Danno renale da farmaci

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UOSD Farmacoepidemiologia Geriatrica

IRCCS INRCA - Cosenza

Danno renale da farmaci

1. Invecchiamento e rene
2. Meccanismi
3. Epidemiologia
4. Problemi diagnostici
5. Prevenzione

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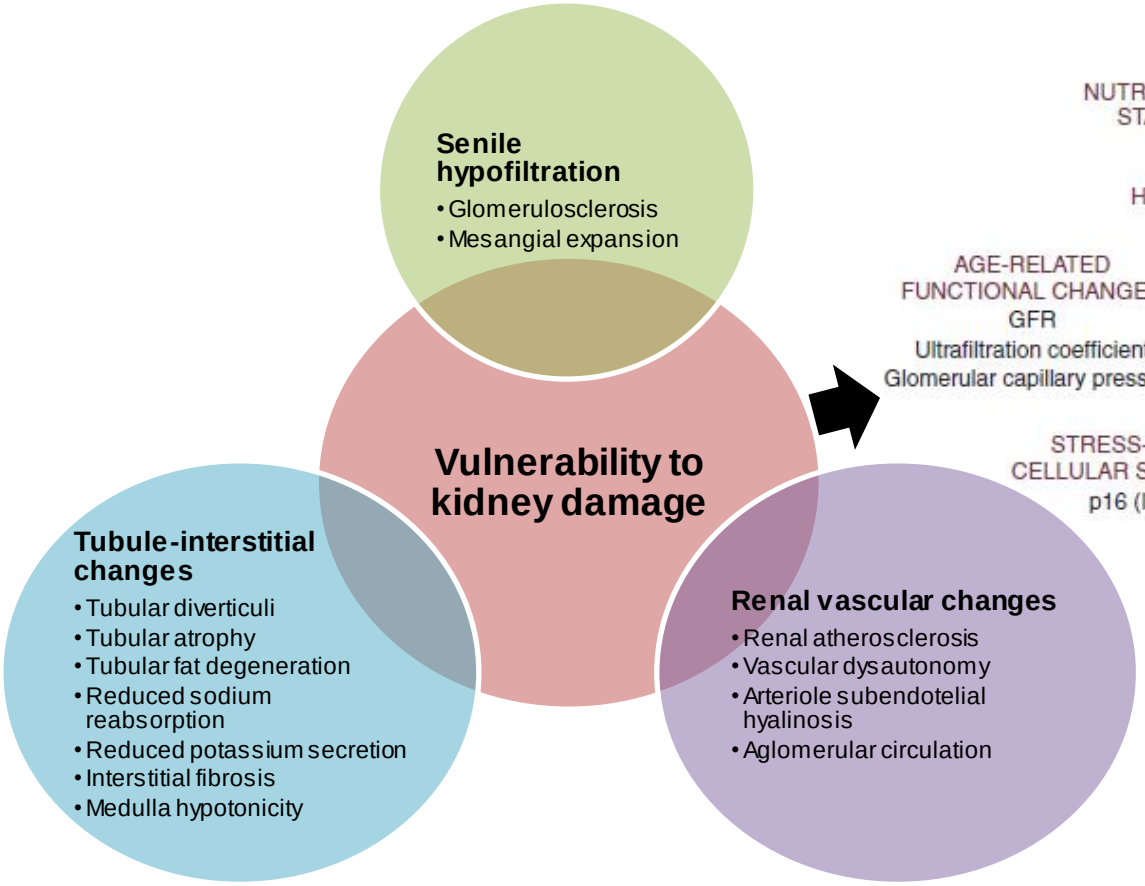
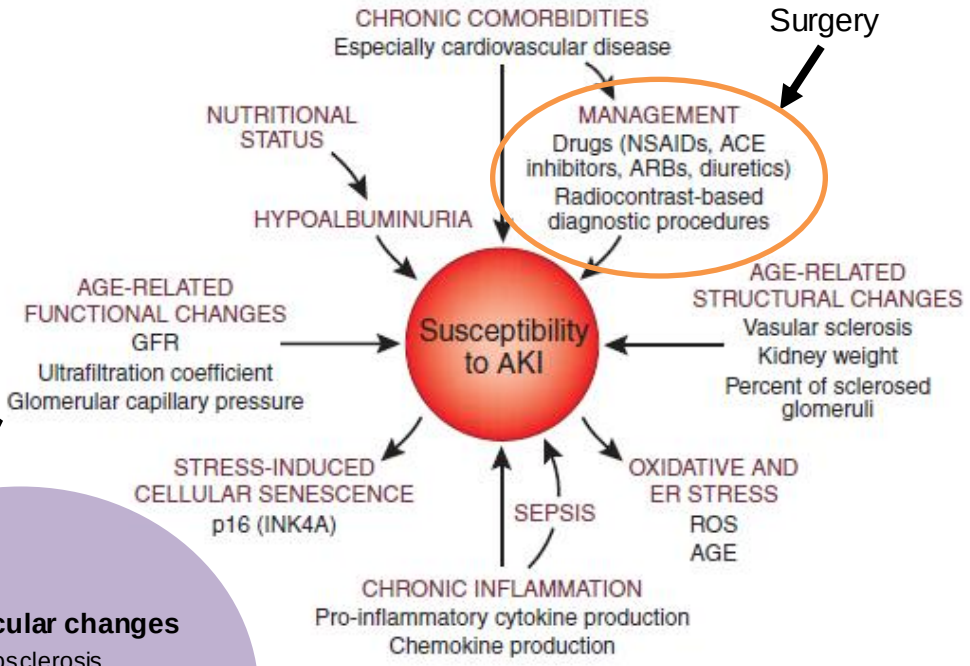
HEALTH AND SCIENCE ON AGING

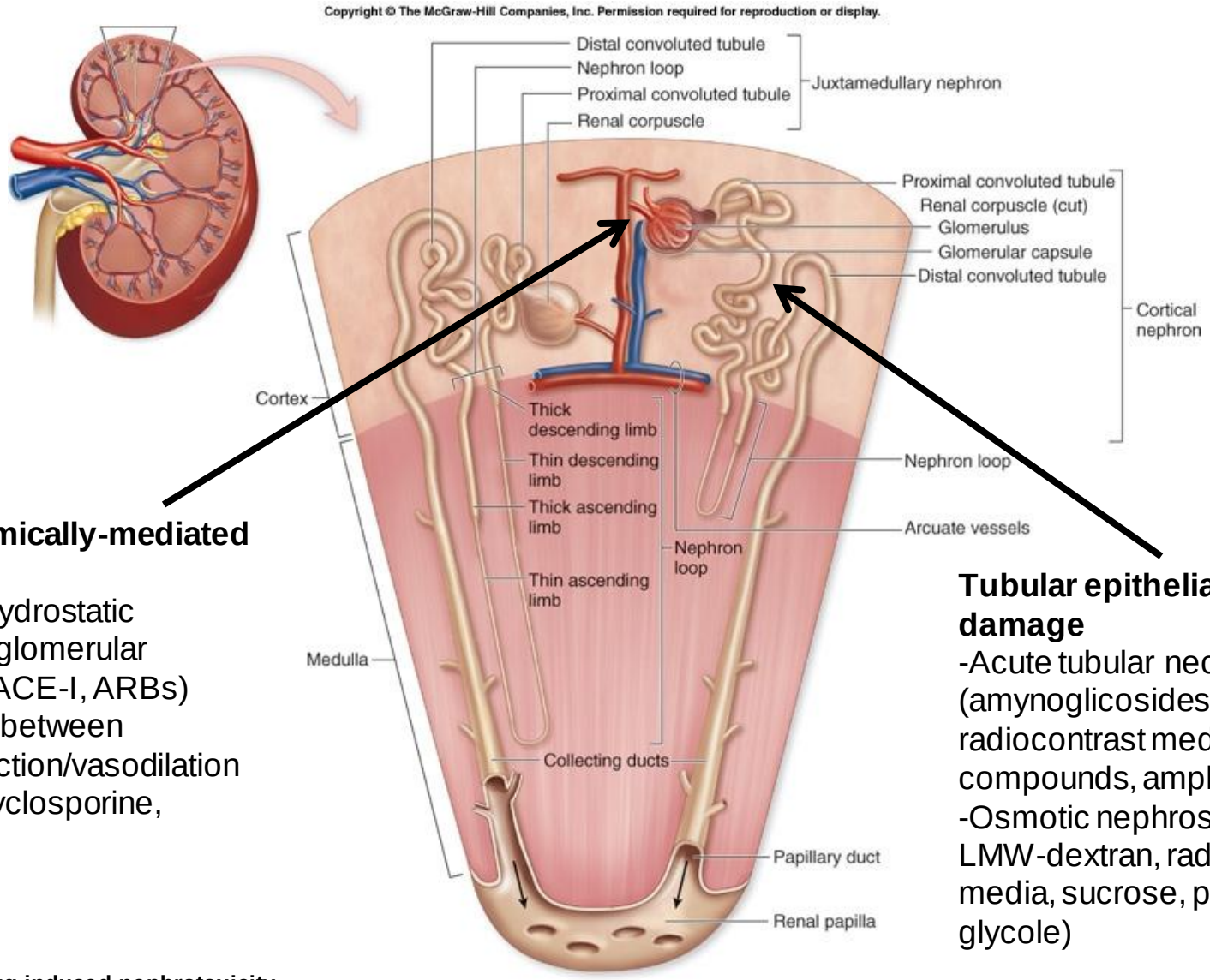
1. The aging kidney





Musso & Oreopulos, Nephron Physiol 2011
Kanasaki et al, Hypertension Research 2012
Anderson et al, Kidney Int 2012

