藥物對腎臟功能的影響

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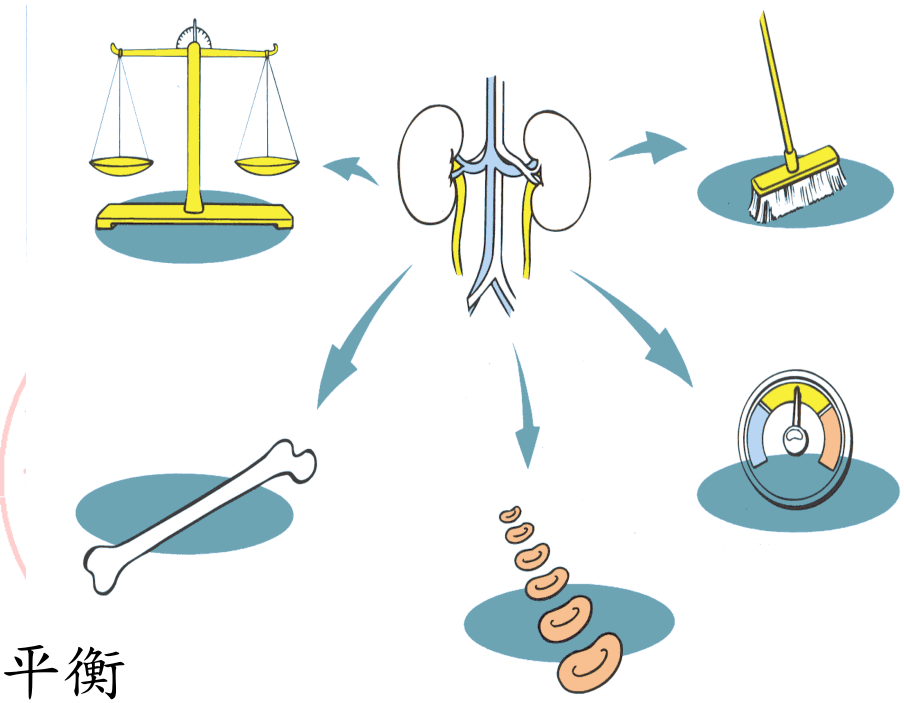
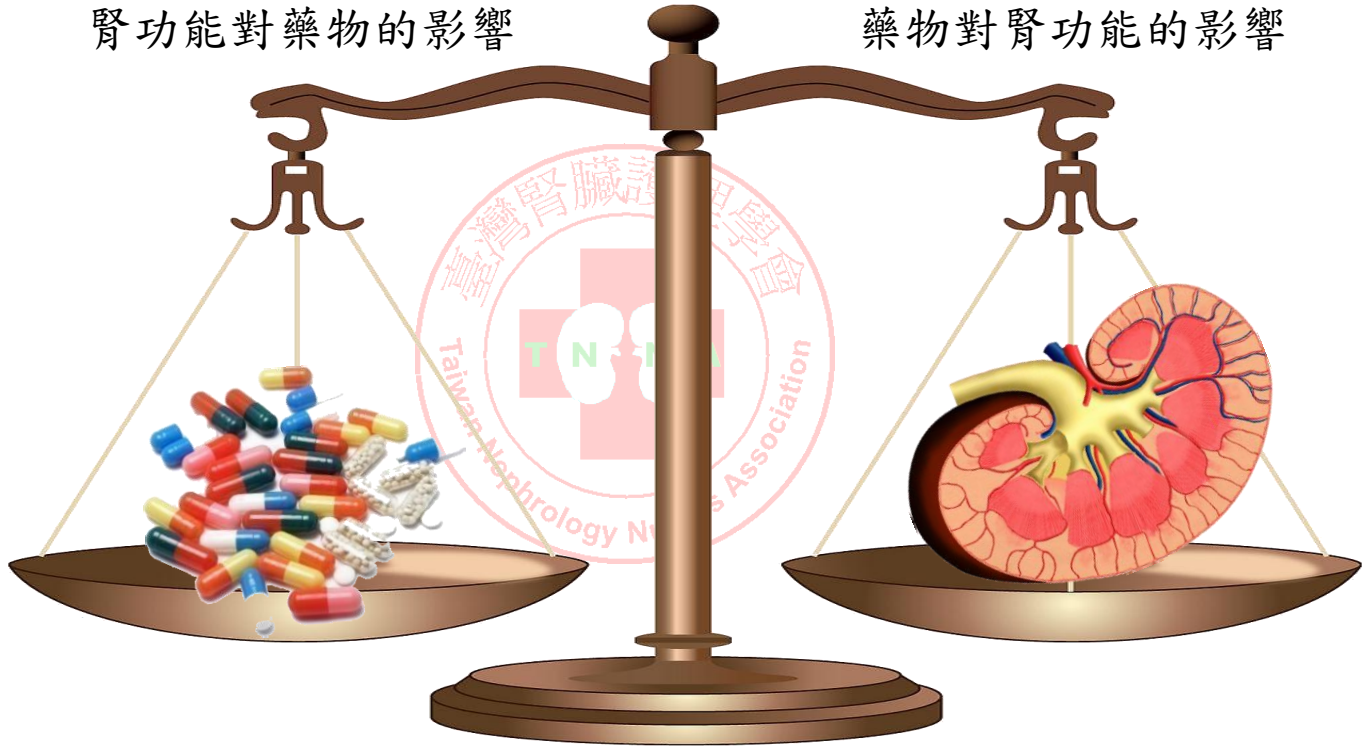
腎臟的功能

