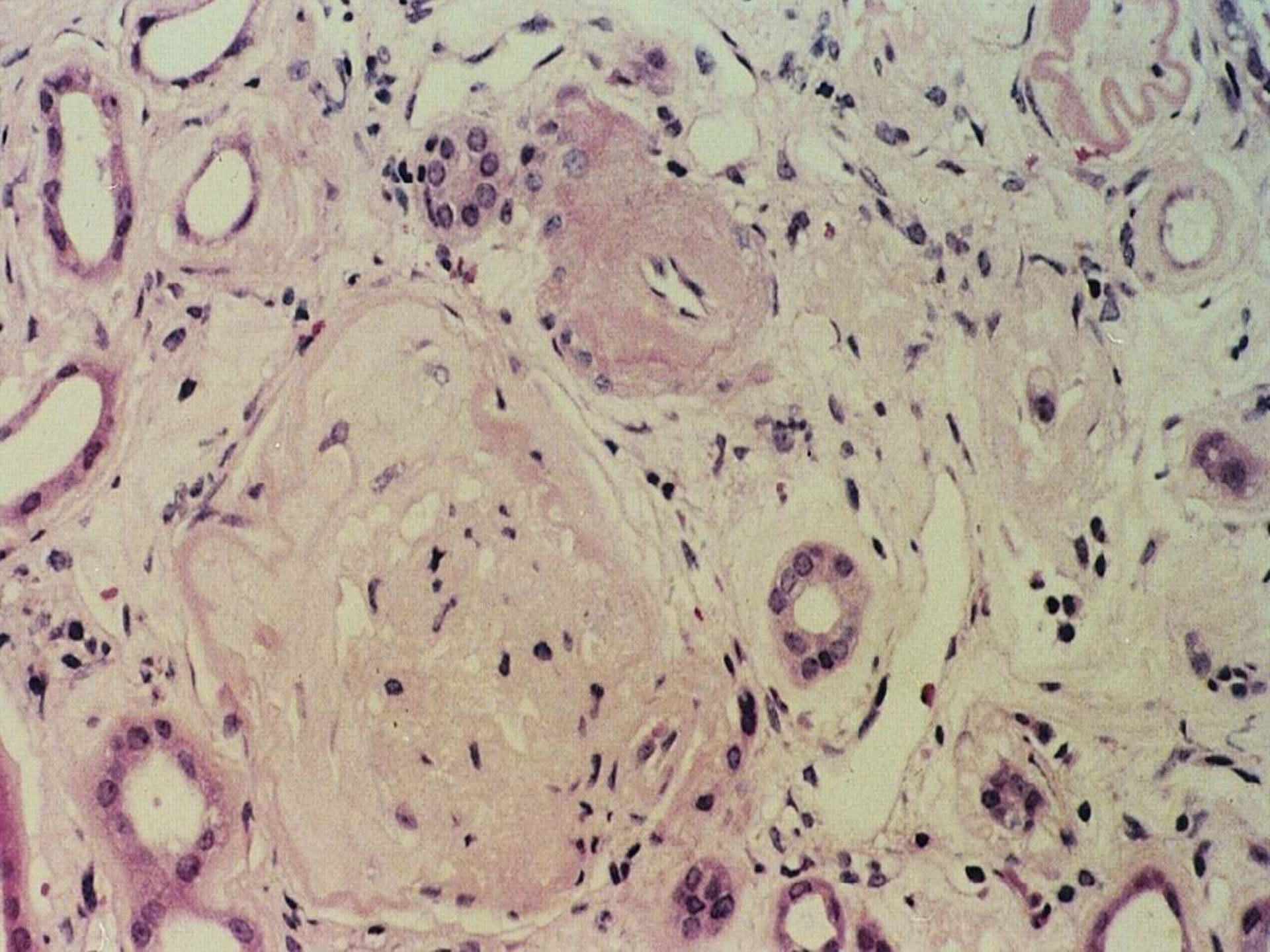


Nephrosclerosis

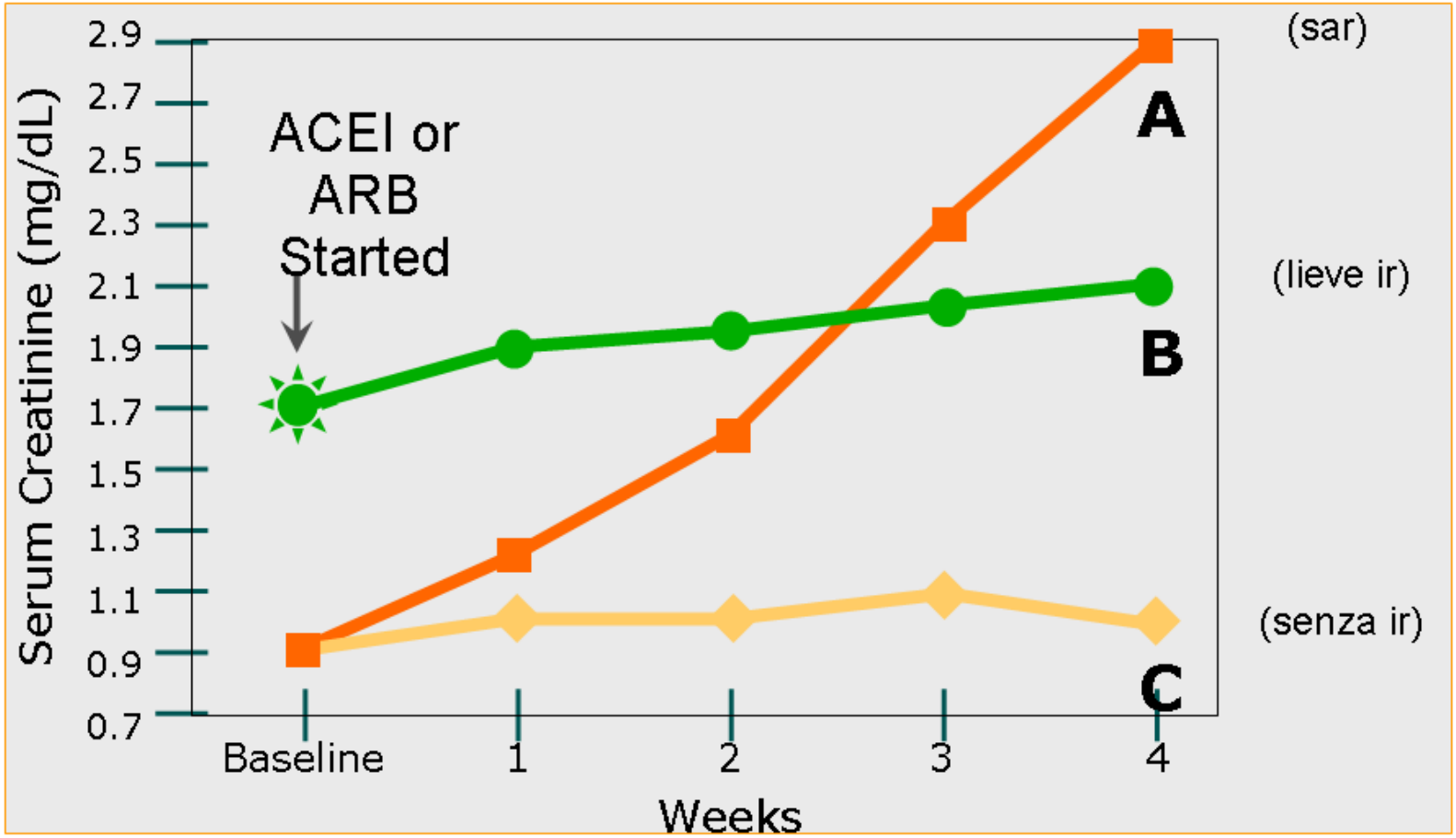
C.Zoccali, 2005



Ialinosi arteriolare in soggetto anziano



Pazienti con IRC and IA hanno minime alterazioni della creatinina in corso di terapia con ACEi o ARBs



terapia

D. Manfellotto

Bakris GL, Weir M. Arch Intern Med. 2000;160(5):685

ALCUNE RACCOMANDAZIONI SUGLI ACEI

- Poiché la riduzione del VFG indotta da un ACEi tipicamente accade pochi giorni dopo l'inizio della terapia, la creatinina e la potassiemia devono essere rimisurate da tre a cinque giorni dopo.
- La dose iniziale dell'ACE inibitore deve essere molto bassa (ramipril 1.25 mg, enalapril 2.5-5 mg). Se la pressione non si riduce, la dose può essere lentamente aumentata. Se tollerati, possono essere associati diuretici per il controllo del volume, trattamento della iperpotassiemia, o altro.
- Il farmaco deve essere interrotto in caso di iperpotassiemia non controllabile o se la creatininemia al primo controllo aumenta di oltre il 30% rispetto al valore di base.

Uso degli ACEi nella insufficienza renale

- C'è un valore di creatininemia al di sopra del quale non si deve usare questa terapia?
- La risposta a questa domanda sembra essere NO.

- Come osservato nel REIN, nei pazienti con un iniziale VFG molto basso (da 11 a 33 mL/min) vi è stato un rallentamento del 20% della perdita di VFG e una riduzione del 33% della incidenza di nefropatia terminale

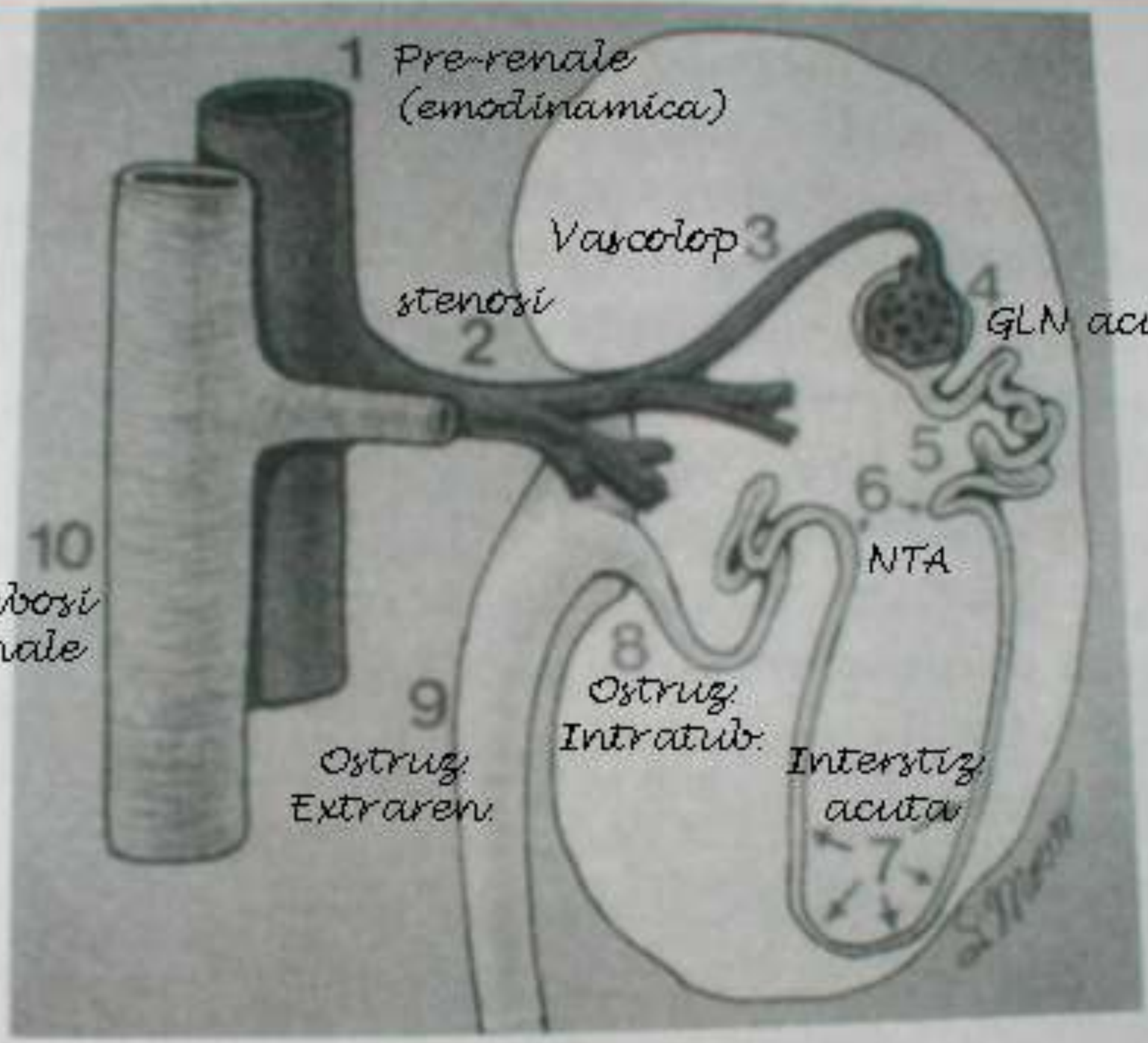
NSAIDs

- Long-term use can cause chronic renal insufficiency
- Patients who experience ARF with NSAIDs have underlying risk factors
- Prolonged NSAID use can cause chronic kidney disease, especially in the elderly
- 1-5 % of all end-stage renal disease (ESRD) patients have analgesic-associated nephropathy
- Risk factors for this nephropathy include gender (women>men), age (>50 years old) and prolonged use of the analgesic

NSAIDs

- **Selective cyclooxygenase (COX-2) inhibitors cause similar renal dysfunction**
- **COX-2 exists as a constitutive enzyme in the thick part of the ascending loop of Henle and in the renal medulla**
- **COX-2 causes natriuresis and diuresis**
- **Inhibition of COX-2 by selective COX-2 inhibitors, such as celecoxib and rofecoxib causes renal dysfunction**
- **particularly in patients who are volume-depleted or haemodynamically unstable**

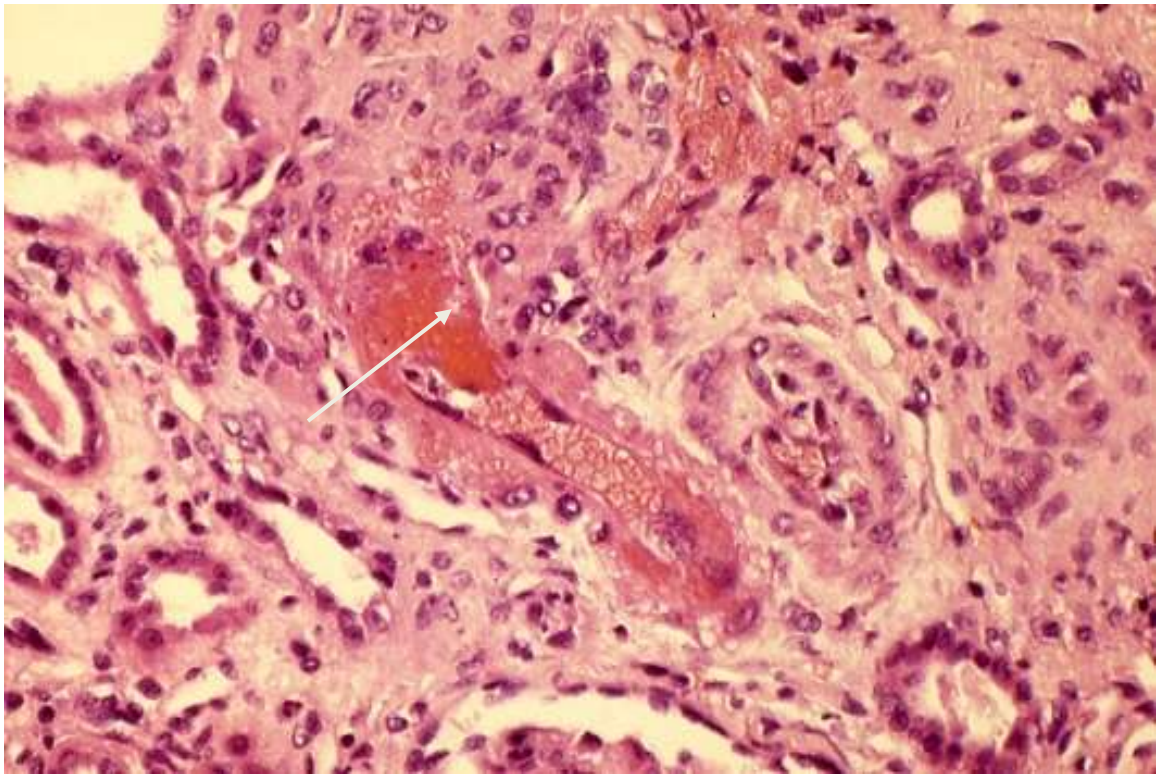
INTRARENAL FAILURE


1 Pre-renale
(emodinamica)
Vascolop 3
stenosi
2
4
GLN acuta
5
6
NTA
10
Trombosi
V.renale
8
Ostruz.
Intratub.
9
Ostruz.
Extraren.
Interstiz.
acuta
7