2. Mechanisms of iatrogenic kidney damage



Hemodinamically-mediated damage

-Reduced hydrostatic pressure in glomerular capillaries (ACE-I, ARBs)

-Unbalance between vasoconstriction/vasodilation (NSAIDs, cyclosporine, tacrolimus)

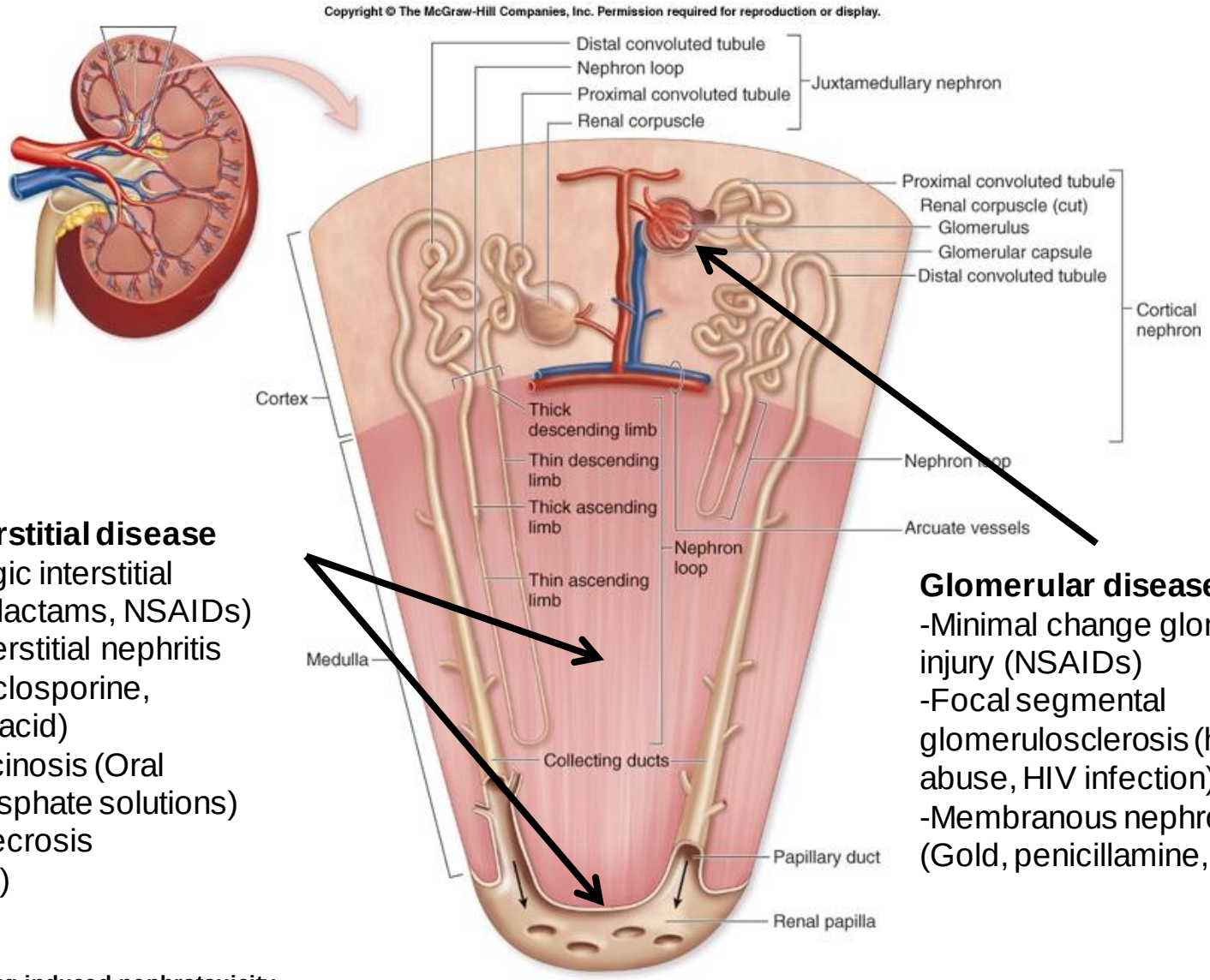
Tubular epithelial cell damage

-Acute tubular necrosis (amynoglicosides, radiocontrast media, platin compounds, amphotericin B)

-Osmotic nephrosis (mannitol, LMW-dextran, radiocontrast media, sucrose, propylen glycole)

Mechanisms of drug-induced nephrotoxicity
Nolin TD, Himmelfarb J. In: Handbook of Experimental Pharmacology 2010

2. Mechanisms of iatrogenic kidney damage

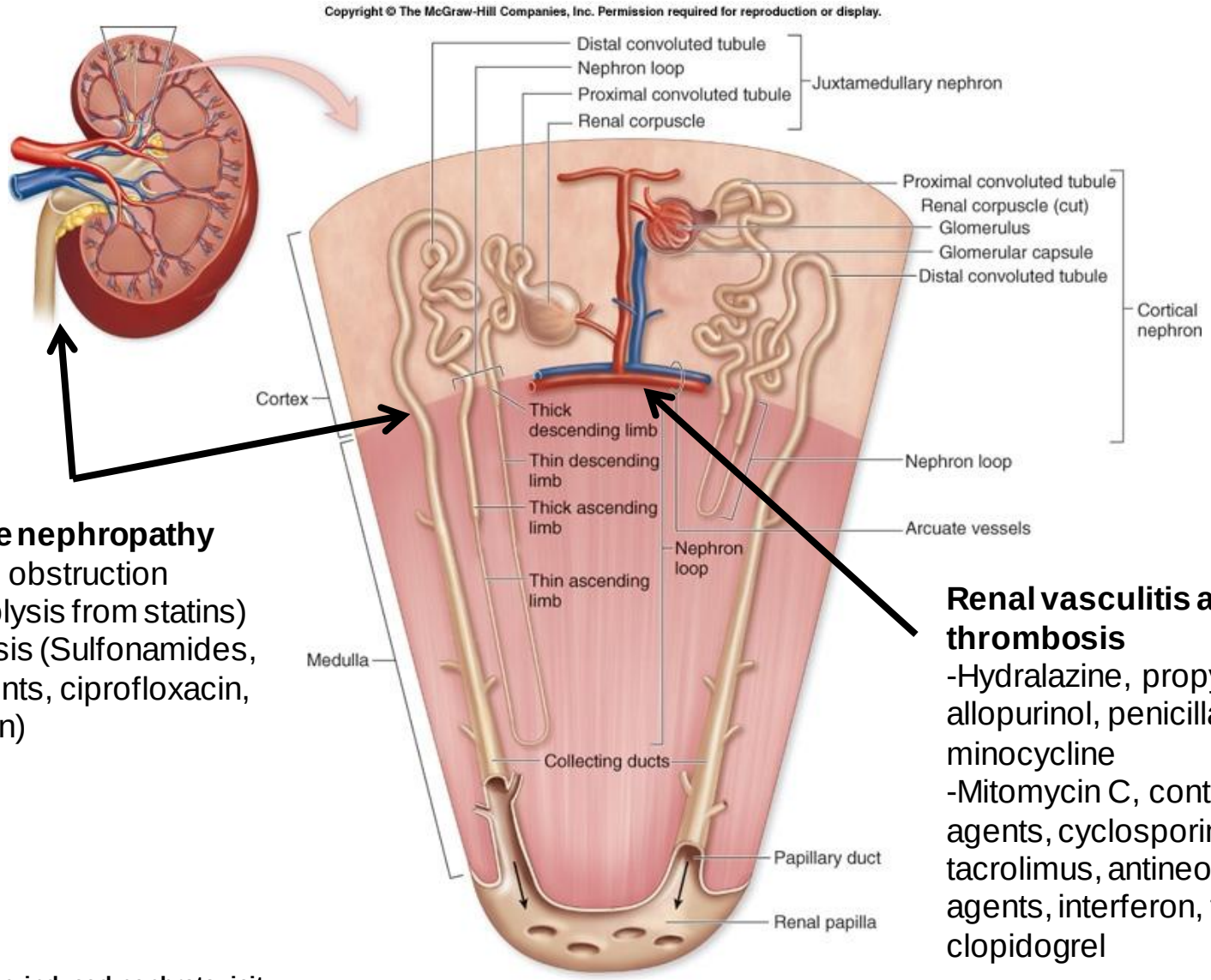


Tubulointerstitial disease
-Acute allergic interstitial nephritis (β-lactams, NSAIDs)
-Chronic interstitial nephritis (Lithium, cyclosporine, aristolochic acid)
-Nephrocalcinosis (Oral sodium phosphate solutions)
-Papillary necrosis (Analgesics)