- 清除廢物與毒素
- 控制血壓
- 維持體液平衡
- 維持電解質平衡
- 調節酸鹼平衡
- 製造紅血球生成激素
- 強化骨骼
- 活化維生素D，保持鈣磷平衡



藥物與腎功能



藥物對腎功能的影響

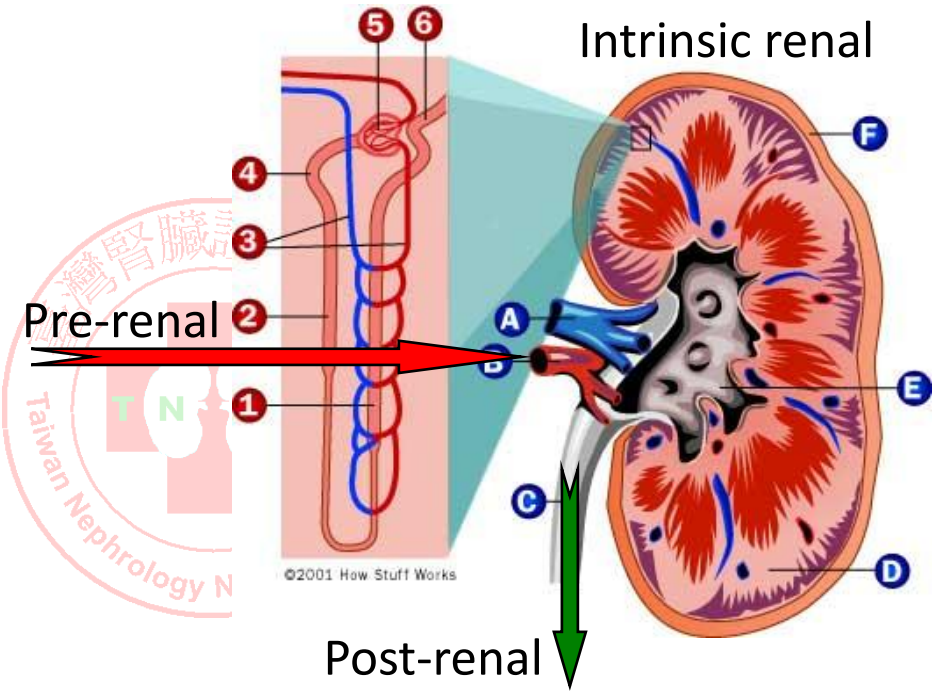
- 腎絲球濾過量（清除毒素）
- 體液量平衡
- 電解質平衡
- 酸鹼平衡
- 血壓調控
- 骨質健康
- 造血功能

藥物對腎絲球濾過量 (GFR) 的影響

- 短期影響
  - 減少腎絲球濾過量 (GFR) ：急性腎損傷 (AKI)
  - 增加腎絲球濾過量 (GFR)
- 長期影響
  - 減少腎絲球濾過量下降速率 (decline in GFR)

急性腎損傷 (AKI) 之分類

- 腎前性 (Pre-renal)
- 腎性 (Intrinsic renal)
- 腎後性 (Post-renal)



藥物引發之急性腎損傷：腎前性 (Pre-renal)

- Prerenal AKI:
  - The most common cause of AKI
  - An appropriate physiologic response to renal hypoperfusion
- Mechanisms of prerenal AKI:
  - Intravascular volume depletion
  - Decreased cardiac output
  - Renal vasoconstriction
  - Specific settings: impaired autoregulation and/or GFR

Drug-induced prerenal AKI

- Intravascular volume depletion
  - Laxatives, drugs inducing diuresis
- Decreased cardiac output
  - Antihypertensives (β-blockers, CCB), anesthetics
- Renal vasoconstriction
  - Norepinephrine, ergotamine
- Specific settings: impaired autoregulation and/or GFR
  - Angiotensin-converting enzyme inhibitors in renal artery stenosis
  - Inhibition of prostaglandin synthesis by NSAID's

藥物引發之急性腎損傷：腎性 (Intrinsic)

- 80% to 90% of intrinsic AKI: Ischemic ATN and toxic ATN
- Mechanisms of intrinsic renal AKI:
  - Diseases involving large renal vessels
  - Diseases of the renal microvasculature and glomeruli
  - Ischemic and nephrotoxic ATN
  - Other acute processes involving the tubulointerstitium

Drug-induced intrinsic renal AKI

- Ischemic ATN: due to volume depletion and/or low cardiac output
- Nephrotoxic ATN:
  - Antibiotics: acyclovir, aminoglycosides
  - Chemotherapeutic agents: cisplatin, etc
  - NSAIDs, including COX-II inhibitors
  - Cyclosporin / tacrolimus
  - Radiocontrast agents
- Drug-Induced Allergic Interstitial Nephritis
  - β-Lactams and other Antibiotics
  - NSAIDs
  - Others: α-methyldopa, allopurinol, etc

藥物引發之急性腎損傷：腎後性 (Post-renal)

- Urinary tract obstruction accounts for less than 5% of AKI
- The most common cause: obstruction of bladder neck
- Mechanisms of postrenal AKI:
  - Ureteric obstruction
  - Bladder neck obstruction
  - Urethral obstruction