VASCULAR INJURY

- Vascular effect:thombotic microangiopathy, Cyclosporin, tacrolimus, mitomycin C, conjugate estrogens,quinine-6- fluorouracil, ticlopidine, clopidogrel, interferon, valaciclovir, gemcitabine, bleomycin
- Clinical finding: fever, microangiopathy,hemolytic anemia, thrombocytopenia
- Treatment: d/c medication, supportive care,plasmapheresis if indicate

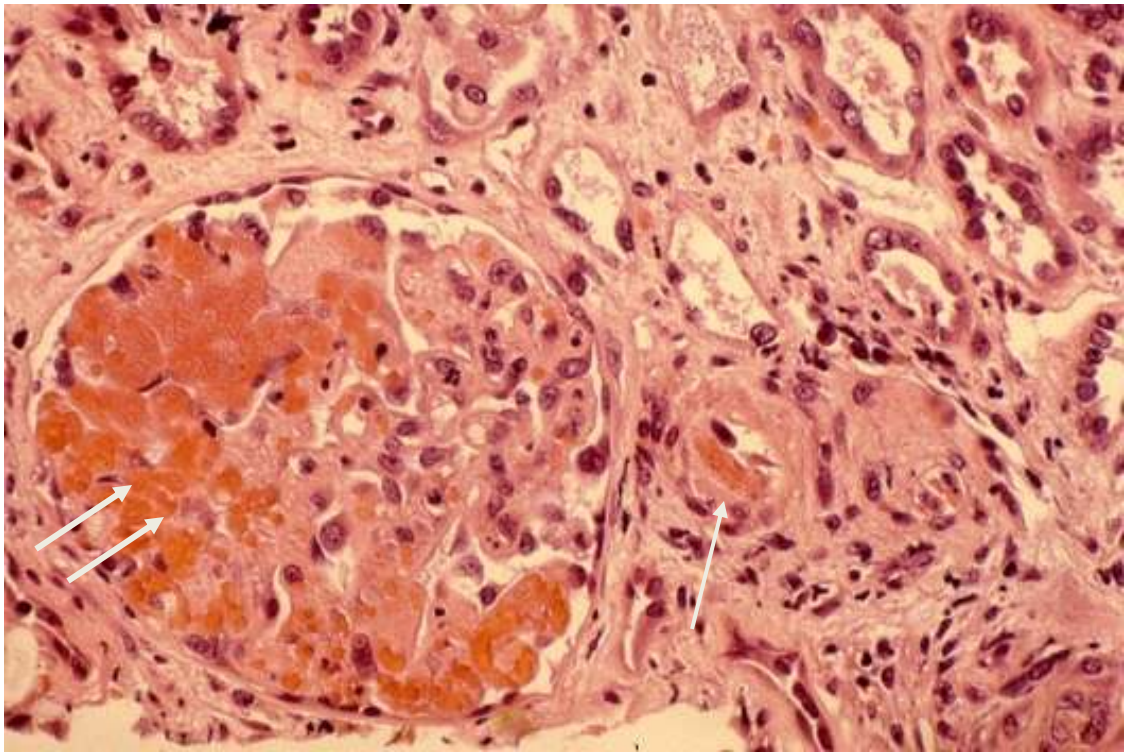
Sindrome Emolitico-Uremica



Necrosi e trombosi di una arteriola (freccia)

Ematossilina -eosina 250x

Sindrome Emolitico-Uremica



Trombosi intraarteriolare (freccia); necrosi glomerulare

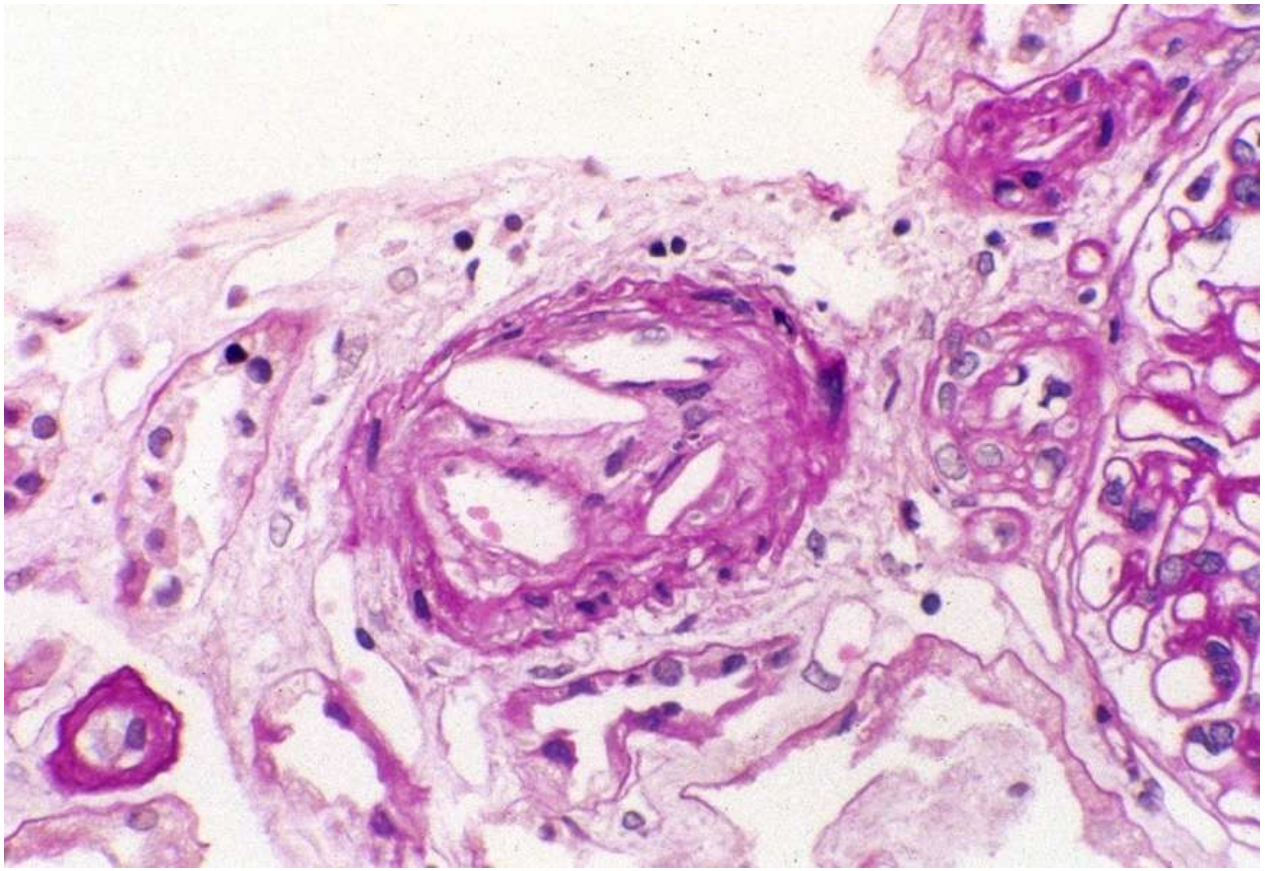
estesa (doppia freccia). *Ematossilina-eosina 250x*

Intrinsic renal injury

Vascular effect: cholesterol emboli

- **Heparin, warfarin, streptokinase**
- **Clinical finding: fever, microangiopathic,hemolytic anemia, thrombocytopenia,**
- **Treatment: d/c medication, supportive care,plasmapheresis if indicate**

Malattia Ateroembolica Renale



GLOMERULAR INJURY

- **Glomerular histology and permeability alteration often cause nephrotic range protienuria.**
- **Toxic lymphokines of interstitial inflammation might be implicated.Humeral factor might also be involve→ eosinophils & lymphocyte present in the interstitial infiltrate.**
- **Red cell and white cells might be observed in the urine,even though hypersensitivity is not clinically event.**

DANNO GLOMERULARE DA FARMACI

Manifestazione renale:

insufficienza renale a rapida progressione,
sindrome nefritica (micro/macro ematuria, cilindruria, proteinuria moderata)

Microangiopatia trombotica:

Ticlopidina 1:1550-5000 casi
Clopidogrel 1:300000 casi
più rari: Mitomicina, Gemcitabina, inibitori VEGF

Vasculiti ANCA positive: Propiltiouracile (rara)

Glomerular injury

- nal biopsy→ Glomerular

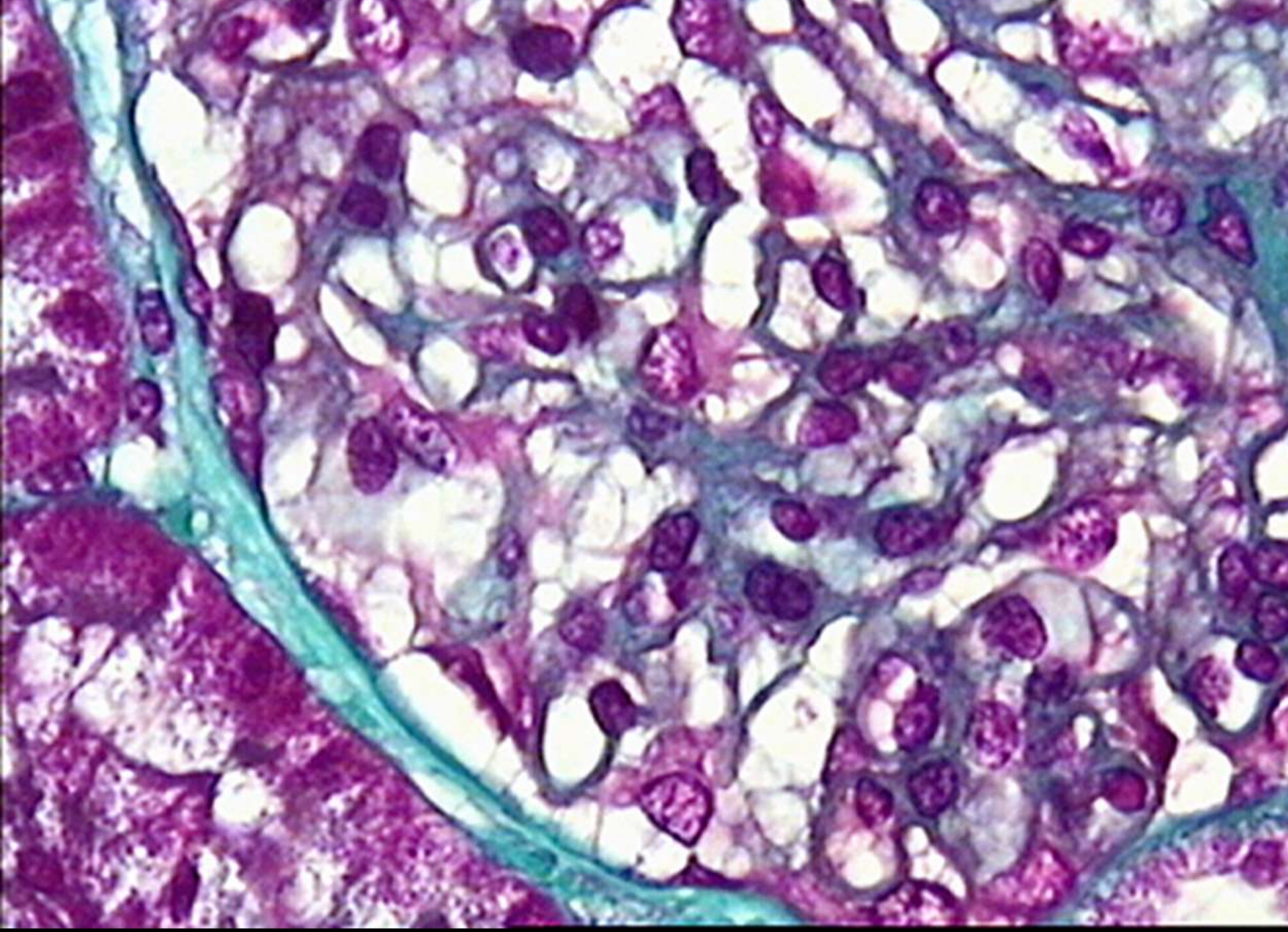
- NSAIDs(mefenamic, fenbufen): minimal change
- Gold,D-penicillamine,ACEI,foscarnet: membranous lesion
- Interferon alfa:severe glomerular lesion

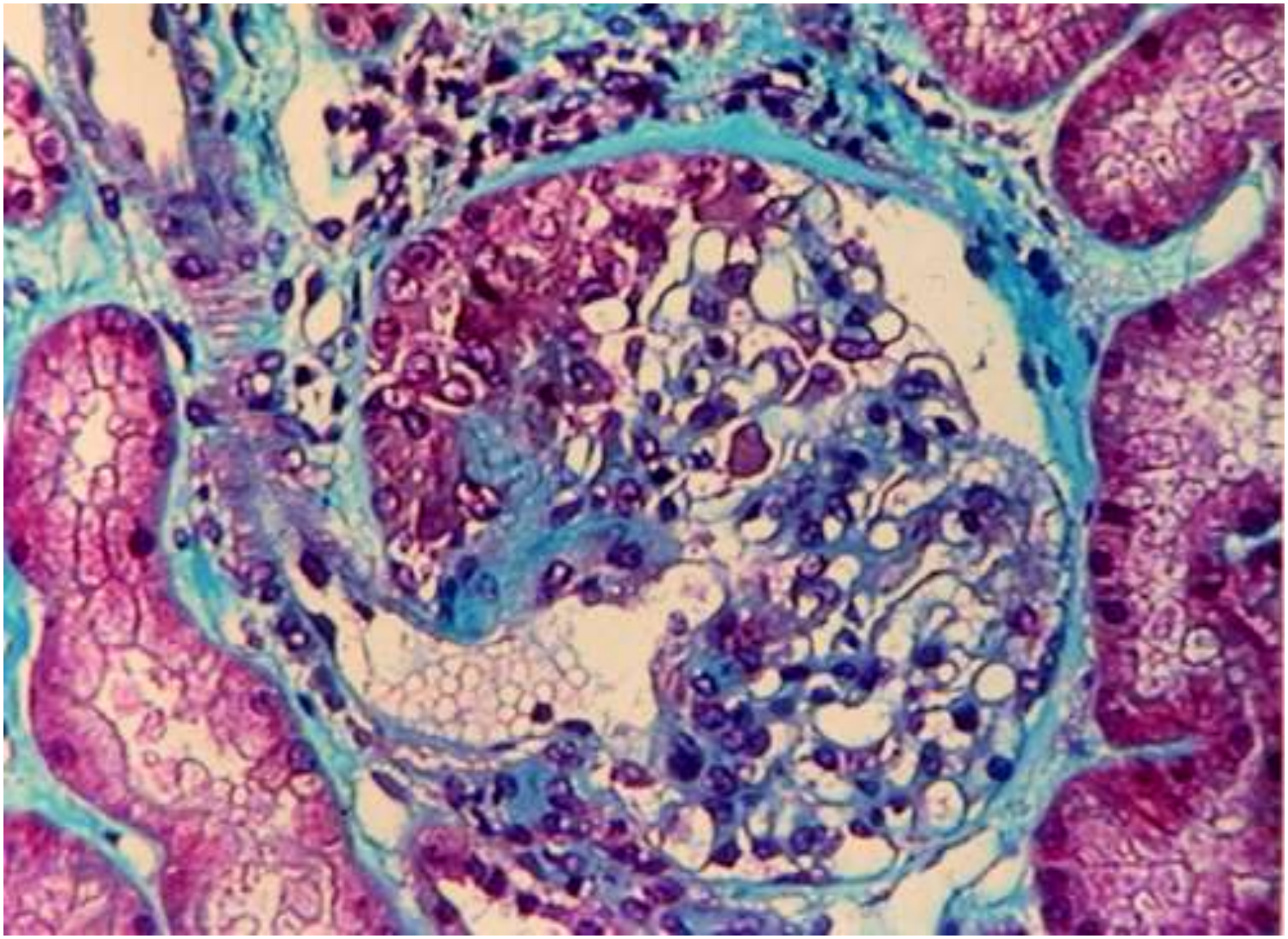
Nephrotic syndrome

- Abnormal amounts of protein in the urine
- Drugs : NSAIDs, penicillamine and gold
- damage the glomerulus and alter the ability of the glomerulus to prevent protein from being filtered
- Stopping the drug may resolve the damage to the glomerulus

GLOMERULOPATIE DA FARMACI MANIFESTANTISI CON SINDROME NEFROSICA

- GLOMERULONEFRITE MEMBRANOSA:	D-Penicillamina Sali d'oro
-LESIONI MINIME:	**FANS** Litio Interferone
-GLOMERULOSCLEROSI FOCALE:	Pamidronato Sirolimus Steroidi anabolizzanti





INTERSTITIAL INJURY

Mech.