Glomerular disease
-Minimal change glomerular injury (NSAIDs)
-Focal segmental glomerulosclerosis (heroine abuse, HIV infection)
-Membranous nephropathy (Gold, penicillamine, NSAIDs)

Mechanisms of drug-induced nephrotoxicity
Nolin TD, Himmelfarb J. In: Handbook of Experimental Pharmacology 2010

2. Mechanisms of iatrogenic kidney damage



Obstructive nephropathy
-Intratubular obstruction (rhabdomyolysis from statins)
-Nephrolitiasis (Sulfonamides, antiviral agents, ciprofloxacin, nitrofurantoin)

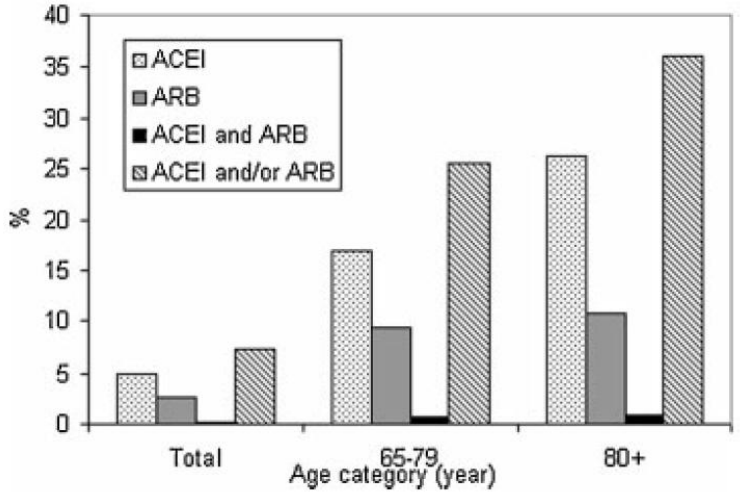
Renal vasculitis and thrombosis
-Hydralazine, propylthiouracil, allopurinol, penicillamine, minocycline
-Mitomycin C, contraceptive agents, cyclosporin, tacrolimus, antineoplastic agents, interferon, ticlopidine, clopidogrel

Mechanisms of drug-induced nephrotoxicity
Nolin TD, Himmelfarb J. In: Handbook of Experimental Pharmacology 2010

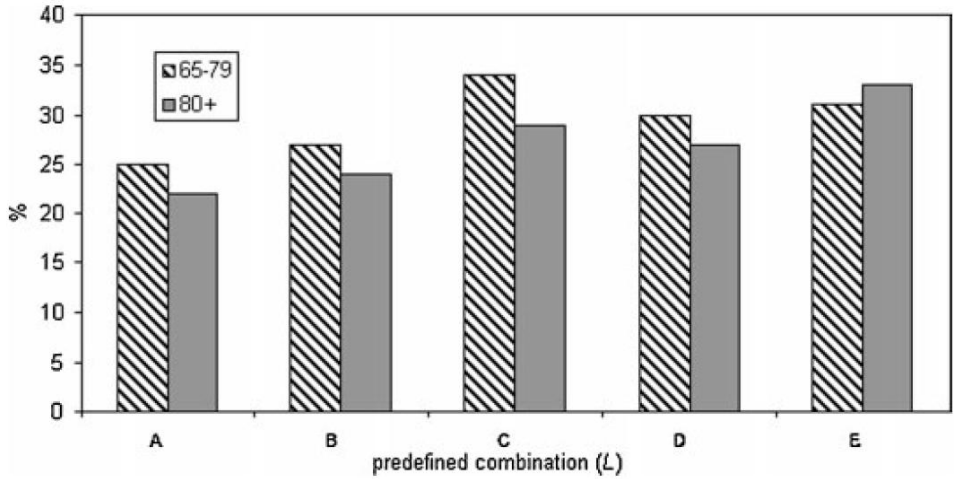
3. Epidemiology

Exposure of the elderly to potential nephrotoxic drug combinations

Percentage of population chronically treated with ACEI/ARBs



Percentage of patients receiving NSAIDs



Group A, patients chronically treated with ACEI/ARB.
Group B, patients of group A + diuretic.
Group C, patients of group A + spironolactone.
Group D, patients of group A + β-blocker + diuretic.
Group E, patients of group A + β-blocker + spironolactone.

Smets et al, Pharmacoepidemiol Drug Saf 2008

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3. Epidemiology

- Drug-induced kidney injury accounts for 18-27% of all AKIs (Leape et al, NEJM 1991; Choudhuri et al, MCNA 1997; Nash et al AJKD 2002)
- Between 1983 and 2002 the contribution of nephrotoxicity to AKI rose from 8% to 18% (Hou et al, AJM 1983; Nash et al AJKD 2002)
- In a biopsy study of acute on chronic renal failure, 35% appeared to be drug-related (Zhang et al, Clin Nephrol 2005)
- In a Dutch study of 21277 hospital admissions, 5909 patients had at least one drug-drug interaction. Of them, 12.6% were nephrotoxicity (Zwart-van Rijkom et al, Br J Clin Pharmacol 2009)

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3. Epidemiology

Risk factors for nephrotoxicity

Patient-related factors		Drug-related factors
Advanced age (>75 yrs)	Sepsis	Contrast media
Diabetes	Hypotension	Antimicrobial agents
CKD	Hypovolemia (shock, volume depletion, sodium depletion)	Chemotherapeutic agents
Heart failure	Acid-base disturbances	NSAIDs
Liver disease	Hypoalbuminemia	Calcineurin inhibitors
Male sex	**Dangerous interactions**	
Hypoalbuminemia	Triple whammy	Cephalosporins and aminoglycosides
Arterial vascular disease	Vancomycin and aminoglycosides	Cephalosporins and acyclovir

Shetz et al, Curr Opin Crit Care 2005
Munar & Singh, Am Fam Phys 2007
Naughton CA, AFP 2008
Bentley et al, Crit Care Med 2010
Logham-Adham et al, Expert Opin Drug Saf 2012
Bell et al, Austr Fam Phys 2013

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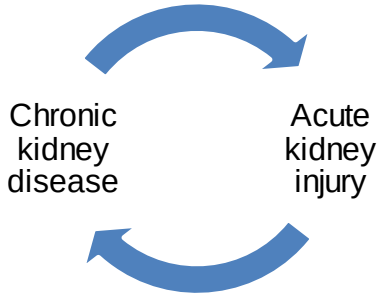
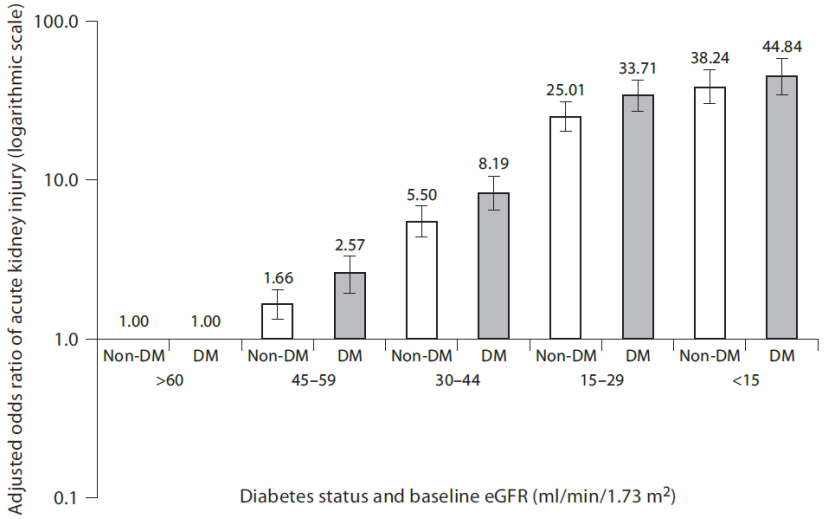
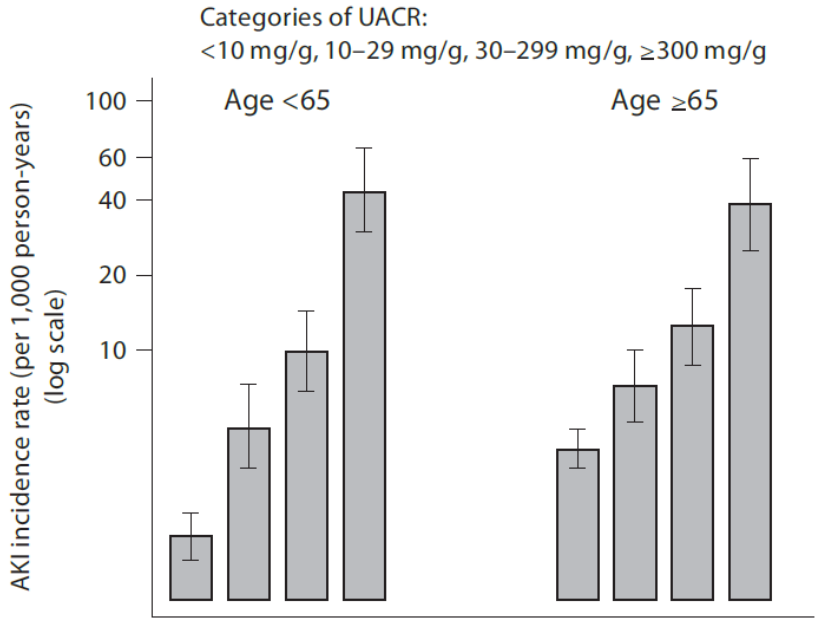
3. Epidemiology