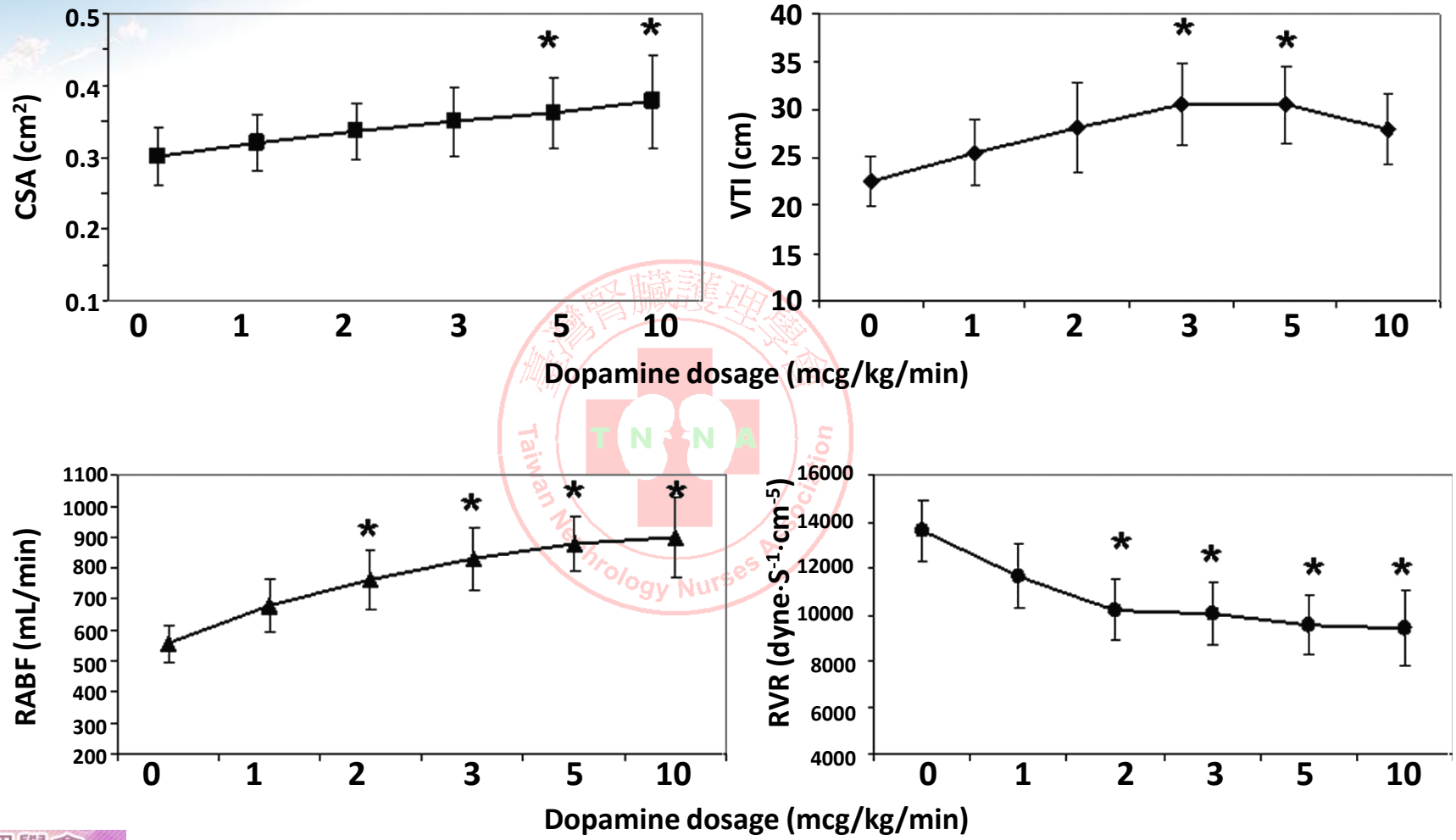
Drug-induced postrenal AKI

- Ureteric obstruction
  - NSAIDs: sloughed renal papillae
- Bladder neck obstruction
  - Tricyclic antidepressants
  - Ganglion blockers
  - Anti-histamines

增加腎絲球濾過量 (GFR) 的藥物

- 藥物對腎絲球濾過量 (GFR) 之影響：
  - 主要係經由增加腎血流量 (Renal blood flow, RBF) 而來
  - 可增加心輸出量 (Cardiac output) 之藥物亦可能增加 RBF
  - Dopamine
  - Dobutamine
  - Digitalis
- Increase RBF = enhance GFR (?)