•Drug-renal tubular Ag.→ induce immuneRx(mediated= T cell)→deposition interstitium →tublitis

•Some drug induce deposition of antitubular basement membrane Ab.

•Numerous drugs →Acute interstititial

Clinical finding

•1/3 pt.→ hypersens classic symtomp (fever, rash, arthralgia, eosinophilia, urine sediment show pyuria, white cell cast, hematouria, mild-moderate proteinuria

•Renal failure occurs in early stages

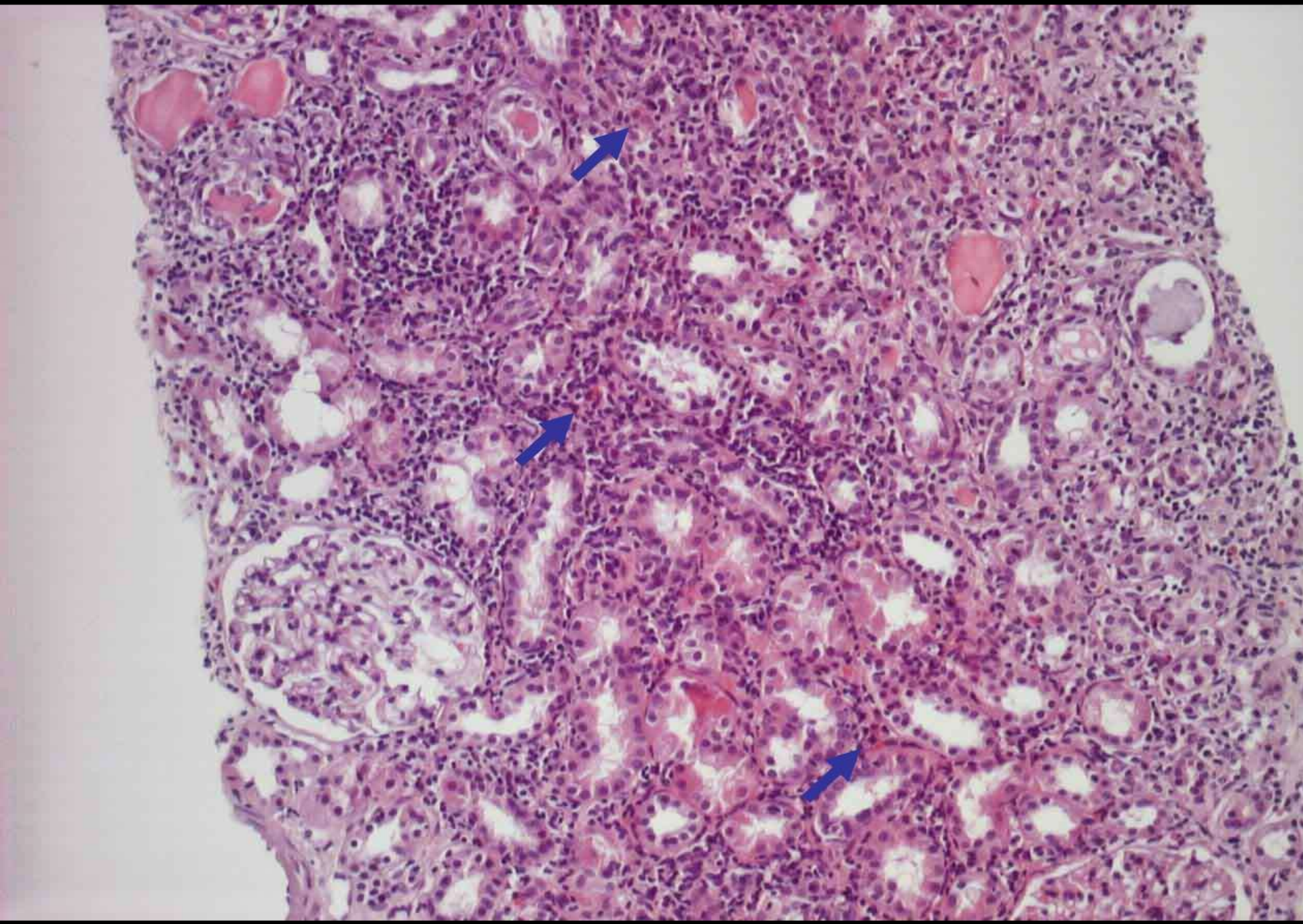
Treatment

•d/c drug → supportive care

•Steriod 0.5-1 mg/kg/d →no of day of renal failure lower than no treat (in some study)

•careful evaluation of renal fn for initiation new medication

•sulfonamide, thiazide, cimetidine, phenytoin allopurinol, cephalosporins, cytosine, arabinoside, furosemide, interferon, NSAIDs, ciprofloxacin, ranitidine, clarithromycin,



NEFROPATIA DA MEZZO DI CONTRASTO IODATO

Incremento della creatininemia del 25 %
entro 72 ore dalla somministrazione di mezzo di contrasto.

Prevalentemente se MdC è iniettato in **arterie** (arteriografie, coronarografia)

SOLO in pazienti a rischio:

- non diabetici con VFG <45 mL/min
- diabetici, proteinurici con VFG< 60 mL/min
- gammopatia monoclonale e VFG <60 mL/min

INCIDENZA MINORE CON SOMMINISTRAZIONE ENDOVENA (10 % vs. 25 % nei pazienti a rischio)

Prevenzione: adeguata idratazione prima e dopo l'esame

Prevenzione del danno da MDC

Fisiologica

N-Acetil Cisteina

Tepel M. N Engl J Med 2000

Safisteir R. N Engl J Med 2000 (editoriale)

Sodio Bicarbonato

Merten G.S. JAMA 2004

The Reno-Protective Effect of Hydration With Sodium Bicarbonate Plus N-Acetylcysteine in Patients Undergoing Emergency Percutaneous Coronary Intervention

o Recio-Mayoral, MD, Marinela Chaparro, MD, Belen Prado, MD, Rocio Cozar, MD, Irene I
ebasish Banerjee, MD, MRCP, Juan C. Kaski, MD, DM, DSC, Jose Cubero, MD, Jose M. Cr

J Am Coll Cardiol 2007;49:1283-8

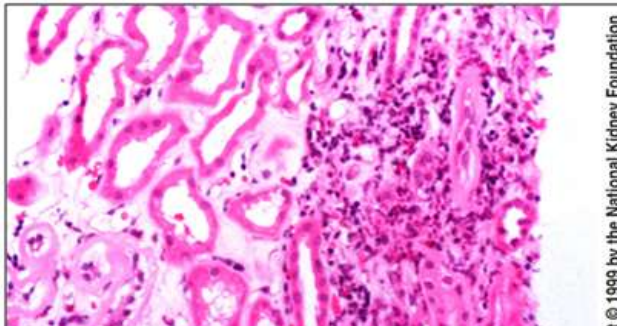
NEFRITE TUBULO-INTERSTIZIALE ACUTA DA MECCANISMO IMMUNOALLERGICO

ANTIBIOTICI:	BETA LATTAMICI, penicilline, rifampicina, cotrimoxazolo, chinolonici, sulfamidici, vancomicina, macrolidi, tetraciclina, aminoglicoisidici, etambutolo, isoniazide.
FANS:	**CoX-1 e COX-2 inibitori**
ANTICONVULSIVANTI:	dintoina, barbiturici, valproato, carbamazepina
DIURETICI:	tiazidici , furosemide, triamterene
ANTIVIRALI:	tenofovir, acyclovir
ALTRI:	allopurinolo cimetidina, inibitori della pompa protonica, interferone alfa

NEFRITE ACUTA TUBULO-INTERSTIZIALE ACUTA DA MECCANISMO IMMUNOALLERGICO

Dose-indipendente (basta una sola dose)

Spesso presenti manifestazioni extrarenali: orticaria
febbre
artralgie
edemi



Laboratorio: ematuria (micro/macro)
proteinuria moderata,
oliguria (incostante)
eosinofiluria
insufficienza renale acuta

Biopsia renale: Infiltrati infiammatori (linfo-monociti, granulociti) nell'interstizio
Necrosi ed atrofia tubulare

ANTIBIOTICS AND ACUTE INTERSTITIAL NEPHRITIS

- AIN is a hypersensitivity or allergic reaction to the drug
- Up to 71% of all cases of acute interstitial nephritis (AIN) are drug-induced
- The most common antibiotic classes associated with AIN are penicillins/cephalosporins and sulfonamides
- Ciprofloxacin
- Rifampin
- acute renal failure, skin rash, increased eosinophils

NEFROPATIA TUBULO-INTERSTIZIALE CRONICA DA FARMACI

Analgesici: fenacetina e associazioni con codeina, caffeina, acetaminofene, aspirina

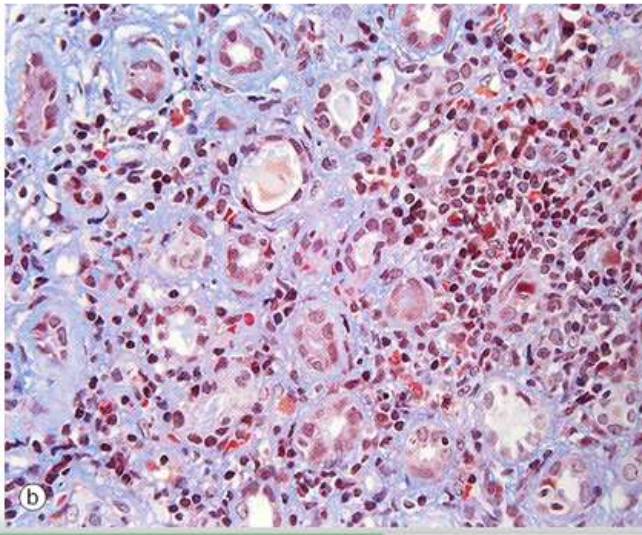
FANS

Litio

Immunosoppressori: ciclosporina e tacrolimus

Manifestazione renale:

Insufficienza renale cronica



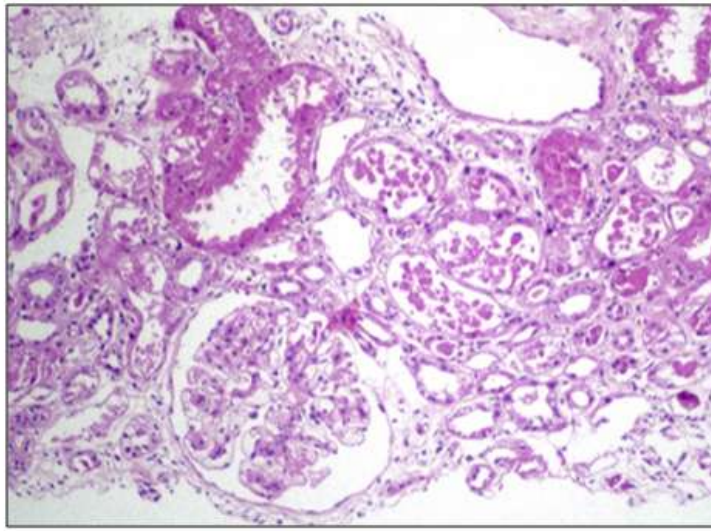
TUBULAR INJURY

- **Damage can be toxic / ischemic / inflammatory / obstructive.**
- **Urine sediment abnormalities range from no cell trough numerous red cells. White cells, and/or brown granular casts,to proteinuria and crystaluria, depending on site and mechanism of injury**

DANNO TUBULARE DIRETTO
NECROSI TUBULARE ACUTA DOSE DIPENDENTE

FANS

Mezzo di contrasto iodato



Antibiotici/antimicotici

aminoglicosidici, vancomicina, amfotericina B

Antivirali

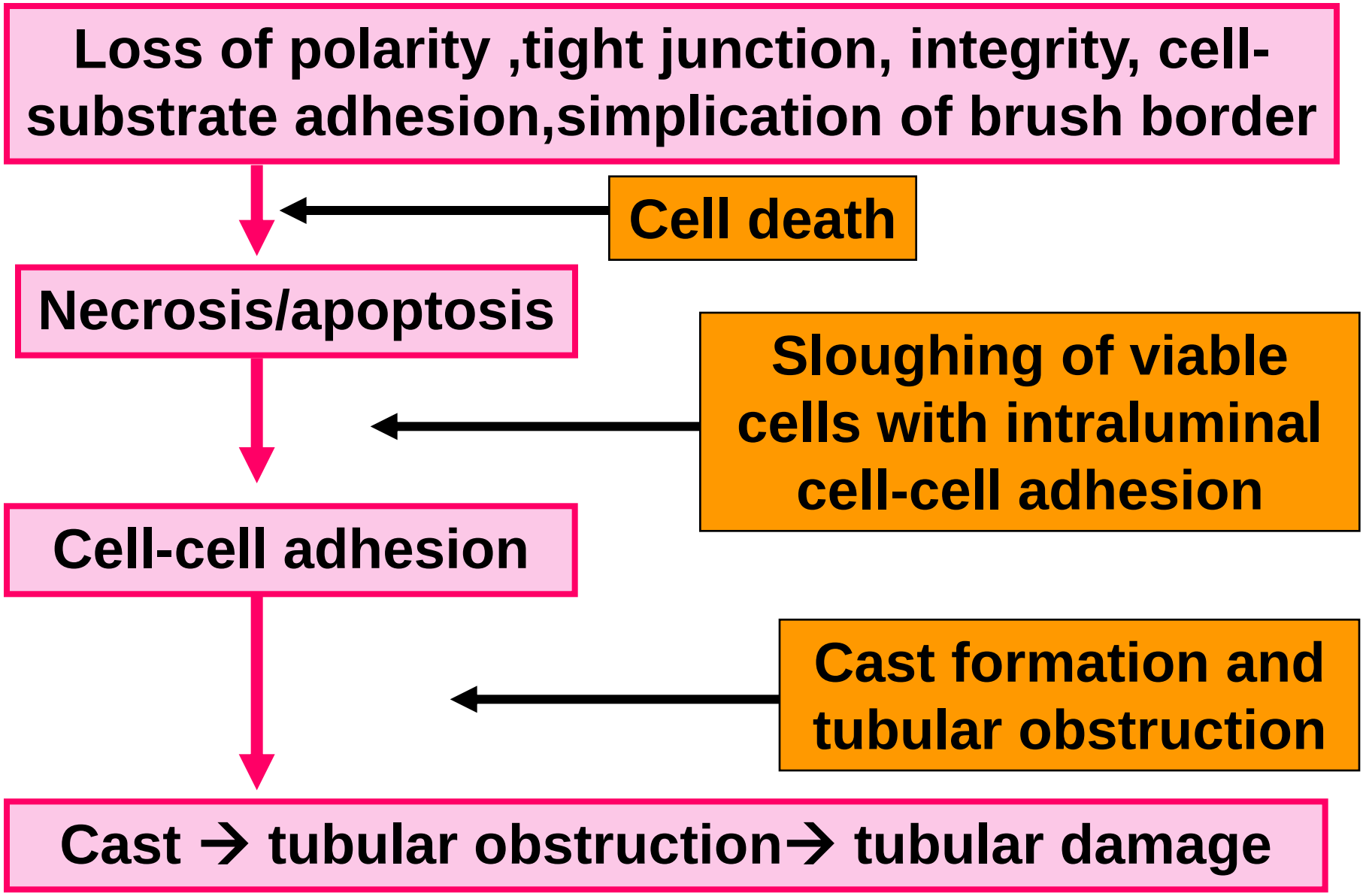
Antineoplastici

cisplatino, metotrexate, ciclofosfamide, ifosfamide, nitrosouree (CCNU, BCNU), lenalidomide