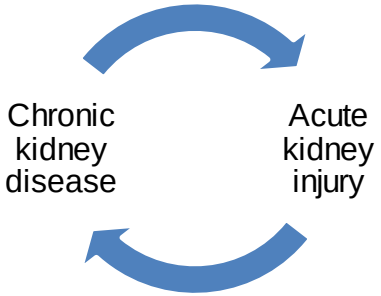
The vicious cycle of AKI and CKD





Coca et al, Nephron Clin Pract 2011

3. Epidemiology



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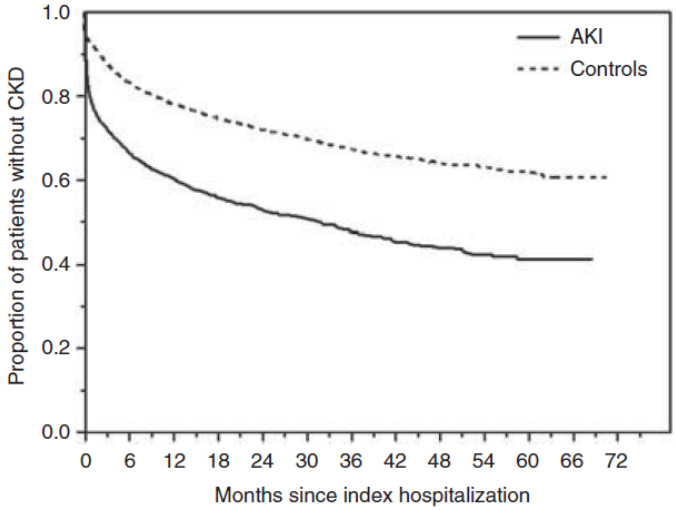
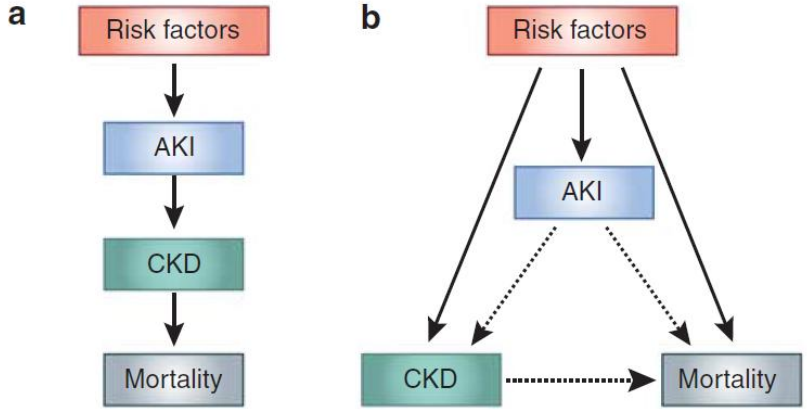


Figure 2 | Cumulative incidence of chronic kidney disease (CKD) by exposure status (recovered acute kidney injury (AKI) group vs. controls) among patients with normal baseline kidney function.



Bucaloiu et al, Kideny Int 2012
Palevsky PM, Kidney Int 2012

3. Epidemiology

AKI and prognosis

Mortality

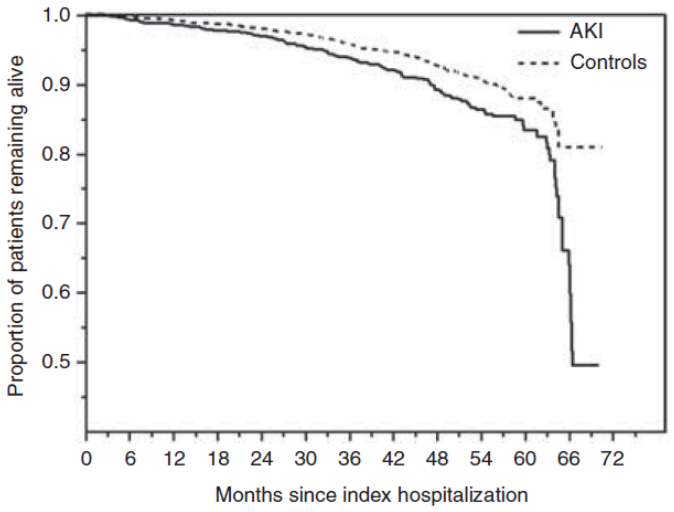
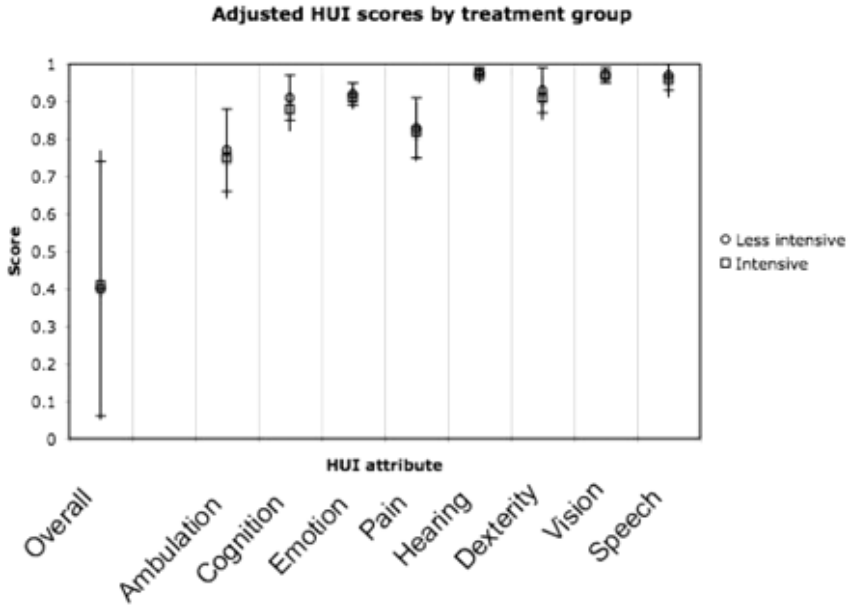


Figure 1 | Unadjusted survival by exposure status (recovered acute kidney injury (AKI) group vs. controls) among patients with normal baseline kidney function.