Renal hemodynamic and dopamine dosage



Elkayam U, et al., *Circulation*. 2008; 117(2): 200-205

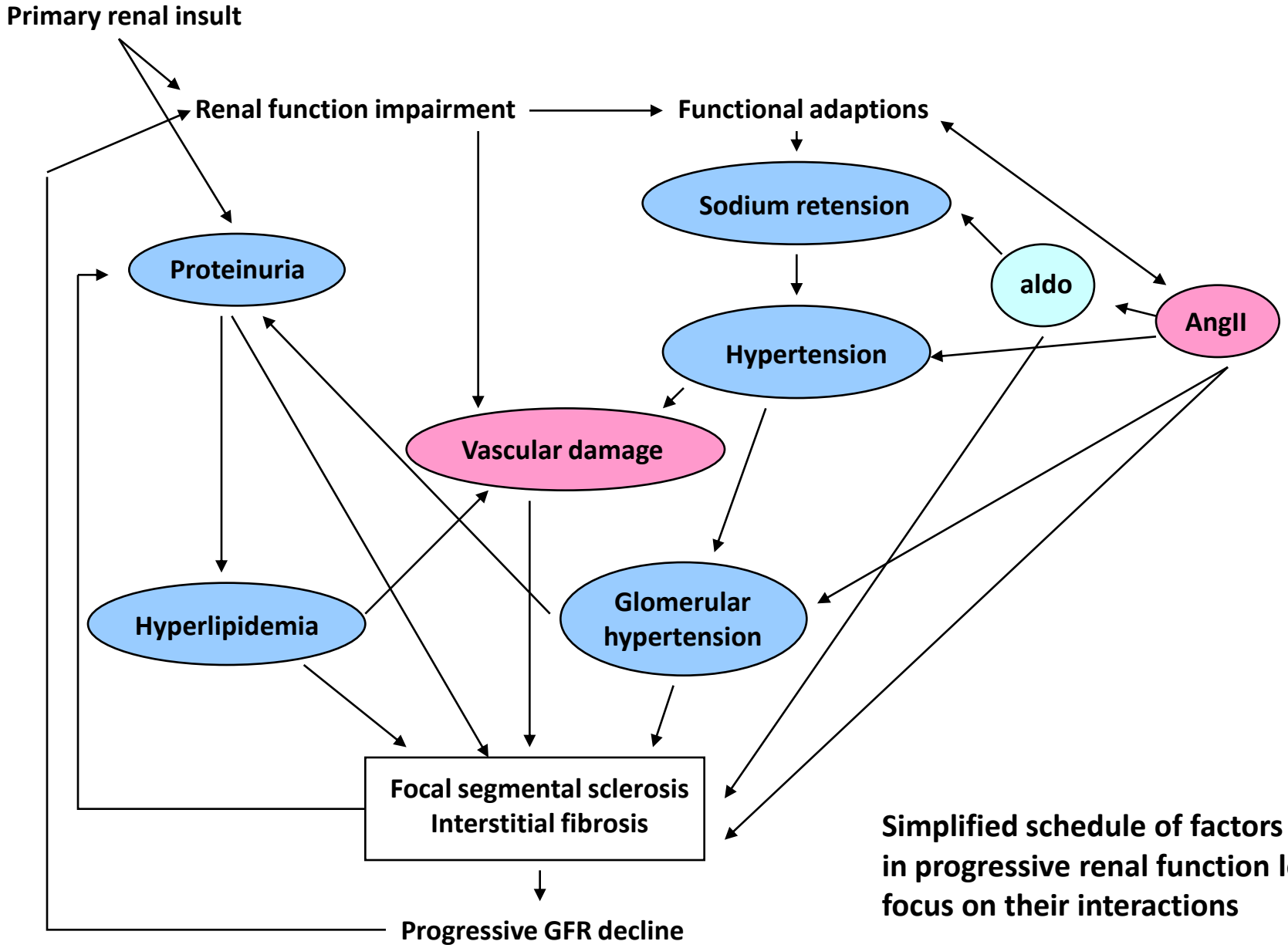
Renal Vasodilatory Action of Dopamine in Patients With Heart Failure

- Dopamine is associated with an increase in renal blood flow in patients with heart failure, due to dilation of both the large conductance and small resistance renal blood vessels.
- Further evaluation of the efficacy and safety of dopamine for improvement of renal function is warranted.

Elkayam U, et al., *Circulation*. 2008; 117(2): 200-205

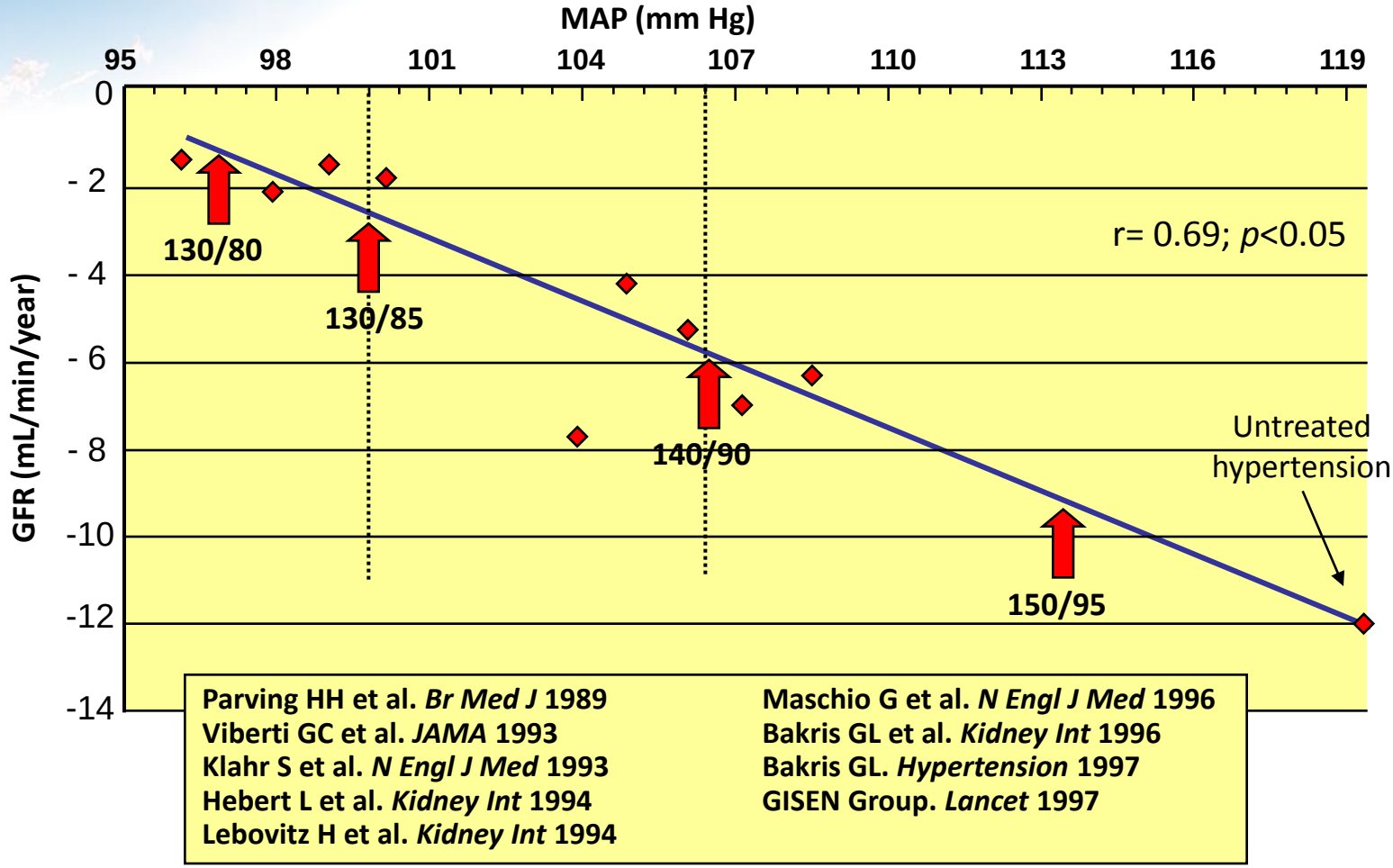
藥物對腎絲球濾過量 (GFR) 的長期影響
腎臟保護作用 (Renal Protection)