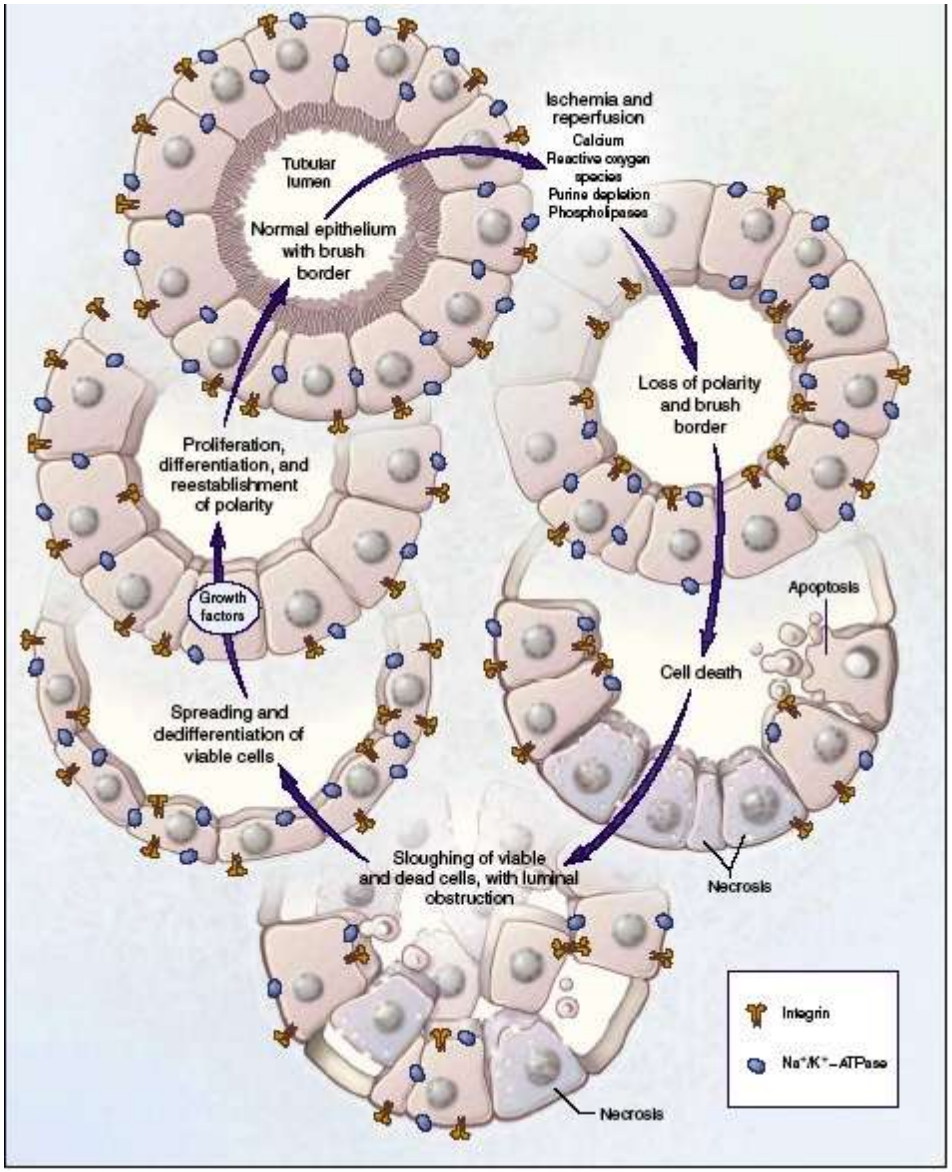
Bifosfonati: zolendronato

Sintomatologia renale: **Insufficienza renale acuta con o senza oliguria**

Tubular Damage



Necrosi Tubulare Acuta



Thadhani, Pascual, Bonventre, NEJM 1996

Tubular injury

- **Tubular toxicity**: **aminoglycosides, radio contrast media, cisplatin, neaplatin, methoxtfluran, outdated tetracycline, amphotericinB, cephaloridine, streptozocin, tacrolimus, carbamazepine, mithramycin, quinolone,foscarnet, pentamidine, IV gammaglobulin, fosfamide, zoledronate, cidofovir, adefovir, tenofovir, mannitol, dextran,hydroxyethylstarch**
- **Clinical finding: FeNa>2%,UOsm<350:urine sediment with casts, tubular epithilium cell**

Tubulointerstitial nephritis: papillary necrosis

Analgesic nephropathy

- **Papillotoxin: paracetamol, phenacetin, ASA**
- **Hemodynamic factor: NSAIDs**

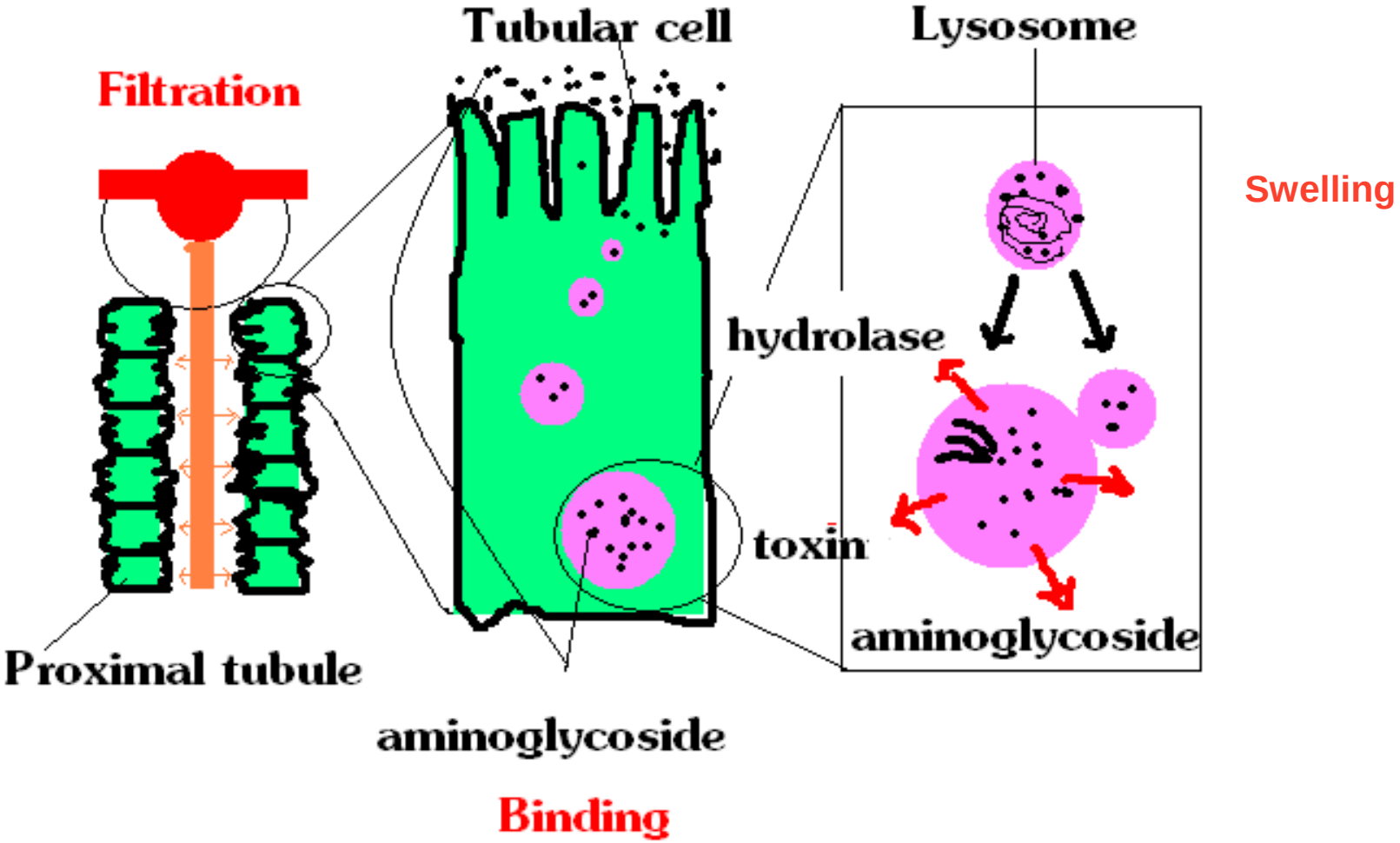
High-dose Dapsone

Aminoglycoside

- **Prototype of drug-induce Acute tubular necrosis (ATN)**
- **Usually reversible:gradual rise in Scr(5-7 d), renal Mg++&K+ wasting, non-oligouria***
- **Pertubation of glomerular filtration is late manifestation of aminoglycoside nephrotoxicity.**
- **The number of cationic amino moieties seems to correlate with the degree of nephrotoxicity:**

Neomycin>Genta>Tobra>Amikacin>Netil>Streptomycin

Aminoglycoside



Risk factor for Aminoglycoside Nephrotoxicity

Related to AMG dosing

- Large total cummulative dose
- Prolong therapy
- High peak or trough conc.
- Recet previous AMG therapy

Related to synergistic nephrotoxicity

AMG combination with

- Cyclosporin
- Amphotericin B
- Vancomycin
- Diuretics

Related to Predisposing condition in the patient

- Preexisting renal insufficiency
- Increased age
- Poor nutrition
- Shock
- Gramnegative bactermia
- Liver disease
- Hypoalbuminemis
- Obstructive jaundice
- K+ or Mg++ deficiency

Irreversible Damage!

Aminoglycoside Nephrotoxicity

Prevention

- Switching to alternative antibiotics
- Avoid volume depletion, concomitant therapy with other nephrotoxic drugs
- Limit total dose
- Decreasing the frequency of AMG dosing to at least daily (as direct by renal clearance)

Management

- Monitor Scr, concentration, renal fn and electrolytes
- Discontinue AMG if changes are seen.

Amphotericin B

Mech.

•tubular cell

•Afferent arterio constriction tubuloglomerular feedback

•Deoxycholate(solvent) tubular cell

•Renal vasoconstriction effect amphotericin B

•Dose-dependent acute renal vasoconstriction

•Cumulative dose>2-3 g:direct distal tubular injury

•ATN at higher dose

Clinical presentation

•Non-oligouria,distal RTA,impaired renal activity to concentrate urine,K+/Na+/Mg++wasting,increase BUN,Scr

•Tubular fn & filtration may improve but damage may be irreversible

Risk

•Baseline renal dysfunction

•Higher average daily dose

•Diuretic use with depletion

•Rapid infusion

•Concomitant use with nephrotoxins

Prevention

•Limiting cumulative dose

•Avoid concomitant nephrotoxiin

•Avoid volume depletion,hypoK

•Provide hydration,Na+ load (full Na+ diset if no C/I, 1L NSS daily)

-Ca blocker, mannitol

Management

•Switch to another drug
•Avoid systemic administration
•K/Mg replacement

- **Toxic tubular necrosis (Derange Na/K-ATPase loss of brush border and apoptosis): Bisphosphonate zoledronate 4 mg IV over 15 min (high dose)**
- **Osmotic nephrosis (cellular uptake nonmetabolizable compounds such as sucrose→swelling→tubular cell injury) : IV Ig, mannitol, dextran, hydroxyethyl starch**
- **Ischemic tubular injury (acute vasoconstriction) : immunosupressives, radiocontrast agents, amphotericin B**

Fanconi-type abnormality of reabsorption

- Saliuresis,kaliuresis, decrease ammonium excretion and glucosuria,proteinuria,bicarbonaturia and phosphaturia
- Cidofovir,adefovir 
- Human organic anion transporter(hOAT)
- Proximal tubule
- Probenecid blocks hOAT→minimizing intracellular accumulation of drugs(+salicylate, urate,methotrexte nucleoside analogs)
- Prophylaxis with probenecid can be considered in pt. recieveing cidofovir and adefovir whose baseline Scr> 1.5 mg/dl.
- nephrotoxic agent cidofovir

Osmotic nephrosis

- high doses of mannitol, immunoglobulins, dextrans and starches are nephrotoxic
- Direct effect on glomerular filtration
- or the uptake of these large molecules by pinocytosis into the proximal tubule
- sucrose-based IVIG: The renal failure began from 1 to 10 days after therapy

POST RENAL CAUSES

- **usually results from a mechanical barrier to moving urine from the collecting tubules into the bladder**
- **Mechanical obstruction :**
  - **enlargement of the prostate**
  - **kidney stones**
  - **Drugs that precipitate in the kidney (acyclovir, ganciclovir)**
  - **Co-trimoxazole**

Post-renal failure

- usually results from a mechanical barrier to moving urine from the collecting tubules into the bladder
- Mechanical obstruction :
  - enlargement of the prostate
  - kidney stones
  - Drugs that precipitate in the kidney (acyclovir, ganciclovir)
  - Co-trimoxazole

Obstructive nephropathy

Extrinsic renal blockage:

1.Ureteral obstruction

- **2nd to retropertoneal fibrosis**
- **Methylsergide, ergotamine, dihydroergotamine, methyldopa, pindolol, hydralazine, atenolol**
- **Clinical finding: benign urine sediment, hydronephrosis on ultrasound.**
- **Treatment: d/c drug, decompress uretal obstruction**

2.Bladder dysfunction

- **Tricyclic antidepressants, disopyramide→Anticholinergic effect**
- **Cyclophosphamide, isophosphamide→Bladder fibrosis**

  →Hemorrhagic cystitis

Obstructive nephropathy

Chemotherapy Obstructive

- Tumor-lysis syndrome (hematologic malignancy-Acute oliguria/anuria

  -Acute uric nephropathy chemotherapy

- hydration,alkalinization,allopurinol (600-800 mg/day *3-4 day)

Nephrolithiasis

Formation of kidney stone

- **Triamterene**
- **Sulfadiazine→toxoplasma gondii >>> hydration, alkalinization**
- **Indinavir → Crystaluria, nephrolithiasis >>> maintain urine vol→increase daily fluid intake to at least 1.5 L during indinavir therapy**
- **Mg trisilicate-Al(OH)3 → Mg-Ammonium phosphate stone**

  → Ca phosphate precipitation
- **Laxative abuse → Unusual formation of ammonium urate stone**
- **Allopurinol**

Nefrotossicità da farmaci con diversi meccanismi

Lithium

- Nephrogenic diabetic insipidus Nephrogenic diabetic insipidus: most common
- Interstitial fibrosis
- Decrease urinary concentration, increased Na excretion and polyuria

Risk

- Elevated lithium level,particularly in association with dehydration
- Concomitant with neuroleptic agent and ACEI
- Cumulative damage →chronic nephrotoxicity

Prevention & management

- Maintaining Li level
- Avoid dehydration
- Monitoring renal fn.→d/c drug if Scr drop
- polyuria,polydipsia amiloride NSAIDs

Rhabdomyolysis

- Lovastatin ,ethanol, cocaine or heroine abuse, codeine, barbiturate, diazepam
- Clinical finding: elevate CPK,ATN urine sediment
- Treatment: d/c drug + supportive care

Severe hemolysis

- Quinine, quinidine, sulfonamides, hydralazine, triamterene, nitrofurantoin, mephenytoin
- Clinical finding: high LDH, decrease hemoglobin
- Treatment: d/c drug + supportive care

STATINS

- Rare but serious cases of rhabdomyolysis
- acute tubular necrosis
- Muscle pain, dark urine, electrolyte abnormalities and renal failure
- Recognizing the process as drug-induced renal failure and stopping the drug is essential

Chronic Interstitial fibrosis

- **Lithium,5-aminosalicylic acid, mesalazine, ifosfamide**
- **Cidofovir, acyclovir, indinavir**
- **Cyclosporin, tacrolimus**
- **Usually progressive, irreversible with interstitail fibrosis, no systemic symptoms**

Analgesic nephropathy

Analgesic use is most common cause of papillary necrosis

Mech.