Bucaloiu et al, Kideny Int 2012

Functional decline

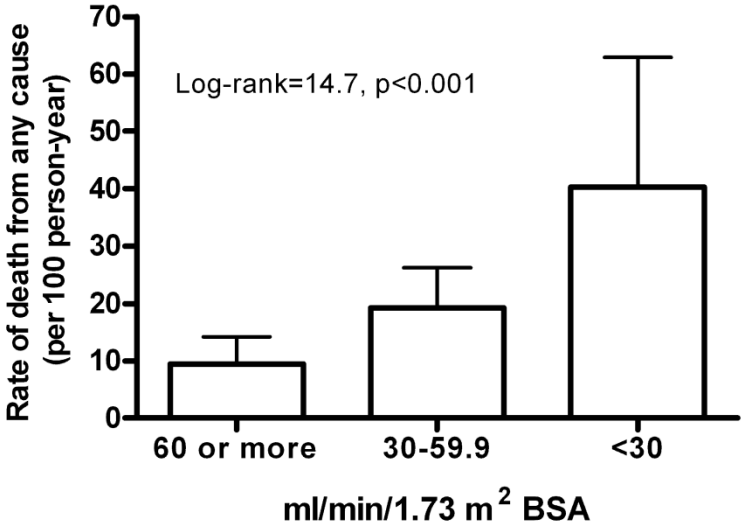


Johansen et al, Clin JASN 2010

3. Epidemiology

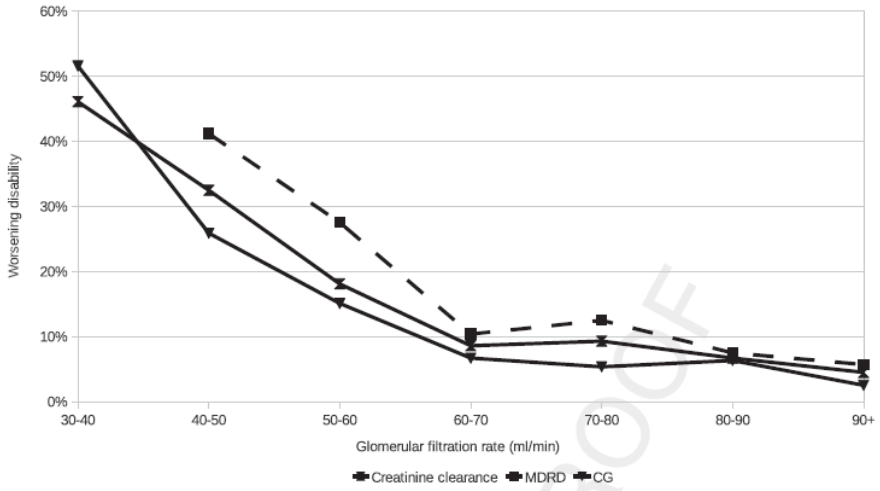
CKD and prognosis

Mortality



Corsonello et al, NDT 2011

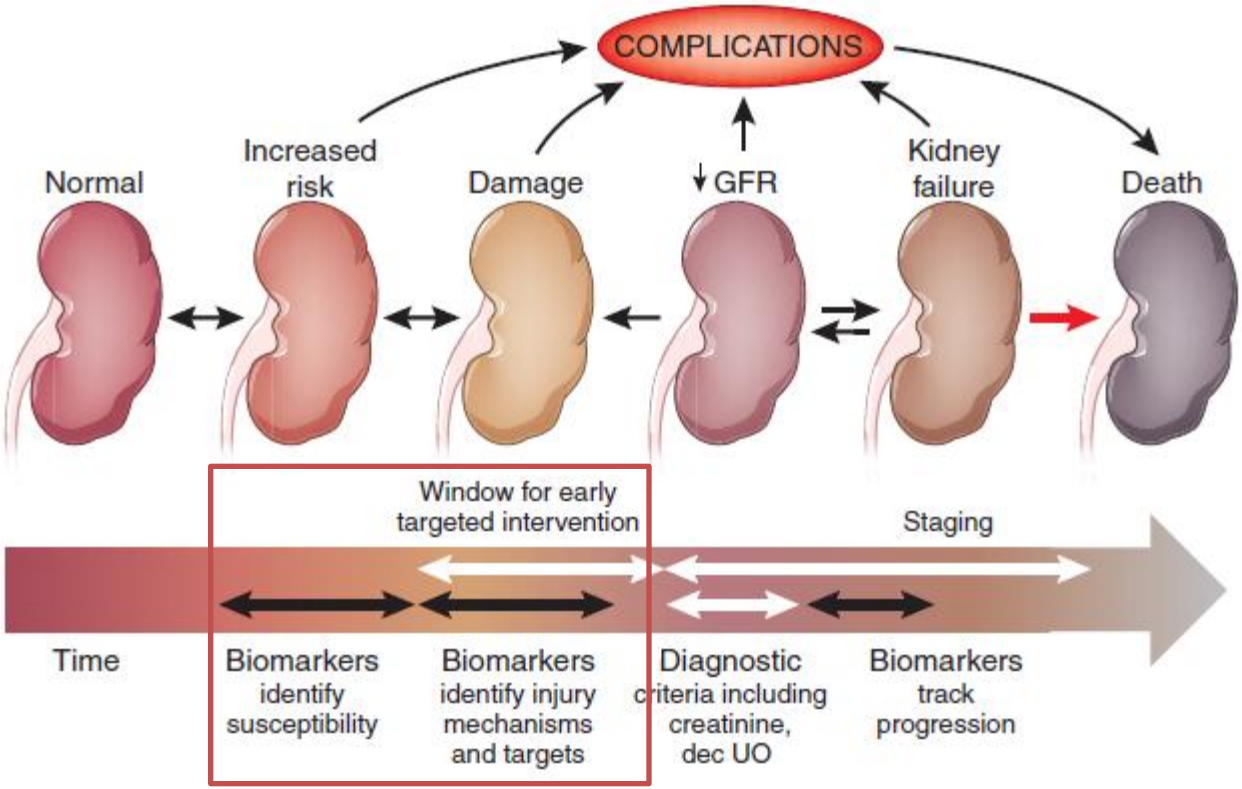
Functional decline



Pedone et al, JAMDA 2012

PROOF

4. Diagnostic accuracy



Anderson et al, Kidney Int 2012

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Doxorubicin
Puromycin
Gold
Pamodronate
Penicillamine

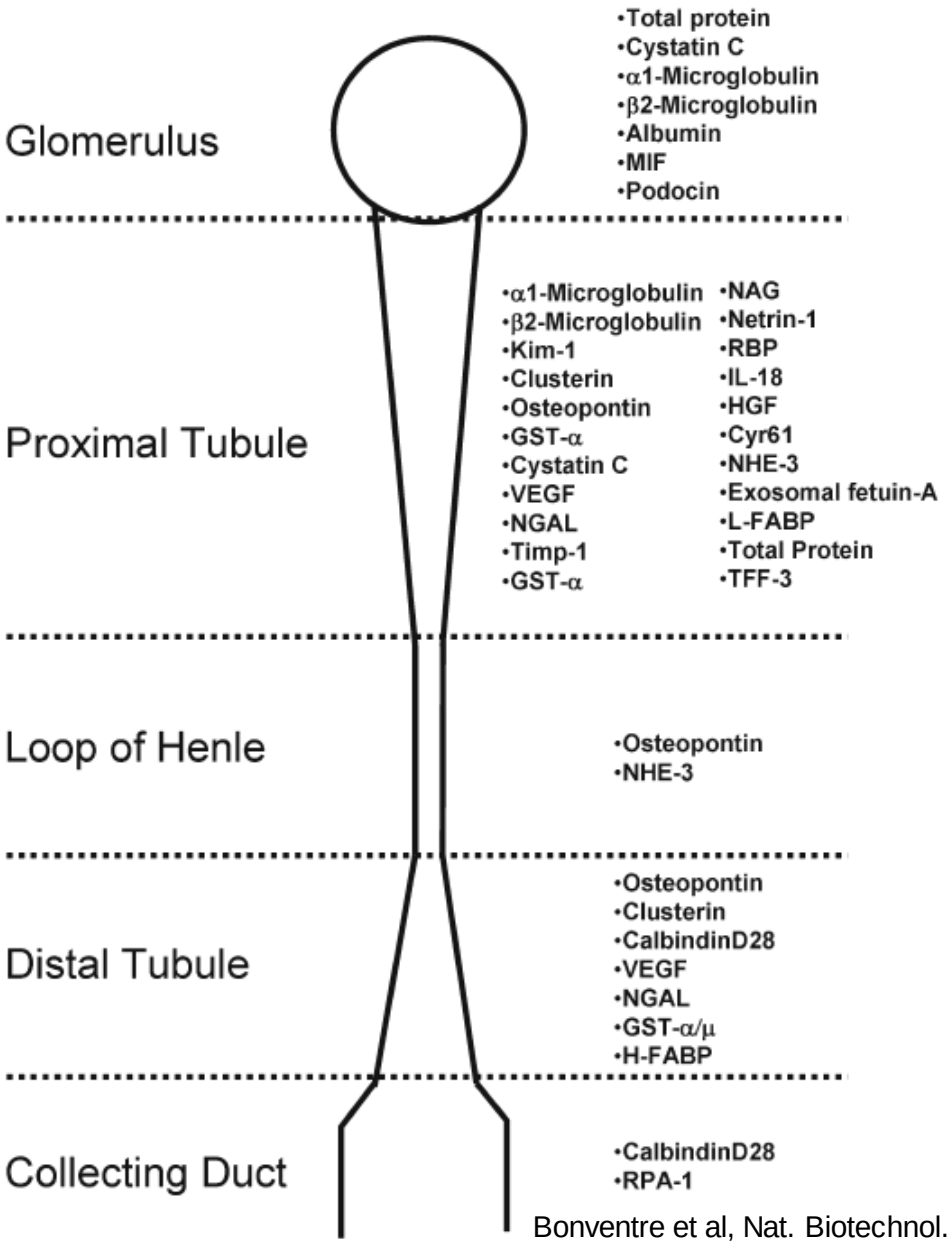
Cyclosporine
Tacrolimus
Cisplatin
Vancomycin
Gentamycin
Neomycin
Tobramycin
Ibandronate
Zoledronate
Contrast agents