- 腎絲球濾過量 (GFR) 隨年齡增加而降低
- 慢性腎病 (CKD) 病患之 GFR 下降速率較常人為高
- 藥物可減緩腎功能惡化速率
  - Angiotensin-I convertizing enzyme inhibitors
  - Angiogensin-II AT1 receptor blockers



Simplified schedule of factors involved in progressive renal function loss, with focus on their interactions

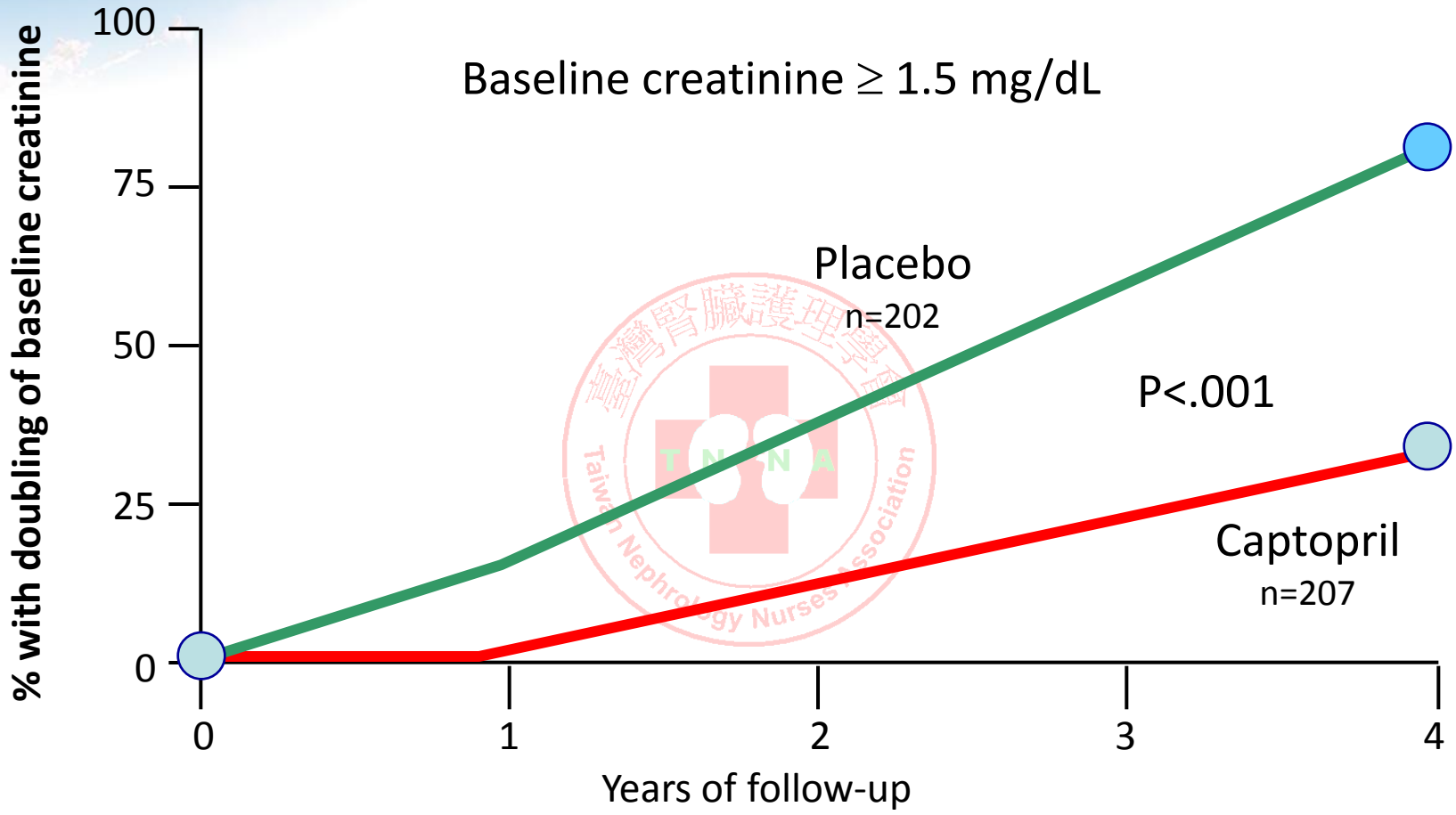
Relationship between achieved BP control and GFR decline in clinical trials of renal disease