- **Drug = high reactive metabolite +glutathione → tissue damge**
- **High levels at the papillary tip**
- **Inhibit of vasodilation PGs by NSAIDs →medullary ischemia**
- **PGs oxidise reactive metabolite medulla**

Diagnosis criteria most sensitive & specific

- **Hx chronic daily anagesic ingestion**
- **IV pyelography, renal ultrasound/CT → decreased renal mass and bumpy renal contours**
- **Papillary calcification pyelonephritis: small kidney with thin renal cortices and blunted calyces)**

Analgesic nephropathy

Analgesic syndrome

- HT& atherosclerosis CVD
- GI cp\omplication
- Hematologic complication: anemia, agranulocytopenia
- Skeletal complication
- Psychosomatic aspect

Urogenital transitional carcinomas& renal cell cancers

Prevention

- Limit dose
- Avoid 2 or more analgesic combination
- Maintain good hydration

→ renal ischemic & papillary conc.

- Use paracetamol in renal insufficiency pt.

Hypokalemia/ hypomagnesemia (increase urinary excretion)

Gentamycin, cisplatin, diuretics, carboplatin, nedaplatin

Clinical finding:

Increase urine excretion of K+ & Mg++ despite low serum levels

Treatment

Discontinue drug, replace K+ and Mg++

ANTIVIRALS

- **Cidofovir, foscarnet, acyclovir and interferons can cause ATN**
- **Acyclovir can precipitate within the renal tubules**

Hyponatremia
increase ADH secretion and sensitivity

Thiazide, chlopropramide, vincristine,

IV cyclophosphamide, cytoxan, clofibrate, narcotics, haloperidal, thioridazine, amitriptyline, fluphenazine, NSAIDs, acetaminophen

Clinical finding:

urine osmolality is less than maximally diluted in presence of low serum Na

Treatment

Discontinue drug, consider fluid

Hyperkalemia

(antialdersterone or antiadrenergic effect: blocking Na channel)

ACEIs,

Beta-blockers,

heparin,

NSAIDs,

K+sparing diuretics,

trimethoprim,

cyclosporin,

pentamidine

Clinical finding

Decreased urine K+ excretion with high serum K+

Treatment

Discontinue drug, treat hyperkalemia,low K+ diet

Renal tubular acidosis from renal tubular injury
(decreased acid excreation:inability to reabsorb bicarbonate)

- Amphotericin B, toluene, Li, cyclamate, analgesics, vitamin D intoxication, foscarnet,
- Carbonic anhydrase inhibitor, outdated tetracycline, mafenide acetate, 6-mercaptopurine, sulfanilamide, cidofovir, tenofovir,

Clinical finding

Hyperchloremic metabolic acidosis with or hypokalemia

Treatment

Discontinue drug, supportive treatment, HCO_3 replacement if indicated

Renal tubular acidosis

(decreased aldosterone levels and response)

Cyclosporin, tacrolimus

Clinical finding

Hyperkalemia, hyperchloremic metabolic acidosis

Treatment

Treat hyper K+, consider HCO3 therapy, low K+ diet, avoid concurrent medications associated with hyper K+

Metabolic alkalosis

(increase K+ and H+ secretion in distal nephron)

Loop and thiazide diuretics

Clinical finding

Alkalemia, hypo K+, hypo Cl-

Treatment

Discontinue drug,

volume replace if neccessary

Nephrogenic diabetes insipidus
(decreased ADH response in collecting tubule)

Li,demeclocycline, cyclophosphamide, ifosphamide, vincristine, cidofovir, tenofovir, didanosine, foscarnet

Clinical finding

Polyuria

Unresponsive to ADH

Treatment

Discontinue drug, supportive therapy

CHEMOTHERAPY-INDUCED RENAL DAMAGE

- **Nephrotoxicity is the major dose-limiting toxicity for cisplatin**
- **Both acute and late-onset toxicities occur**
- **aggressive replacement of magnesium (lost when the proximal tubule is damaged), saline hydration or mannitol infusion**
- **High dose methotrexate : postrenal obstruction by precipitating in the tubules of the nephron also direct toxicity**

IMMUNOSUPPRESSANT

- **Cyclosporine and tacrolimus**
- **acute, dose-dependent reduction in renal blood flow and chronic structural changes in the kidney**

DRUGS OF ABUSE

- **cocaine and heroin**
- **Cocaine use can cause renal artery thrombosis (clotting), severe hypertension and interstitial nephritis**
- **Long-term cocaine use can lead to chronic renal failure**
- **Long-term tobacco use also increases the risk of kidney cancer**

Development of Focal Segmental Glomerulosclerosis after Anabolic Steroid Abuse

Leal C. Herlitz,* Glen S. Markowitz,* Alton B. Farris,† Joshua A. Schwimmer,‡§ Michael B. Stokes,* Cheryl Kunis,‡ Robert B. Colvin,† and Vivette D. D'Agati*

Figure 1. Shown is patient 1, the index case (published with patient's permission).

SINDROMI RENALI INDOTTE DA PREPARATI FITOTERAPICI

Hypertension	• *Glycyrrhiza* species (Chinese herbal teas, gancao, Boui-ougi-tou)[20-27] • *Ephedra species* (ma huang)[30,31,33]
Acute tubular necrosis	• Traditional African medicine: toxic plants (*Securida longe pedunculata, Euphoria matabelensis, Callilepsis laureola, Cape aloes*)[6-16,110] or adulteratio by dichromate[45] • Chinese medicine: *Taxus celebica*[18] • Marocco: *Takaout roumia* (paraphenylenediamine)[48-53]
Acute interstitial nephritis	• Peruvian medicine (*Uno degatta*)[43] • Tung Shueh pills (adulterated by mefenamic acid)[46]
Fanconi's syndrome	• Chinese herbs containing AAs (*Akebia species, Boui, Mokutsu*)[63,66,69-72] • Chinese herbs adulterated by cadmium[44]
Papillary necrosis	• Chinese herbs adulterated by phenylbutazone[47]
Chronic interstitial renal fibrosis	• Chinese herbs or Kampo containing AAs (*Aristolochia species, Akebia species,* Mu-tong, Boui, Mokutsu)[54-65,67,68]
Urinary retention	• *Datura* species, *Rhododendron molle* (atropine, scopolamine)[35]
Kidney stones	• *Ma huang* (ephedrine)[32] • Cranberry juice (oxalate)[42]
Urinary tract carcinoma	• Chinese herbs containing AAs[77-87]

Isnard Bagnis C, et al. AJKD, 2004;44:1-11

Aristolochic acid nephropathy: A worldwide problem

ReNe
Rete Nefrologica Lombarda

Acido aristolocico contenuto nella ARISTOLOCHIA (cinese Han Fan J
confusa con la Stephania (cinese: Guang Fang ji) contenuta in prepara
dimagranti

128 casi in Belgio

In CINA ???

Provoca fibrosi interstiziale → dialisi

Segnalate anche neoplasie uroteliali

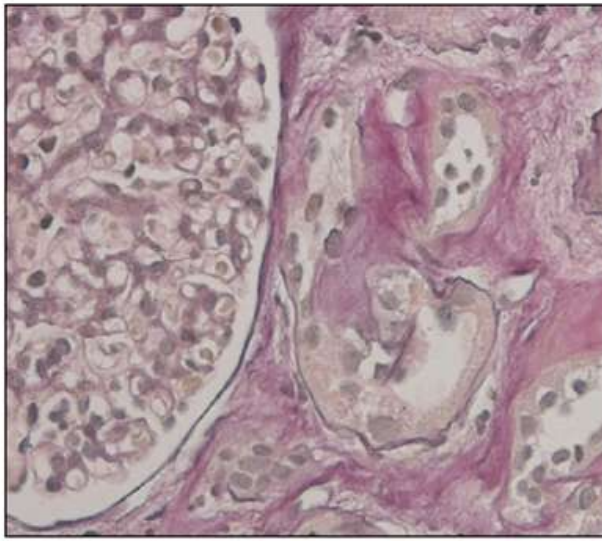


***Figure*: Renal biopsy**
Interstitial fibrosis (pink) with no inflammatory-cell infiltrate. Elastic van
x400.

Debelle FD, et al. Kidney International 2008;74:158-169

RegioneLombar

Principles for pharmacotherapy

- Knows the potential nephrotoxicity of Dx and therapeutic pharmacologic agents.
- Compare the potential risks and expected benefits for each course of treatment.
- Consider alternative diagnostic and therapeutic approaches.
- Use the lowest dose and shortest course of therapy that is efficacious.
- Monitor appropriately for potential toxicity.
- Monitor therapy if toxicity is occurs.

La Nefroprotezione da farmaci

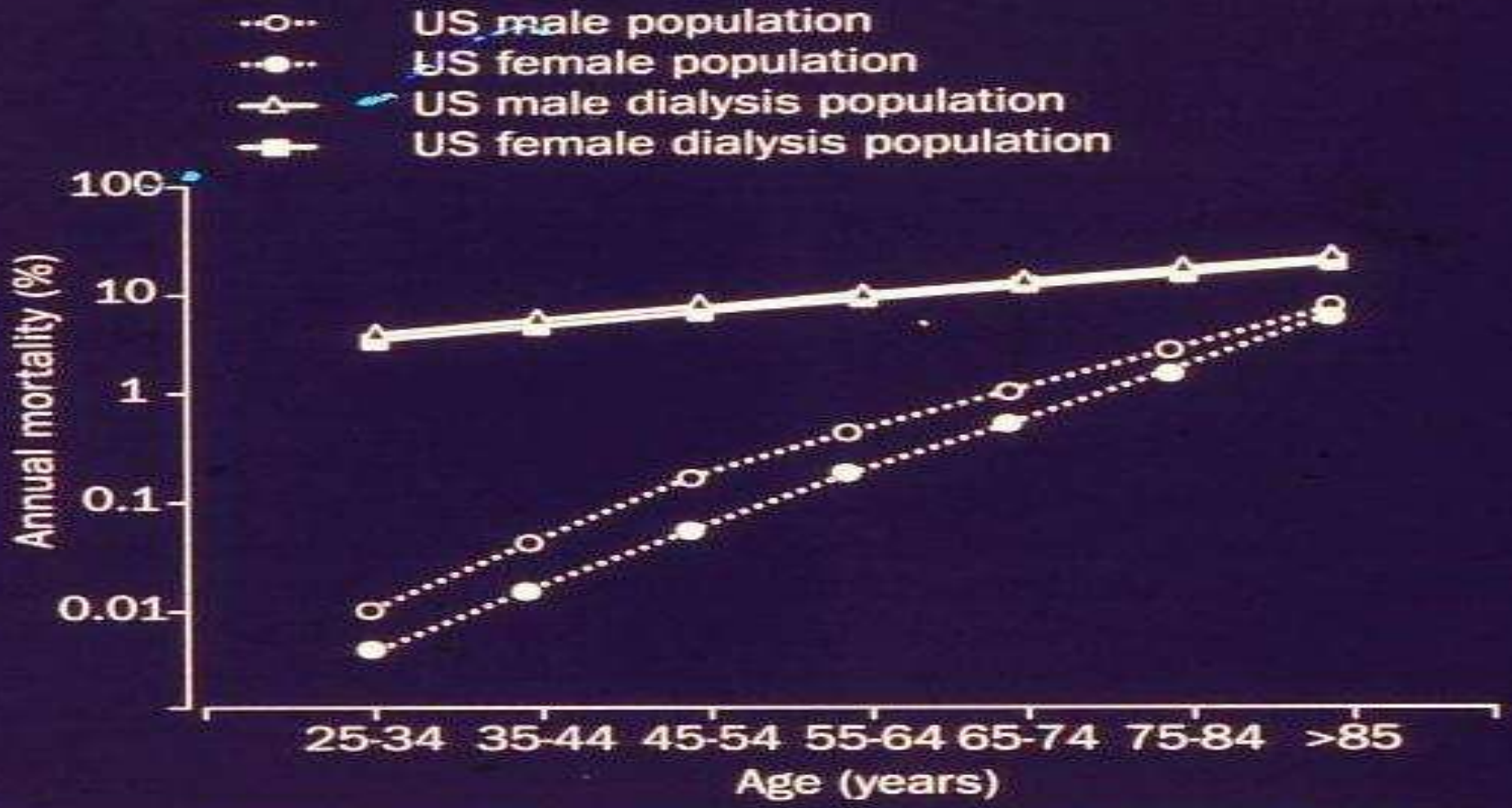
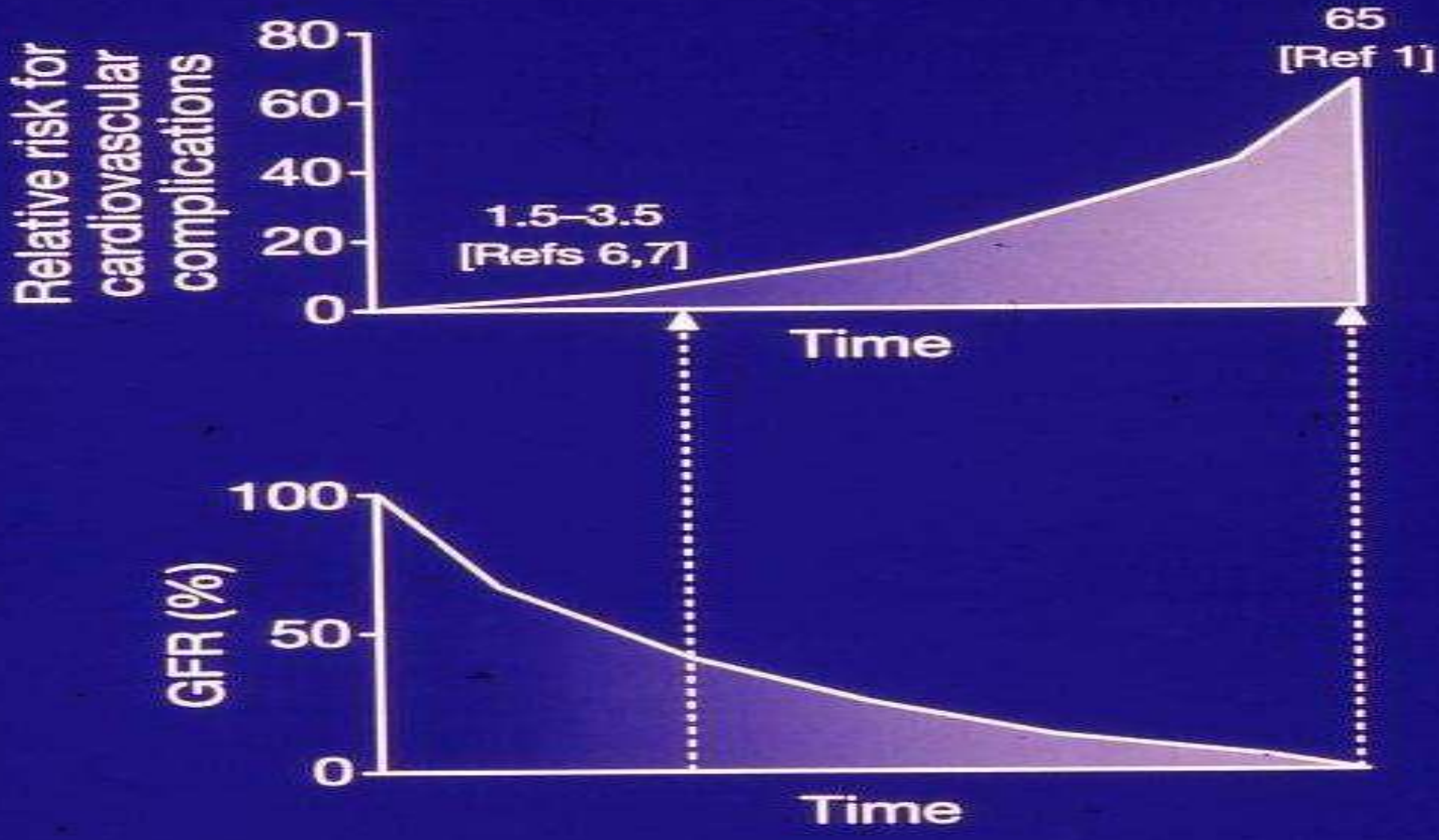
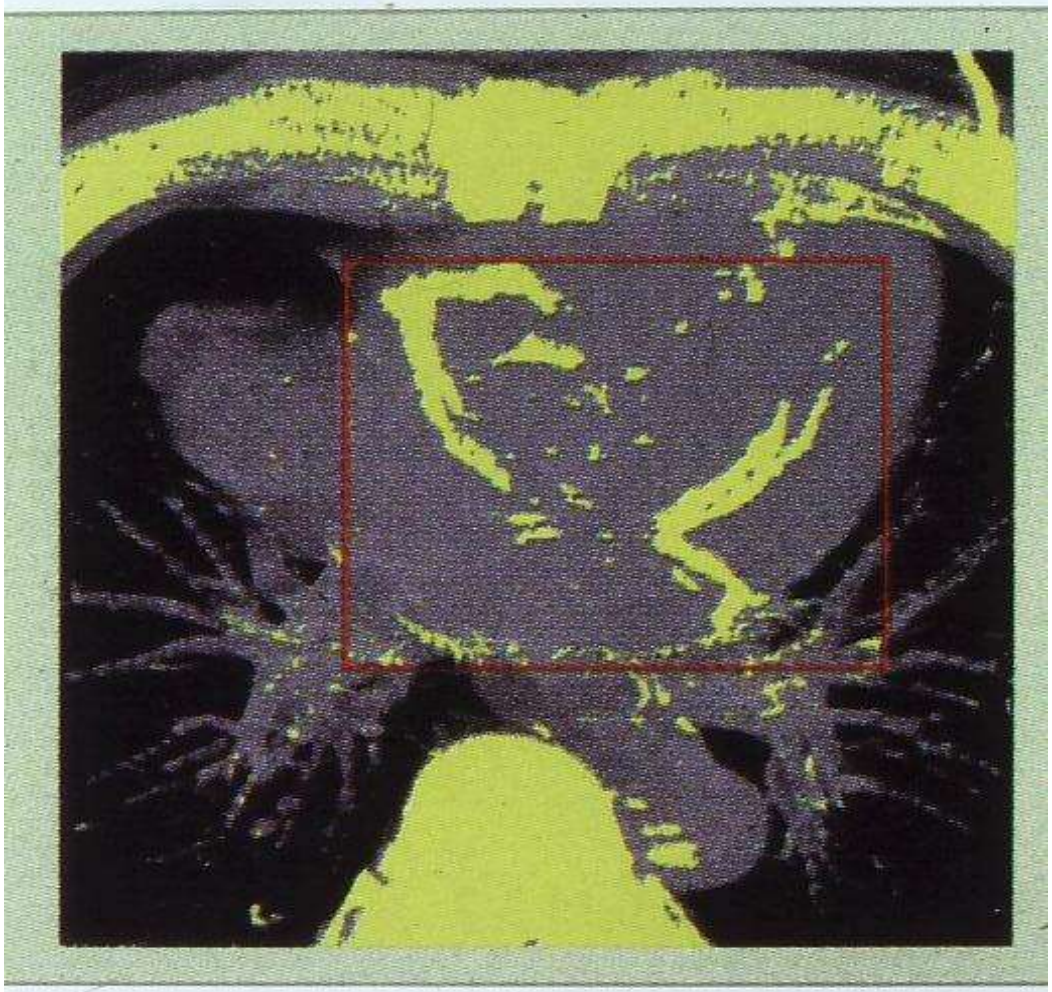