Ciclofovir
Adefovir
Tenofovir
I.V. immunoglobulins

Analgesics

Cyclosporine
Tacrolimus
Sulfadiazine
Lithium
Amphotericin B

Amphotericin B
Acyclovir
Lithium

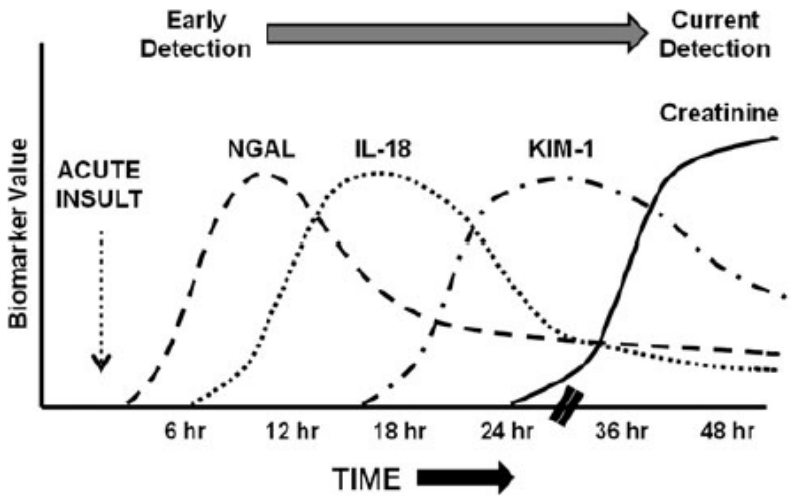


Bonventre et al, Nat. Biotechnol. 2010
Fuchs & Hewitt, AAPS Journal 2011

4. Diagnostic accuracy

Urinary and serum biomarkers for the diagnosis of acute kidney injury

NGAL = neutrophil gelatinase-associated lipocalin; IL-18 = interleukin-18; KIM-1 = kidney injury molecule-1; L-FABP = L-type – fatty acid binding protein

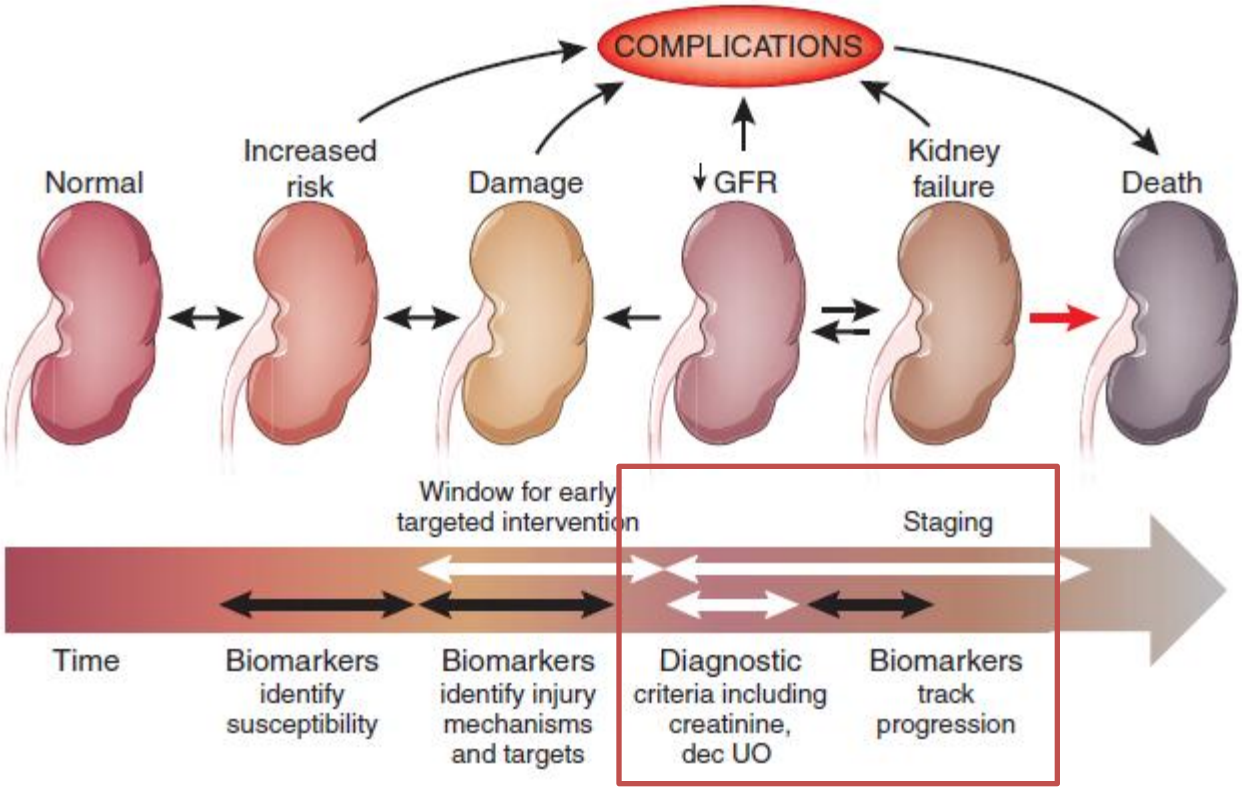


Bagshaw et al, Can J Anesth 2010

!! Whereas biomarkers can increase our understanding of the pathophysiology of AKI, it appears that the promising results with new biomarkers for early detection and differential diagnosis of AKI in clinical practice can only be confirmed in the setting of children without co-morbidities and with a well-defined timing of renal injury. **Results are far less robust when we search for validation in adult heterogenic populations, including patients with co-morbid conditions such as diabetes mellitus, vascular disease and CKD.**

Vanmassenhove et al, NDT 2013

4. Diagnostic accuracy



Anderson et al, Kidney Int 2012

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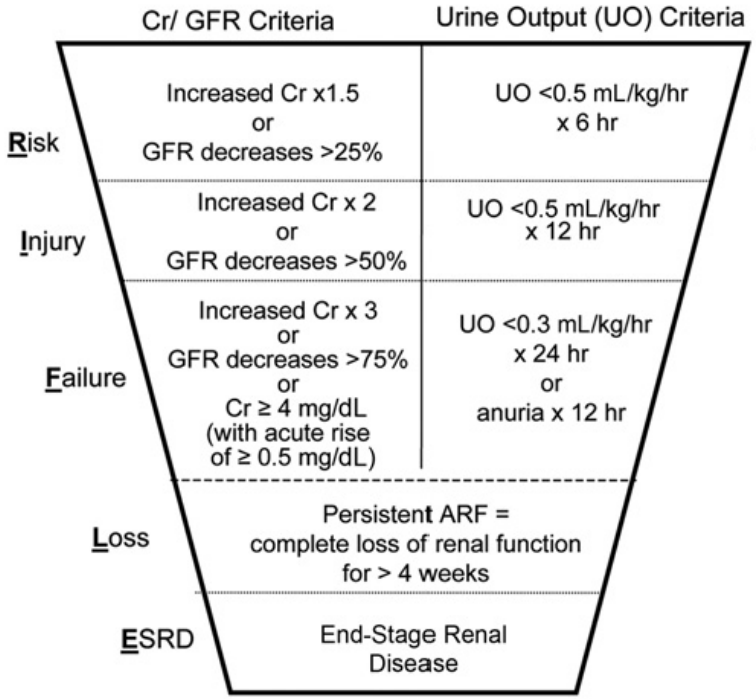
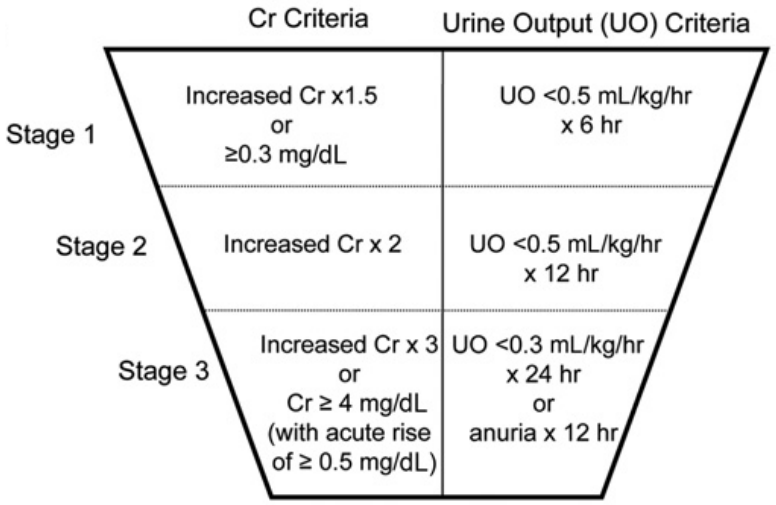
4. Diagnostic accuracy