Parving HH et al. *Br Med J* 1989
Viberti GC et al. *JAMA* 1993
Klahr S et al. *N Engl J Med* 1993
Hebert L et al. *Kidney Int* 1994
Lebovitz H et al. *Kidney Int* 1994
Maschio G et al. *N Engl J Med* 1996
Bakris GL et al. *Kidney Int* 1996
Bakris GL. *Hypertension* 1997
GISEN Group. *Lancet* 1997

Bakris GL, et al., *Am J Kindey Dis* 2000, 36(3): 646-661

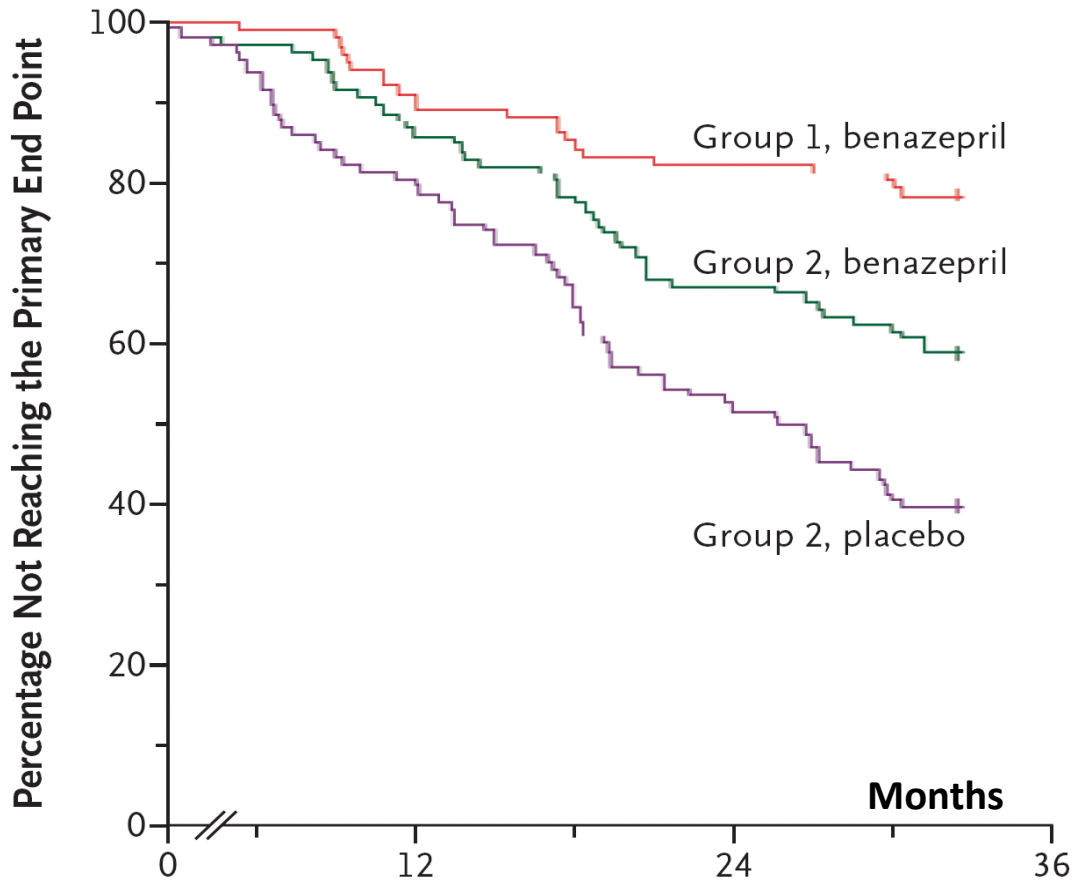
ACE-I is More Renoprotective in Type 1 diabetes