Figure 1: **Cardiovascular mortality (death due to arrhythmias, cardiomyopathy, cardiac arrest, myocardial infarction, atherosclerotic heart disease, and pulmonary oedema) in dialysis patients**

From reference 3, with permission.



The inverse relationship between renal function and cardiovascular risk. The figures illustrate a hypothetical increase in relative risk in patients with progressive nephropathies as compared with the general population.



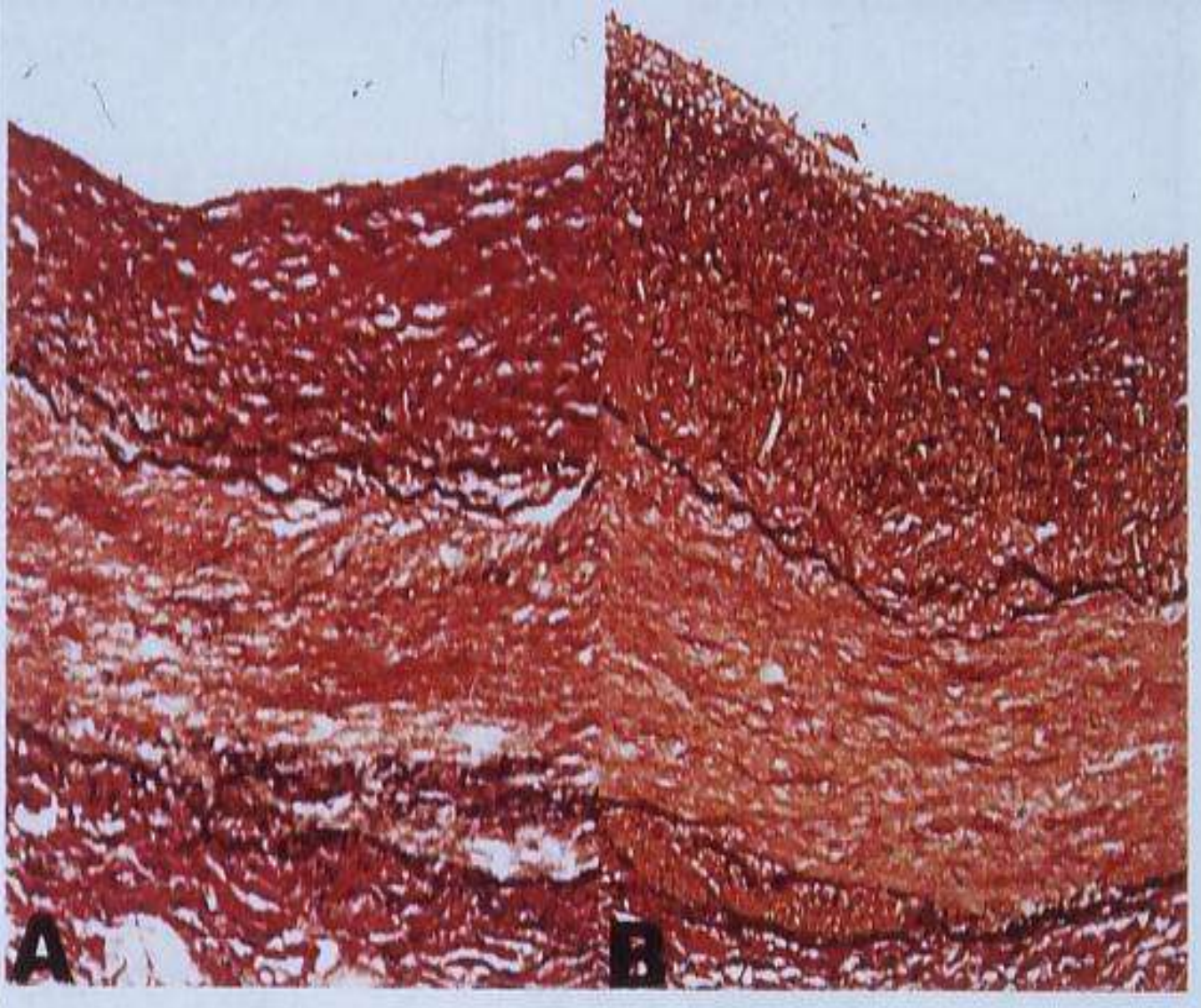
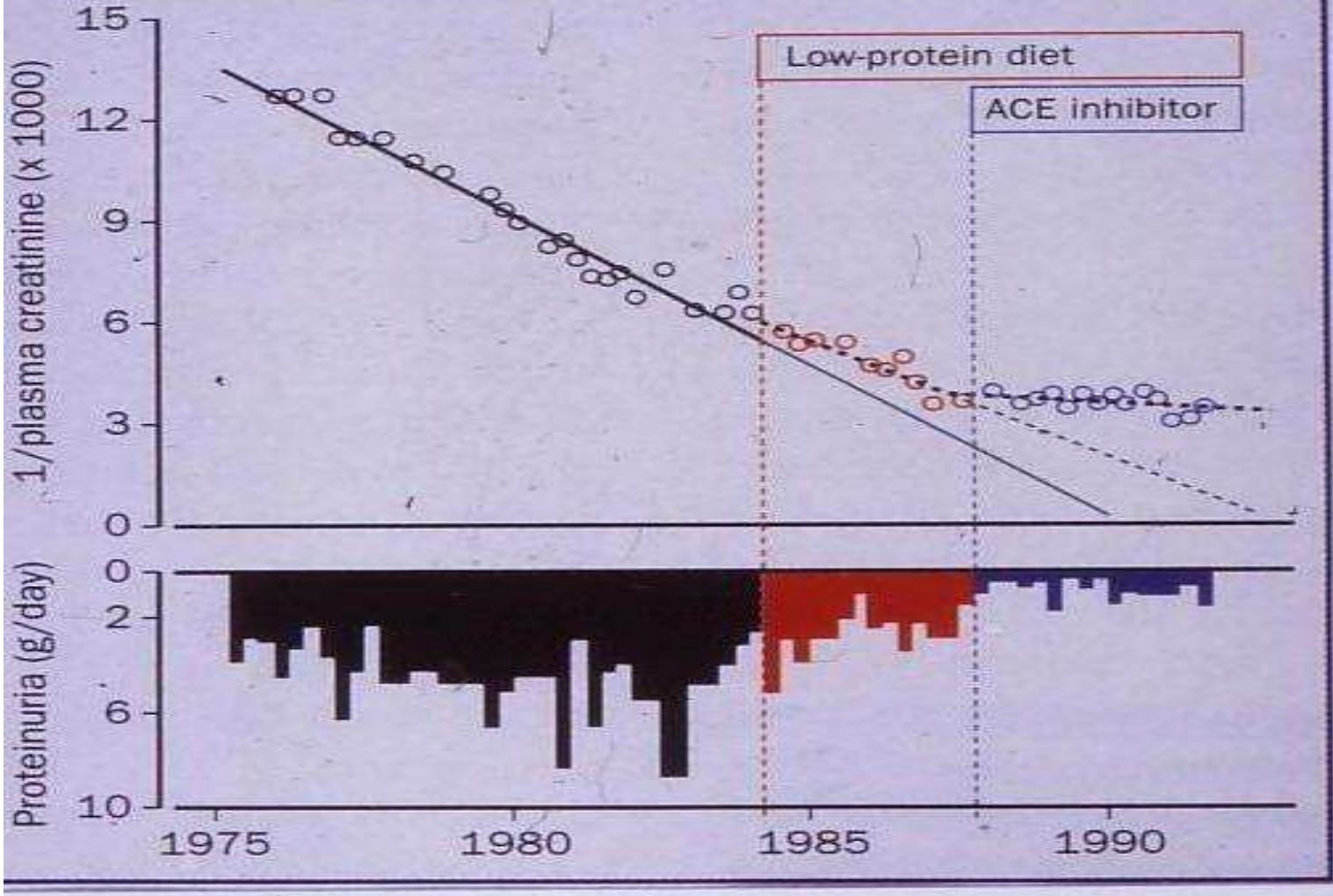


Fig. 2. Representative coronary arteries of a non-renal control patient (A) and a patient with end stage renal disease (B). Please note thickening of the media and intima in renal disease. Elastica-van-Gieson stain; magnification: 1 : 200.

Effect of low-protein diet plus ACE inhibitor on proteinuria and renal function in a patient



REGOLAZIONE DELLA MICROCIRCOLAZIONE RENALE

Pressione glomerulare normale

"riduzione del "pre-load"
Ipertensione sistemica e normotensione glomerulare

"riduzione del "post-load"
ACE inibitori

"aumento del post-load"
Normotensione sistemica e ipertensione glomerulare (diete iperproteiche in pazienti con malattie renali)