Classification of acute kindey injury

RIFLE



AKIN

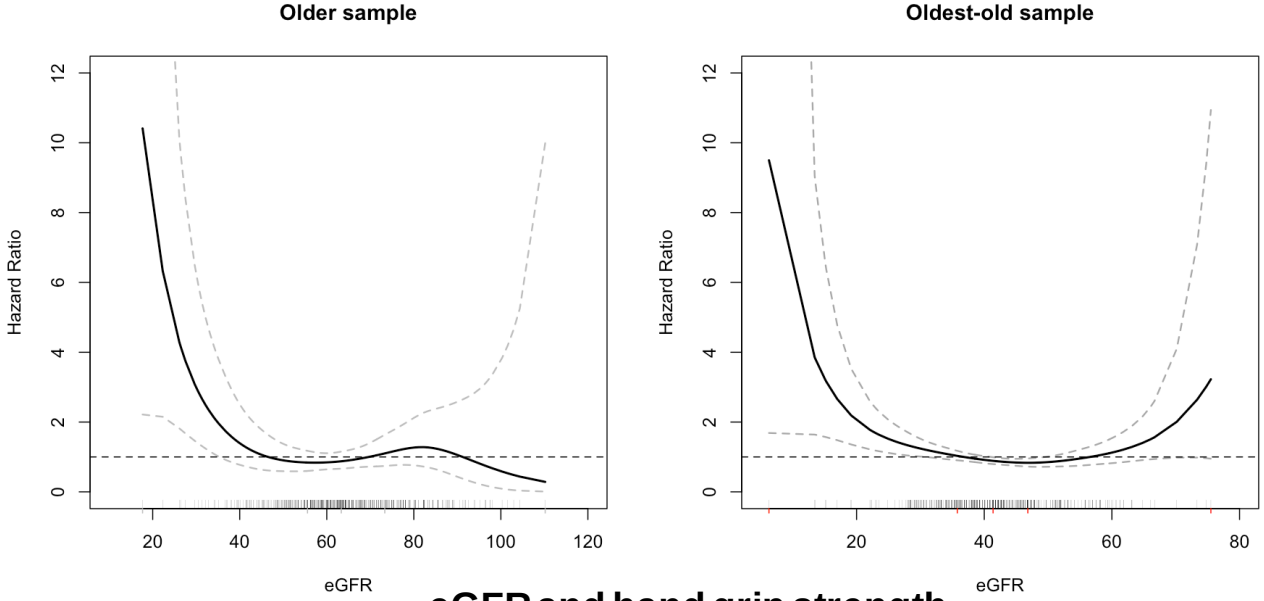


Patients who receive renal replacement therapy (RRT) are considered to have met the criteria for stage 3 irrespective of the stage that they are in at the time of commencement of RRT.

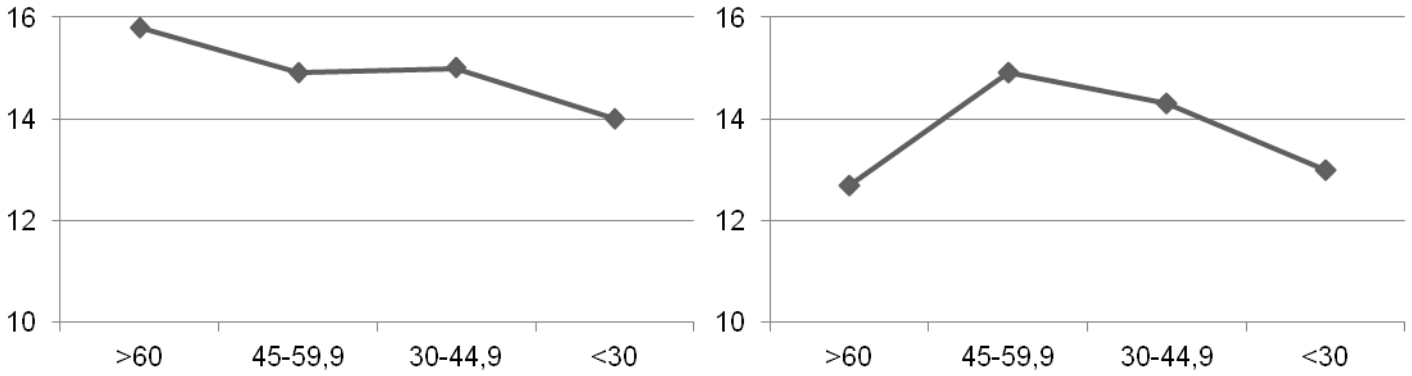
eGFR in old and oldest old people

BIS1 equation: 3736 X creatinine$^{-0.87}$ X age$^{-0.95}$ X 0.82 (if female)

eGFR and mortality



eGFR and hand grip strength



Passarino et al, 2013 *submitted*

5. Preventing nephrotoxicity

General preventing measures

- Adjust medication dosages to renal function
- Assess baseline renal function, and consider patient's renal function when prescribing a new drug.
- Avoid nephrotoxic combinations.
- Correct risk factors for nephrotoxicity before initiation of drug therapy.
- Ensure adequate hydration before and during therapy with potential nephrotoxins.
- Use equally effective non-nephrotoxic drugs whenever possible.

Shetz et al, Curr Opin Crit Care 2005
Munar & Singh, Am Fam Phys 2007
Naughton CA, AFP 2008
Bentley et al, Crit Care Med 2010
Logham-Adham et al, Expert Opin Drug Saf 2012
Bell et al, Austr Fam Phys 2013

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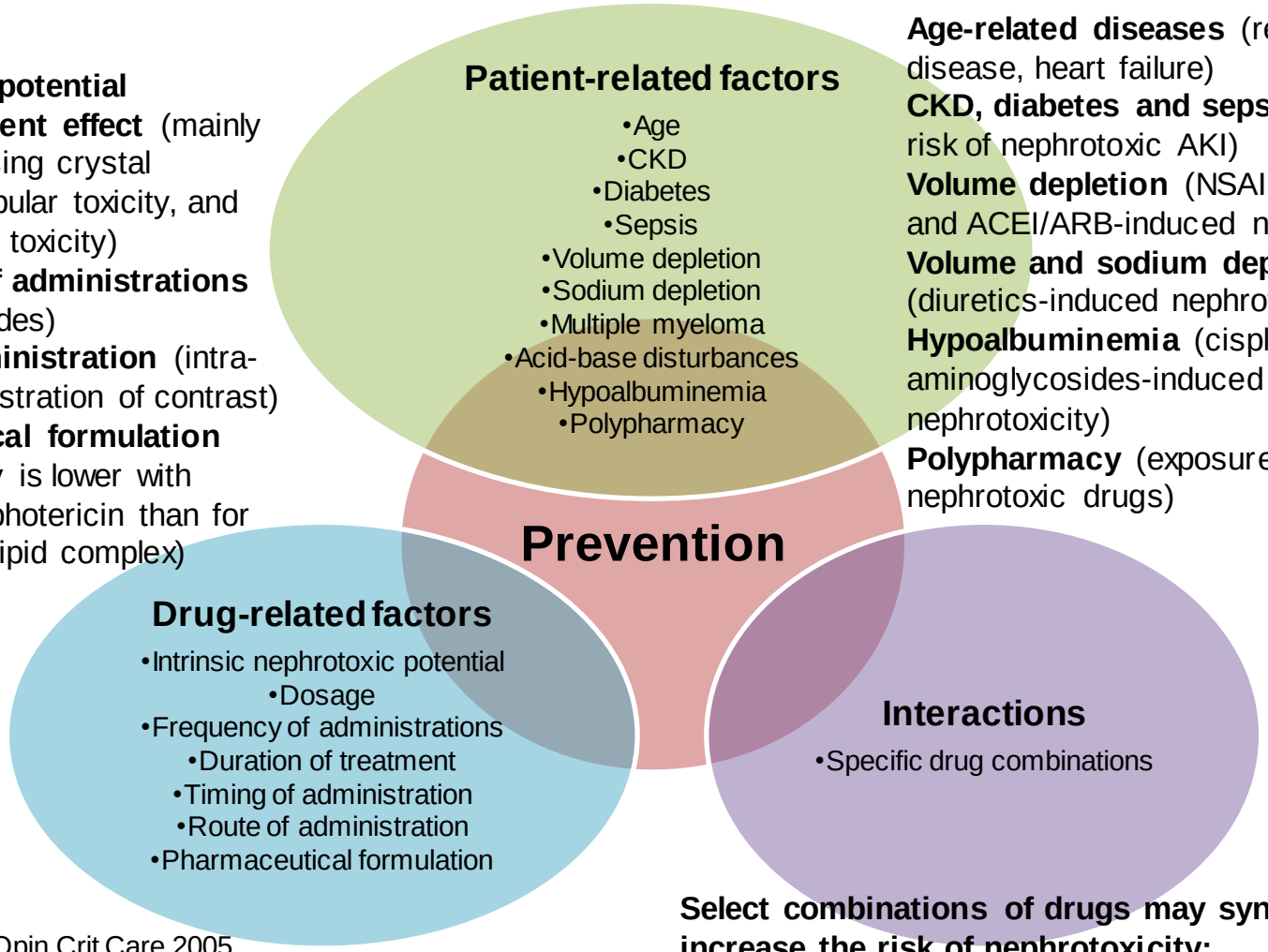
5. Preventing nephrotoxicity