Lewis EJ, et al. *N Engl J Med*. 1993;329(20):1456-1462

ESBARI Study: Primary End Point

Primary End Point:
*** Doubling of SCr**
*** ESRD**
*** Death**

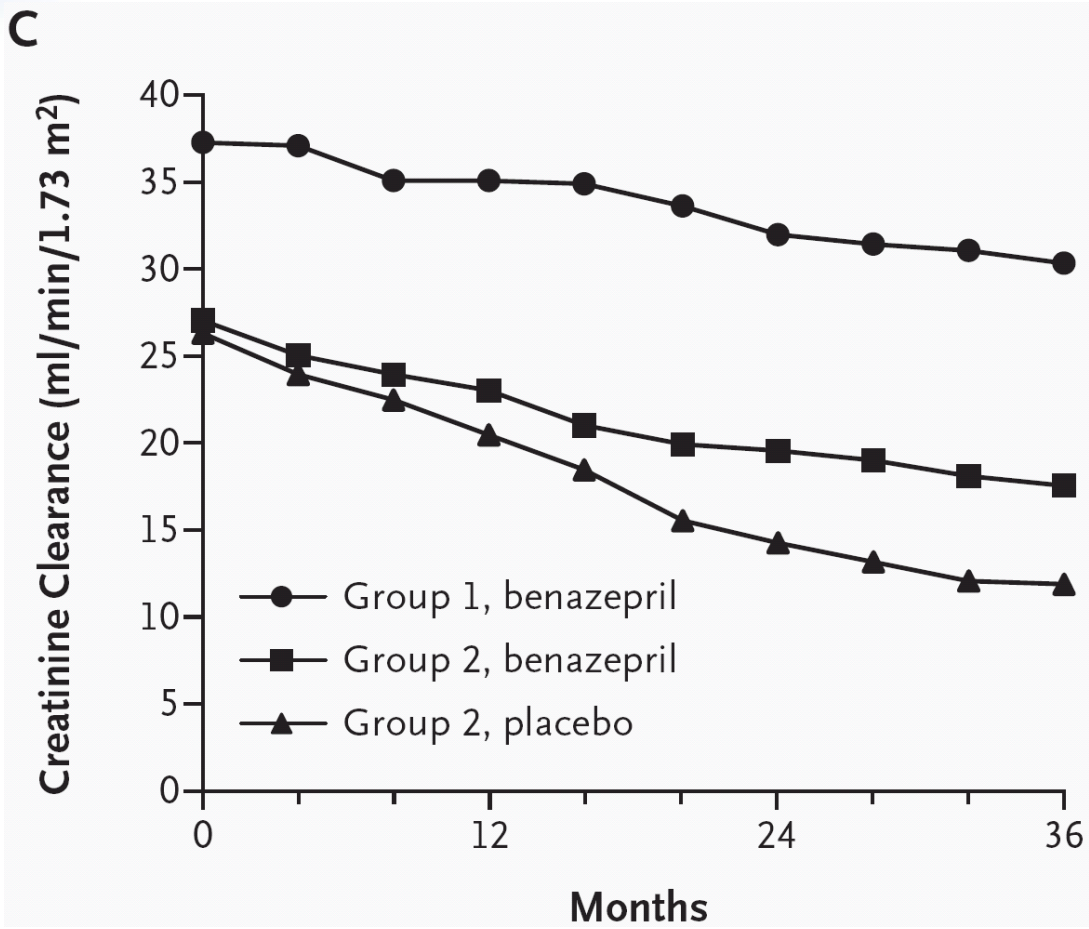


Risk reduction 43%

Group 1 serum creatinine level of 1.5 to 3.0 mg/dl
Group 2 serum creatinine level of 3.1 to 5.0 mg/dl at baseline.

Hou FF, Zhang X, et al; *N Engl J Med* 2006; 354: 131-40

ESBARI Study: change in decline of CCr



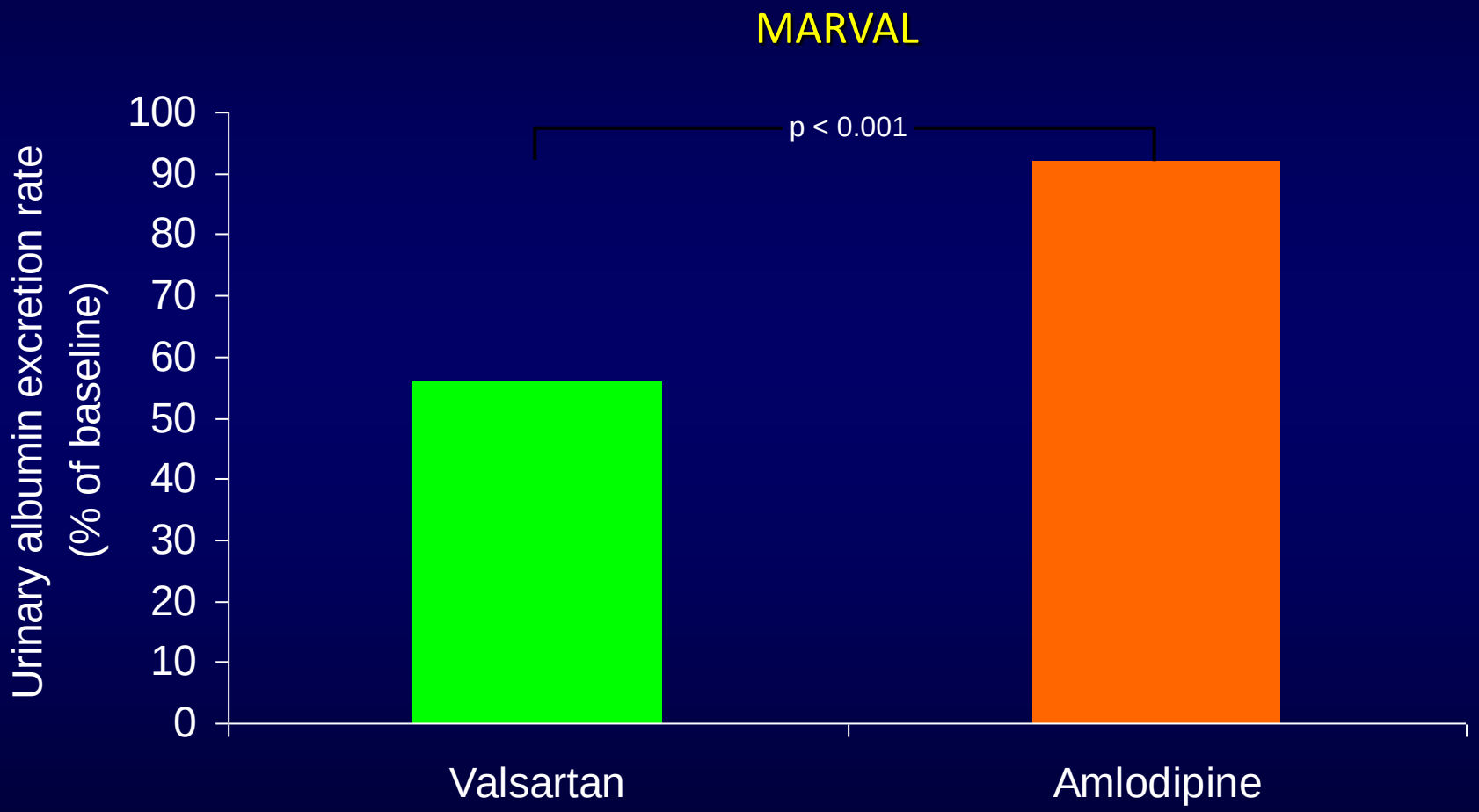
23%

Group 1 serum creatinine level of 1.5 to 3.0 mg/dl
Group 2 serum creatinine level of 3.1 to 5.0 mg/dl at baseline.