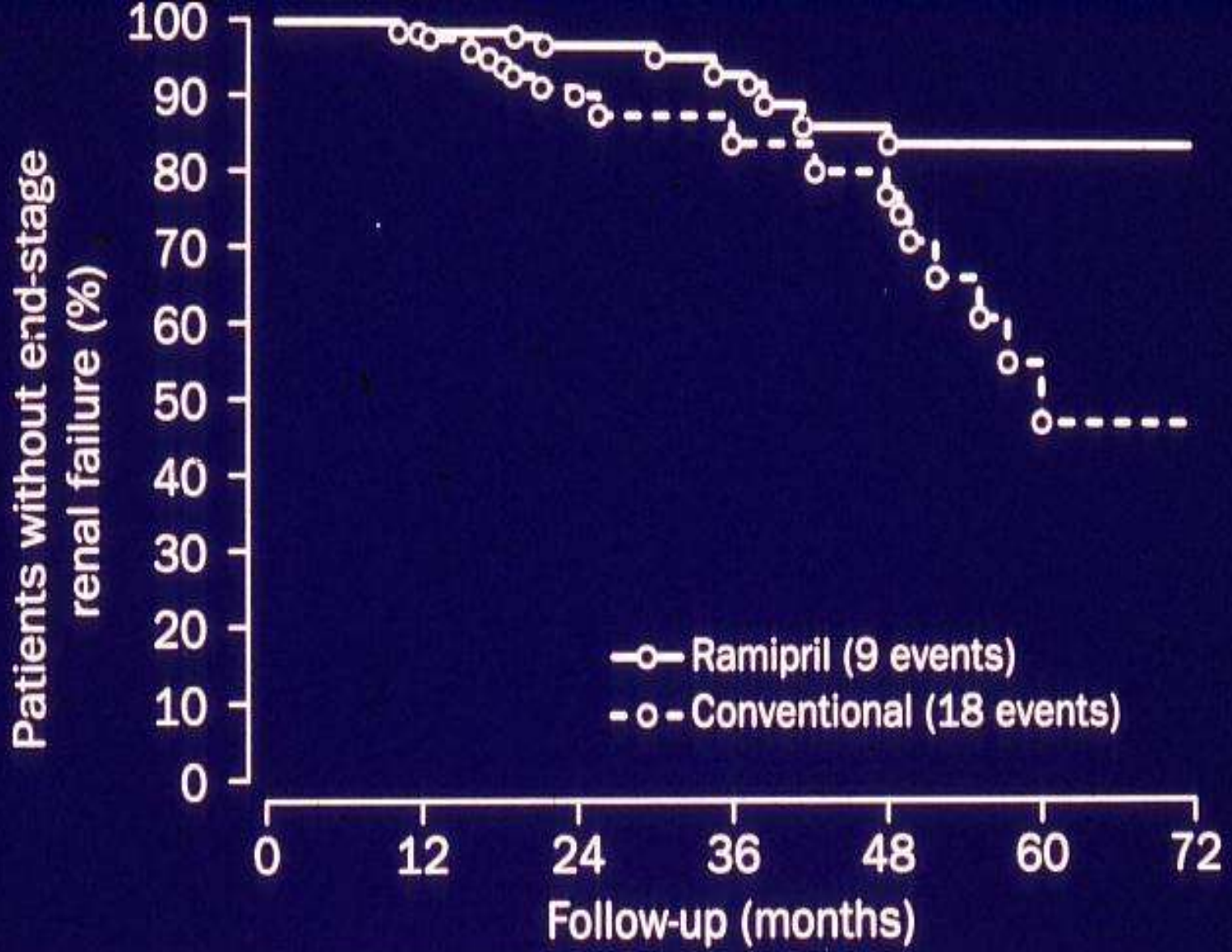
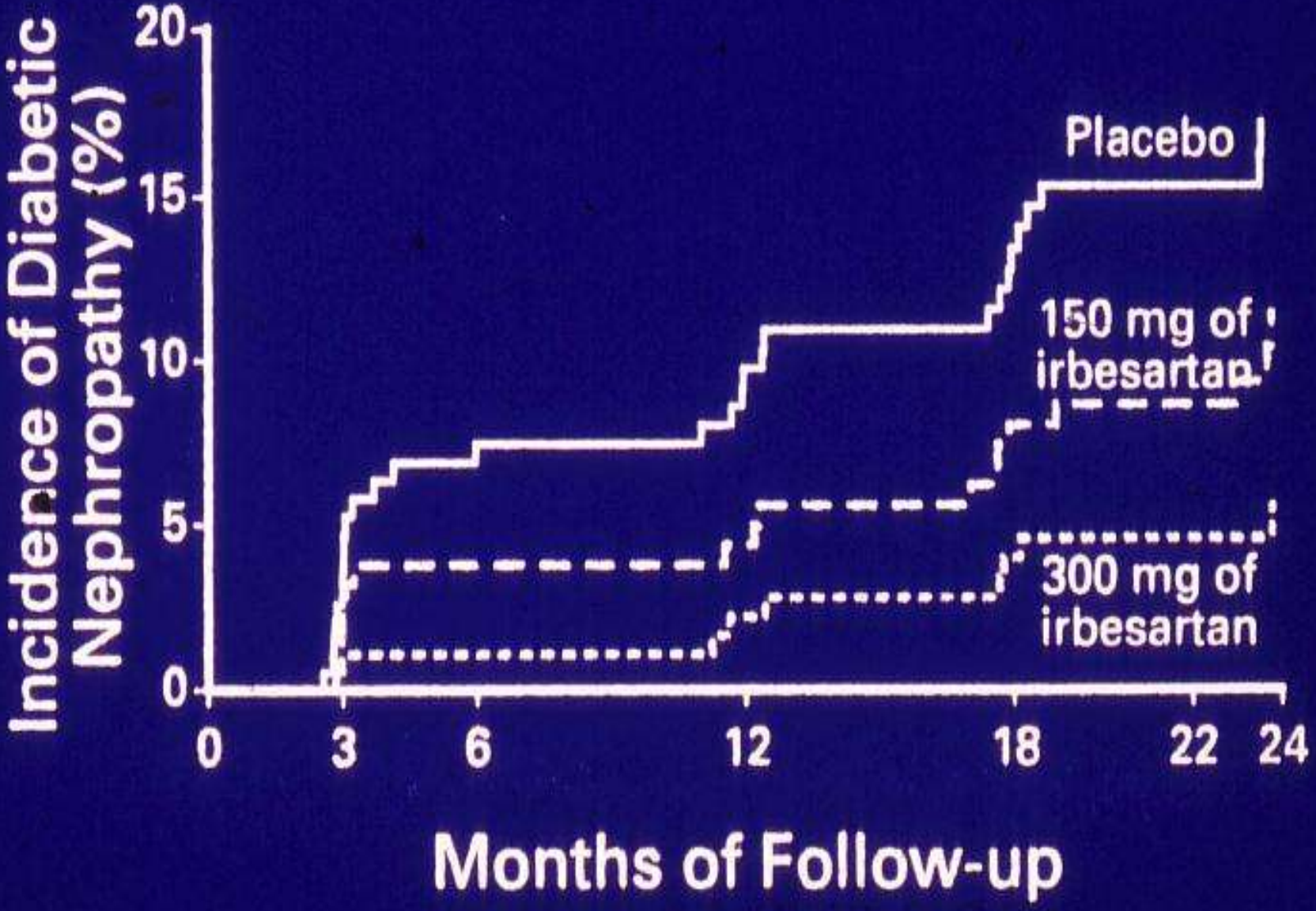


Figure 2: **Kaplan-Meier estimation of renal survival among patients on ramipril or conventional treatment**

RR 2·72 (95% CI 1·22–6·08), p=0·01.

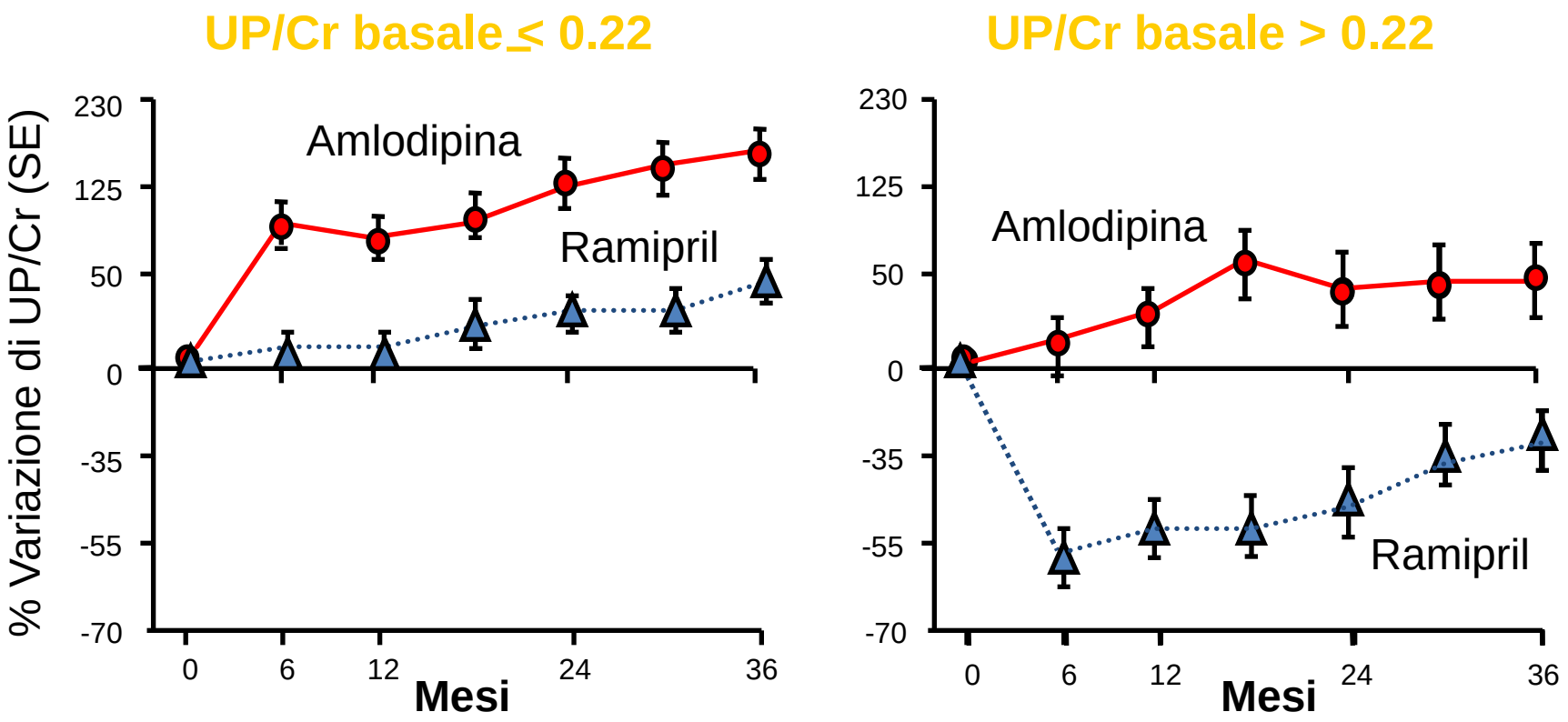

Incidence of Diabetic Nephropathy (%)
20
15
10
5
0
Placebo
150 mg of irbesartan
300 mg of irbesartan
0
3
6
12
18
22
24
Months of Follow-up

RENAAL: Studio di protezione renale con Losartan

Evoluzione naturale della nefropatia diabetica

Breyer JA et al *Am J Kid Dis* 1992;20(6)

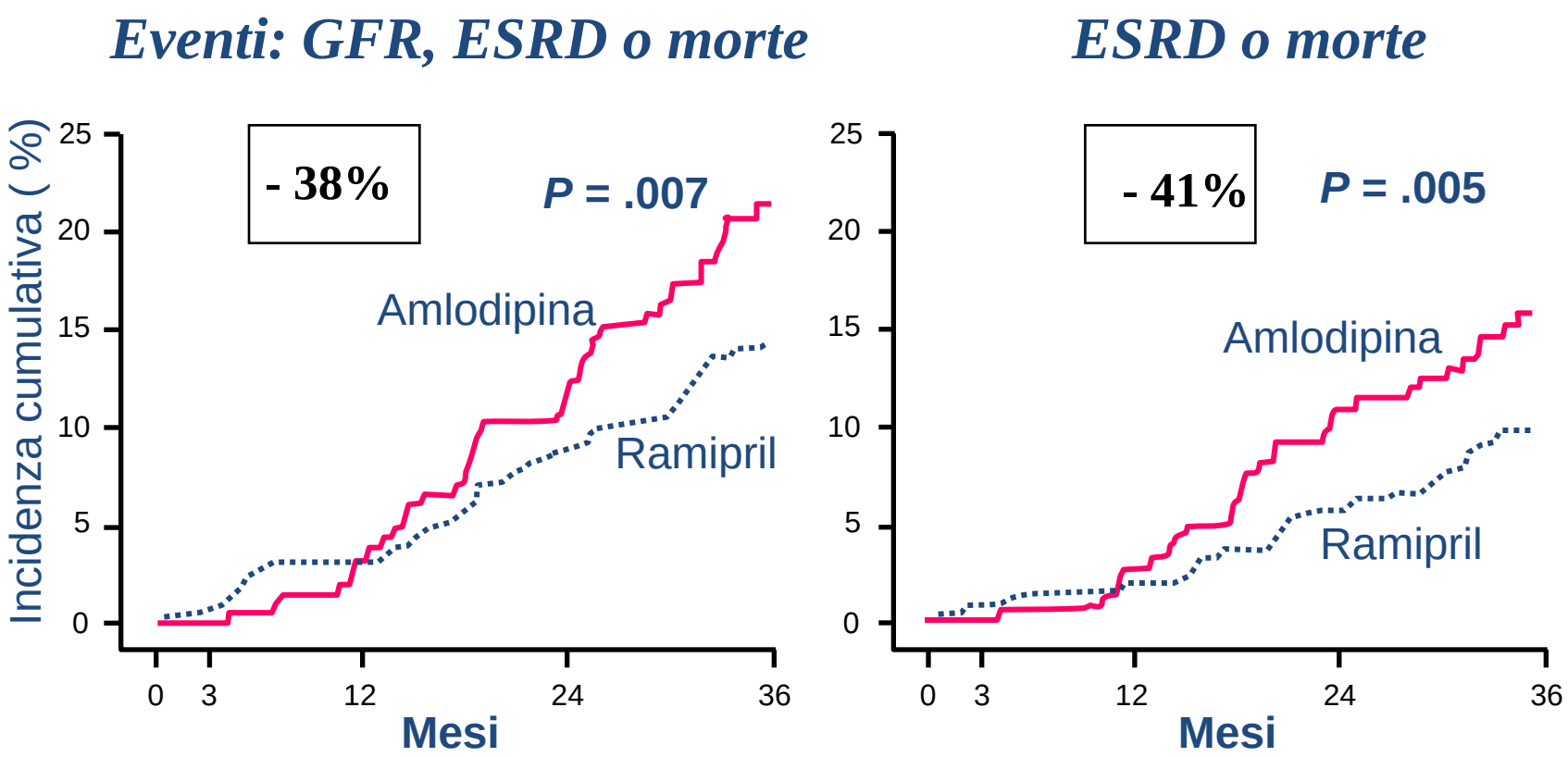
Studio AASK: effetto del trattamento sulla proteinuria



UP/Cr = rapporto proteine/creatinina urinarie
UP/Cr pari a 0.22 corrisponde approssimativamente a una proteinuria di 300 mg/die

Agodoa L. JAMA 2001;285(21):2719-2728

Studio AASK: effetto del trattamento

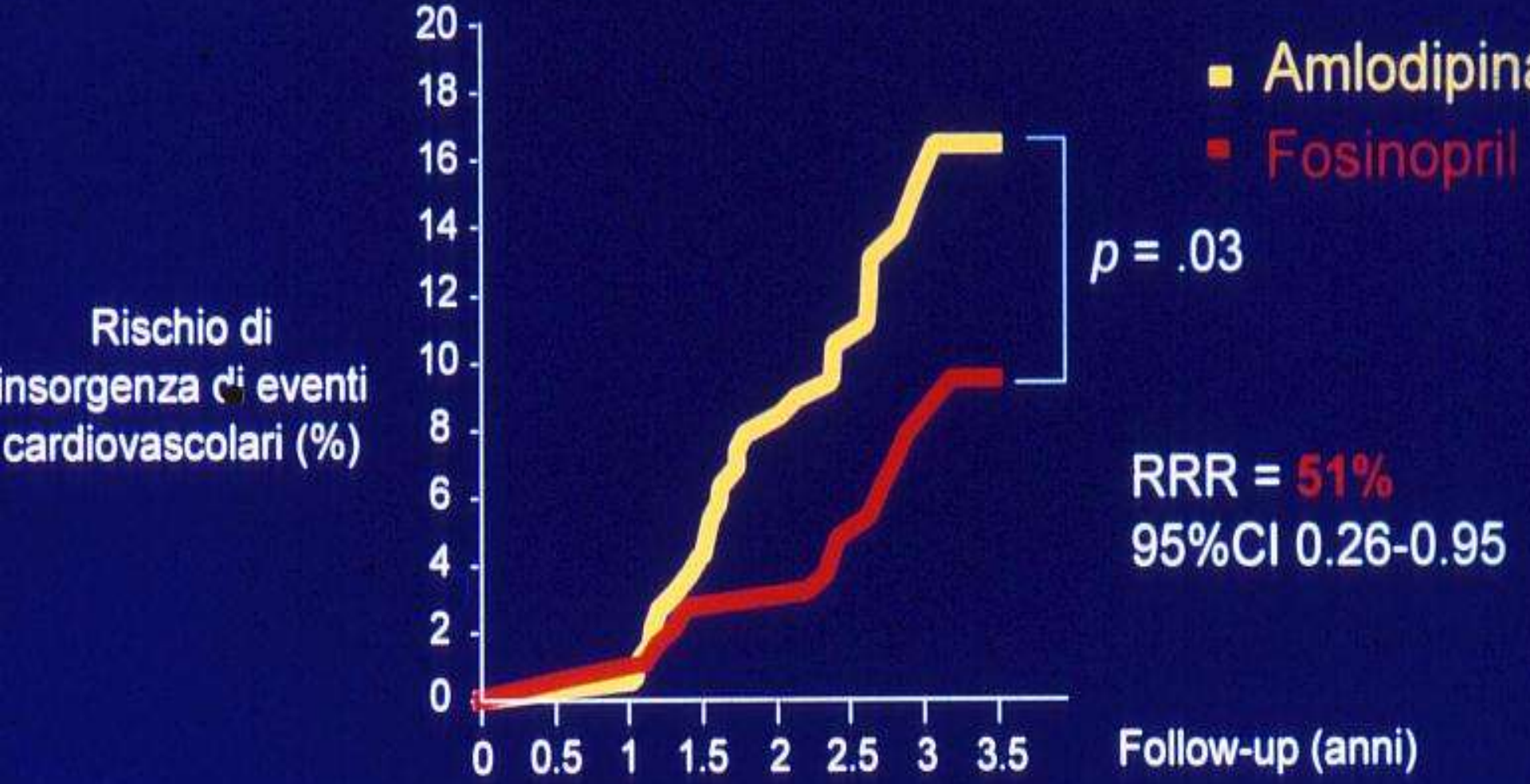


(Agodoa LY, et al. *JAMA*. 2001)