Nephrotoxic potential
Dose-dependent effect (mainly for drugs causing crystal deposition, tubular toxicity, and hemodynamic toxicity)
Frequency of administrations (aminoglycosides)
Route of administration (intra-arterial administration of contrast)
Pharmaceutical formulation (nephrotoxicity is lower with liposomal amphotericin than for amphotericin lipid complex)



Age-related diseases (renovascular disease, heart failure)
CKD, diabetes and sepsis (increased risk of nephrotoxic AKI)
Volume depletion (NSAID-induced and ACEI/ARB-induced nephrotoxicity)
Volume and sodium depletion (diuretics-induced nephrotoxicity)
Hypoalbuminemia (cisplatin- and aminoglycosides-induced nephrotoxicity)
Polypharmacy (exposure to multiple nephrotoxic drugs)

Select combinations of drugs may synergistically increase the risk of nephrotoxicity:

1. Cephalosporins and aminoglycosides
2. Vancomycin and aminoglycosides
3. Cephalosporins and acyclovir

Shetz et al, Curr Opin Crit Care 2005
Munar & Singh, Am Fam Phys 2007
Naughton CA, AFP 2008
Bentley et al, Crit Care Med 2010
Logham-Adham et al, Expert Opin Drug Saf 2012
Bell et al, Austr Fam Phys 2013

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5. Preventing nephrotoxicity

Primary care pharmacists supporting drug safety in renal impairment

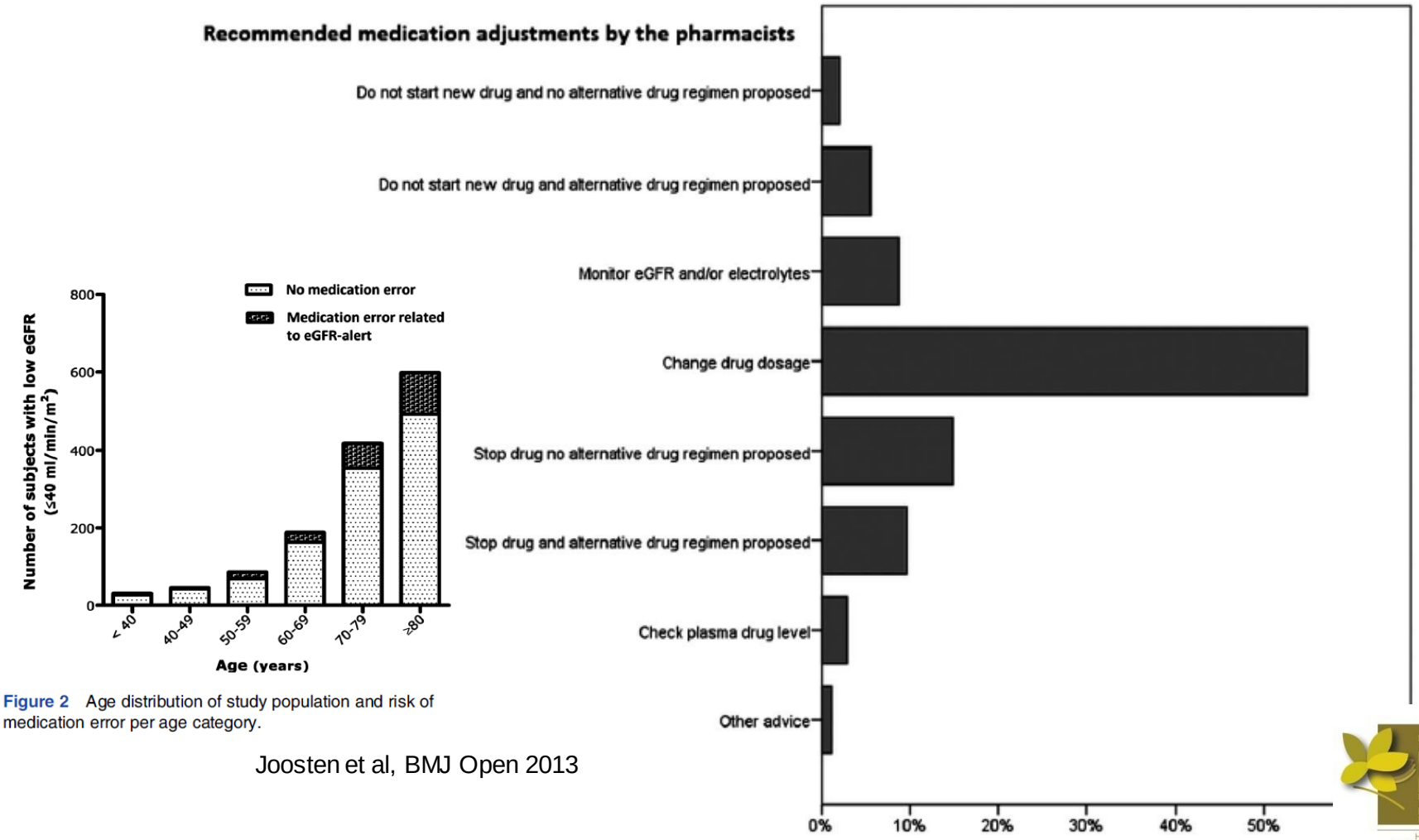

Figure 2 Age distribution of study population and risk of medication error per age category.

Joosten et al, BMJ Open 2013

5. Preventing nephrotoxicity

THE COCHRANE COLLABORATION®

Computerized advice on drug dosage to improve prescribing practice (Review)

Gillaizeau F, Chan E, Trinquart L, Colombet I, Walton RT, Rège-Walther M, Burnand B, Durieux P

Analysis 5.5. Comparison 5 Clinical adverse events, Outcome 5 Aminoglycoside antibiotics.

Review: Computerized advice on drug dosage to improve prescribing practice

Comparison: 5 Clinical adverse events

Outcome: 5 Aminoglycoside antibiotics

Study or subgroup	Intervention n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
1 Nephrotoxicity					
Begg 1989	4/22	10/23		21.0 %	0.42 [0.15, 1.14]
Burton 1991	4/75	7/75		15.0 %	0.57 [0.17, 1.87]
Destache 1990	6/75	10/70		23.0 %	0.56 [0.21, 1.46]
Leehey 1993	13/80	12/73		41.0 %	0.99 [0.48, 2.03]
Subtotal (95% CI)	**252**	**241**		**100.0 %**	**0.67 [0.42, 1.06]**

Total events: 27 (Intervention), 39 (Control)

Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 2.18$, df = 3 (P = 0.54); $I^2 = 0.0\%$

Test for overall effect: Z = 1.73 (P = 0.084)

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6. Take home messages

- La nefrotossicità è un problema molto frequente e pericoloso in età geriatrica
  - frequente esposizione a farmaci e combinazioni farmacologiche potenzialmente nefrotossiche nel paziente anziano complesso
- Aumenta il rischio di mortalità, declino funzionale e progressivo peggioramento della funzione renale
- Molti aspetti necessitano di ulteriori studi
  - …individuare biomarcatori dotati di maggiore accuratezza diagnostica in una popolazione così eterogenea
  - …migliorare l'accuratezza diagnostica delle equazioni GFR
  - …aumentare la consapevolezza sull'esposizione (combinazioni pericolose di farmaci) e migliorare le metodiche di prevenzione (collaborazione con farmacisti, prescrizione assistita)

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