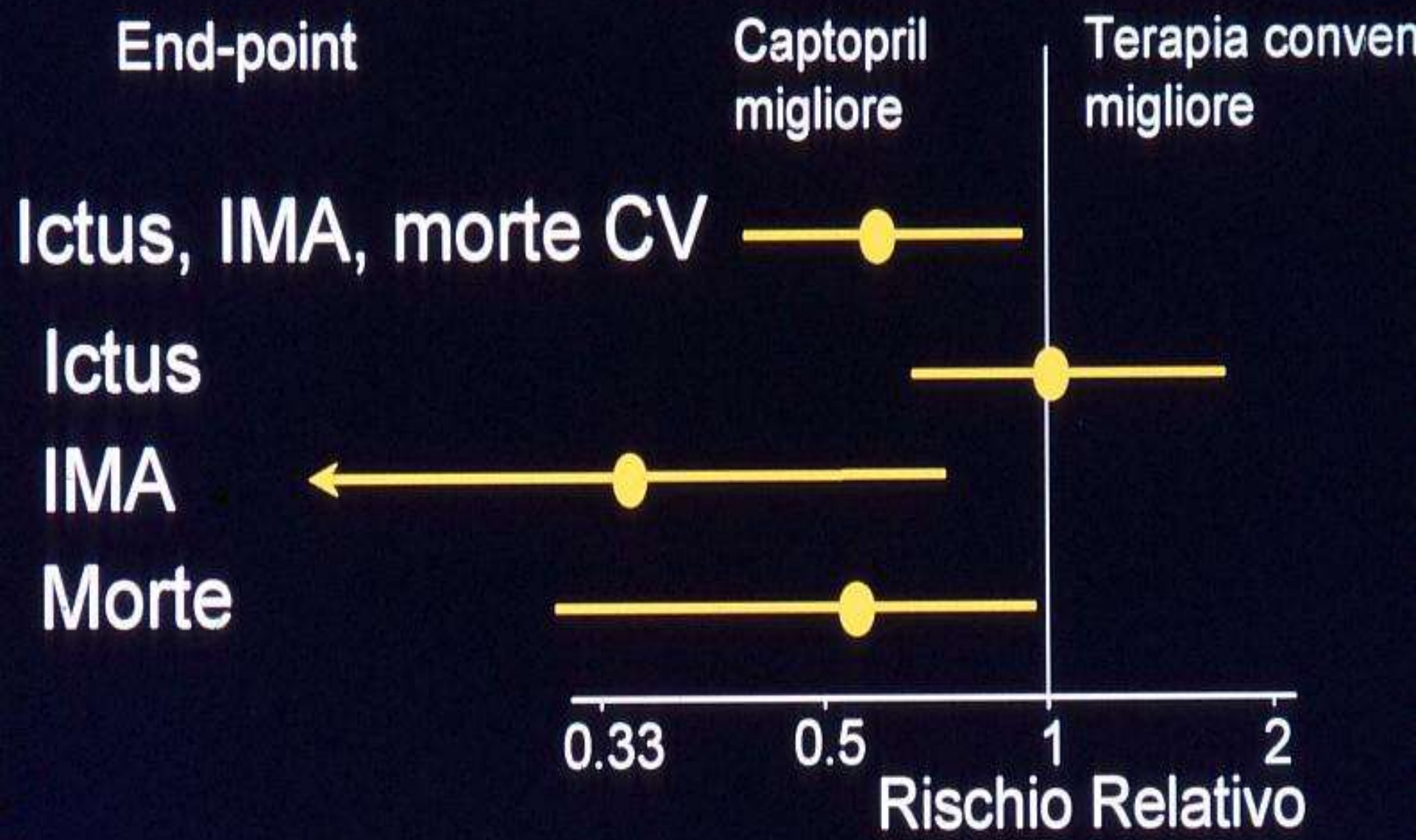
Studio *ABCD*

Disegno	Studio prospettico randomizzato
Pazienti	Diabetici tipo 2: un gruppo normotes e un gruppo ipertesi
Terapie	Enalapril / Nisoldipina in doppio cieco
Obiettivi	- Primari: funzione renale - Secondari: eventi CV, PA
Follow-up	5 anni

Studio *FACET*: risultati sugli eventi cardiovascolari (ictus, infarto, angina)



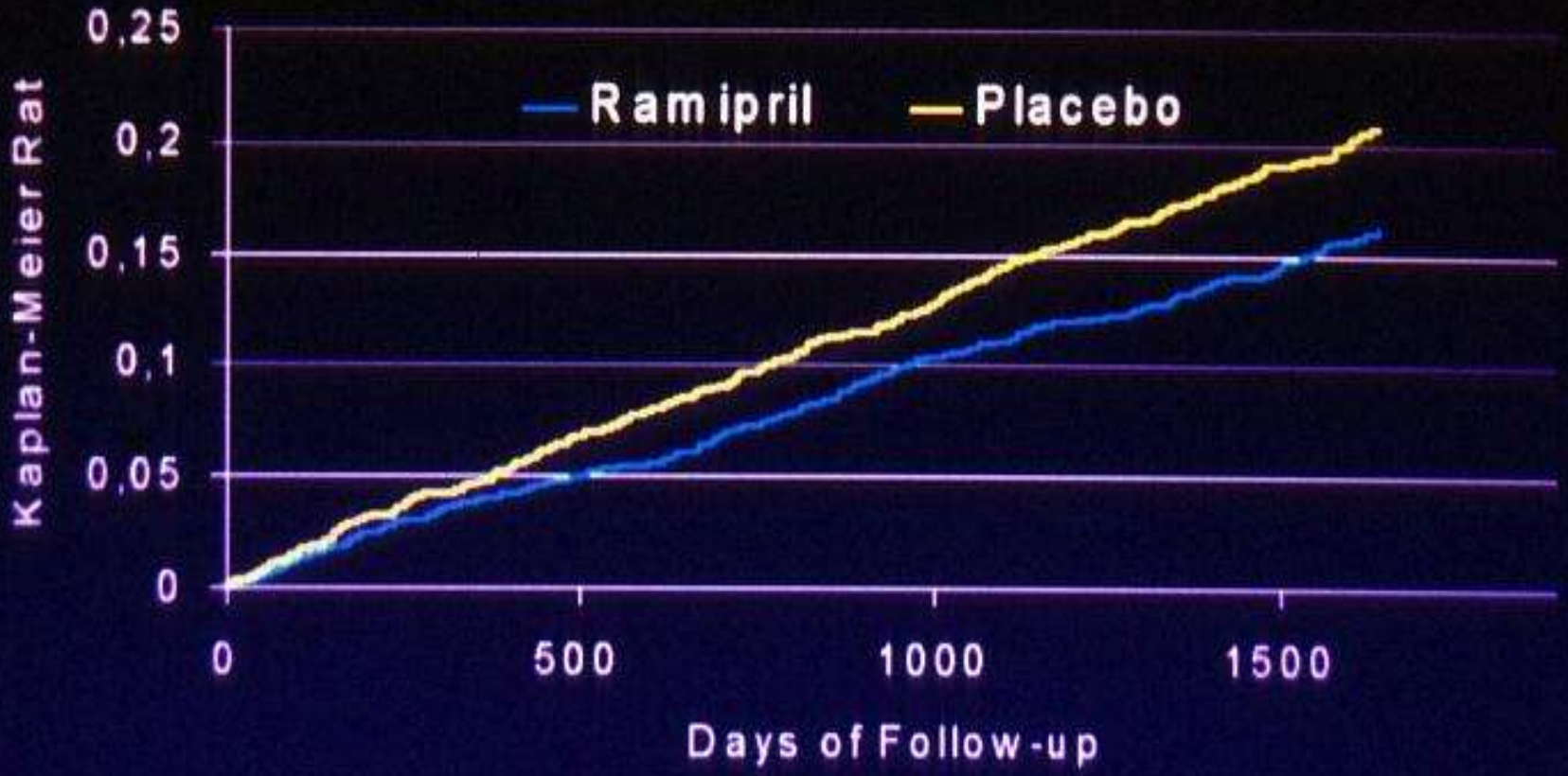
CAPPP - Pazienti con diabete



Hansson et al *Lancet 1999;353:611*

Hope

Pazienti Diabetici: Endpoint primario (morte CV + IMA +Ictus)



RR=0.75 (0.64-0.88) P=0.0004

Hope

Riassunto

- Nei pazienti diabetici ad alto rischio di eventi CV, l'aggiunta di ramipril alle terapie efficaci e già in corso previene :
  - Morte CV, ictus e IMA
  - Mortalità totale
  - Procedure di rivascolarizzazione coronarica
  - Nefropatia diabetica
- Il beneficio è independente dagli effetti sulla PA
- L'unico effetto collaterale è stato un 5% di tosse.

Linee guida per la prevenzione della microalbuminuria (prevenzione primaria)

Normoalbuminuria e PA <130/85

- Accurato controllo glicemico
- ACE-inibitori?
-

Normoalbuminuria e PA ≥130/85

Accurato controllo glicemico, correzione dell'eccesso ponderale, riduzione dell'apporto sodico, abolizione del fumo, riduzione dell'apporto di alcool

Linee guida per la prevenzione della nefropatia clinica (prevenzione secondaria)

- Accurato controllo glicemico
- PA ottimale: 120/70-75 se <50 anni; 125-130/80-85 se >50 anni
- ACE-inibitori (di scelta nel DM tipo 1); sartani (di scelta nel DM tipo 2)
- Altri antipertensivi da sostituire ai suddetti se poço tollerati: ACE-I, sartani, calcioantagonisti a lento rilascio
- Altri antipertensivi, eventualmente da associare per raggiungere la PA ottimale: calcio antagonisti, α-bloccanti, diuretici tiazidici, β-bloccanti
- Dieta iposodica se PA ≥130/85
- Controllo della dislipidemia, riduzione del sovrappeso, abolizione del fumo e dell'apporto di alcool
- Dieta normoproteica (0.9-1 g/kg/die)

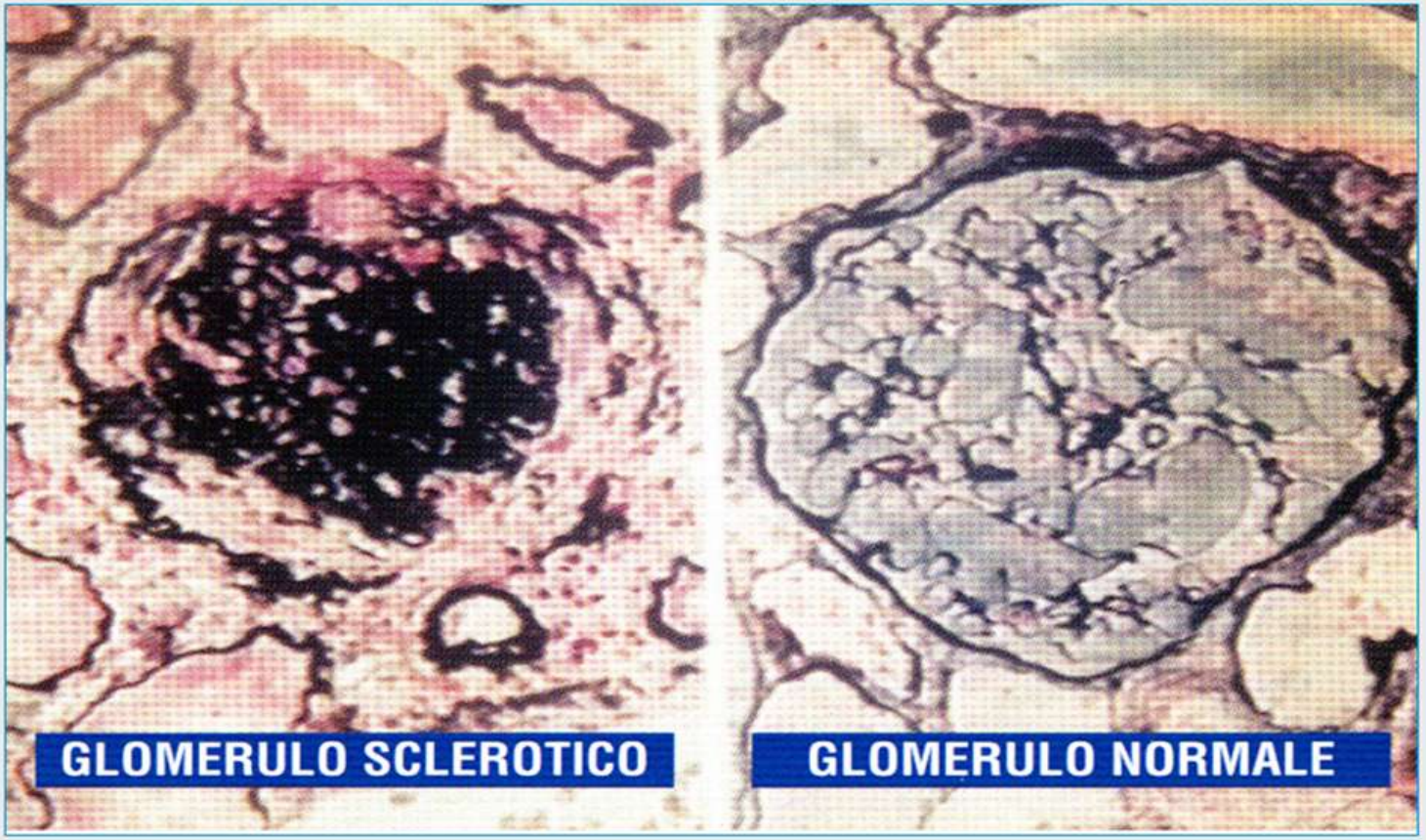
Linee guida per rallentare la progressione della nefropatia diabetica (prevenzione terziaria)

- Controllo glicemico?
  PA ottimale: 120/70 se <50 anni 125-130/80-85 se >50 anni
- ACE-inibitori (di scelta nel DM tipo 1) o sartani (di scelta nel DM tipo 2)
- Altri antipertensivi da sostituire ad ACE-I o sartani se poco tollerati: calcio antagonisti a lento rilascio
- Altri antipertensivi utili per raggiungere la PA ottimale: calcio antagonisti, α-bloccanti, β-bloccanti, clonidina, ecc.)
- Dieta iposodica (5-6 g/die) e riduzione del peso
- Controllo della dislipidemia, abolizione di fumo e alcool
- Dieta lievemente ipoproteica (0.7-0.9 g/kg/die)

Box 14 Position statement: Antihypertensive therapy in patients with deranged renal function

- Renal protection in diabetes has two main requirements:
  - strict blood pressure control (<130/80 mmHg and even lower if proteinuria is >1 g/day);
  - lowering proteinuria to values as near to normal as possible.
- To reduce proteinuria either an angiotensin receptor blocker or an ACE inhibitor is required.
- To achieve the blood pressure goal, combination therapy is usually required, with addition of a diuretic and a calcium antagonist.

ESC-ESH



D. Manfellotto

OBIETTIVI DELLA REMISSIONE CLINICA DELLE NEFROPATIE

- PA < 120/80
- Proteinuria < 0.5 g
- LDL < 100
- VLDL < 130
- HbA1C < 7.5

Ruggenenti, 2003

EVOLUZIONE DELLA NEFROPATIA (Remuzzi 2006)

	progressione	remissione	regressione
Proteinuria	> 1 g	< 1 g	< 0.3 g
Filtrato glomerulare	si riduce	stabile	aumenta
Alterazioni morfologia renale	peggiorano	stabili	migliorano

- 0.1 ml/mese è la perdita "fisiologica" del VFG oltre i 50 anni: circa 1 ml/anno