Hou FF, Zhang X, et al; *N Engl J Med* 2006; 354: 131-40

ARBs prevent diabetic renal disease progression

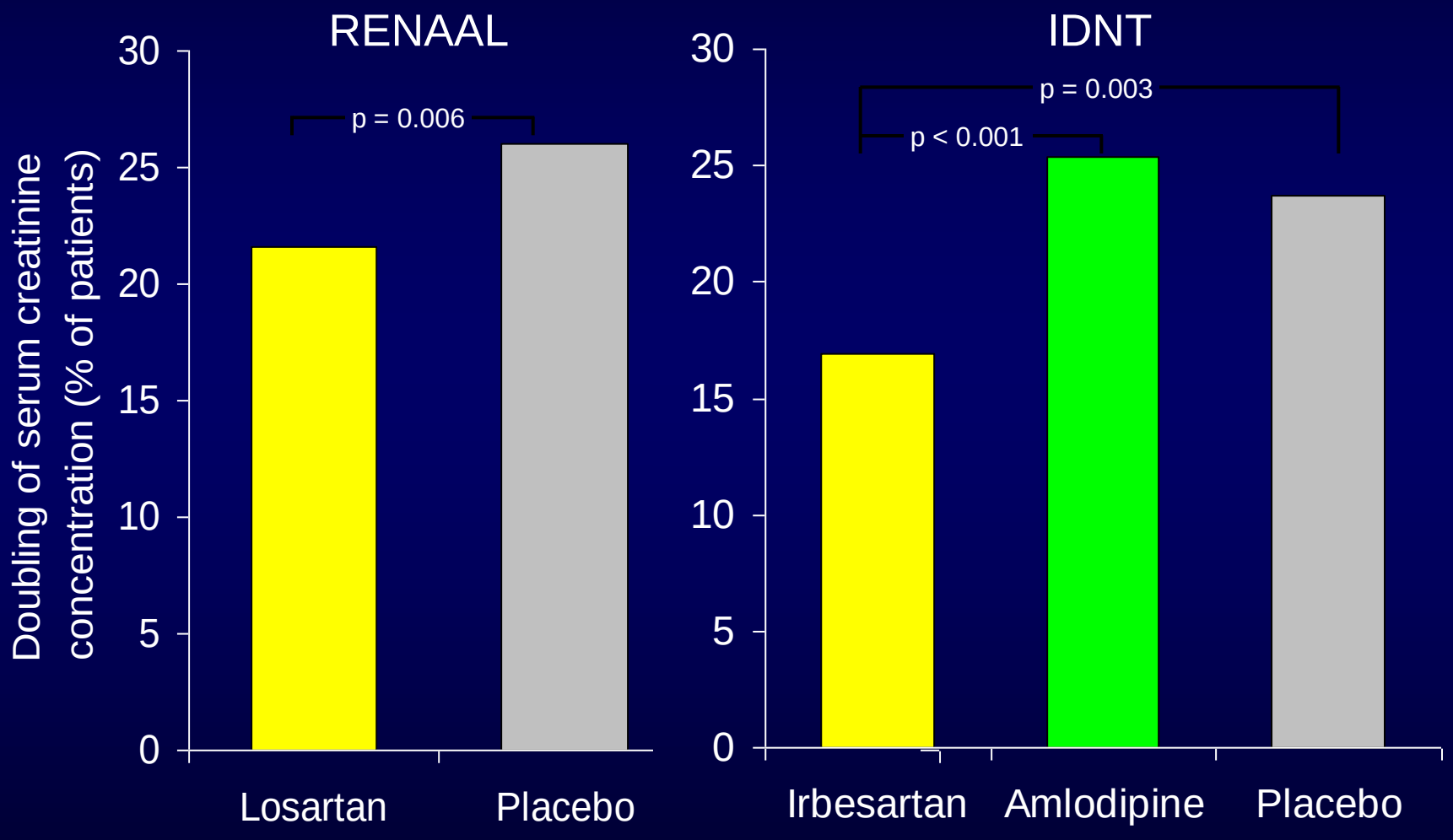
Albumin excretion in patients with microalbuminuria



Viberti et al. *Circulation* 2002;106:672–678

ARBs prevent diabetic renal disease progression

Serum creatinine in patients with macroproteinuria



Brenner et al. *N Engl J Med* 2001;345:861–869.

Lewis et al. *N Engl J Med* 2001;345:851–860

藥物對腎功能的影響

- 腎絲球濾過量（清除毒素）
- 體液量平衡
- 電解質平衡
- 酸鹼平衡
- 血壓調控
- 骨質健康
- 造血功能

藥物對體液、電解質、酸鹼平衡的影響

- 腎臟：調節體液、電解質、酸鹼平衡的主要器官
- 藥物對體液、電解質、酸鹼平衡的影響：
  - 輸液
  - 利尿劑
  - 作用於水通道 (Water channel) 藥物：Desmopressin, etc

利尿劑 (Diuretics)

Diuretics

- Di-: A form of dia- before a vowel

  Dia- from **ancient Greek** prefix διᾰ (*dia-*)

  means “through, across, by, over”
- -uretic: Suffix, means “urine”

Diuretics: Definitions

- Diuretic:

  Substance that promotes the excretion of urine
  - ADH antagonist: Conivaptan, Tolvaptan, lithium
  - Inotrophic agents: digitalis
- Natriuretic:

  Substance that promotes the renal excretion of sodium

Diuretics:

Classification & Mechanism

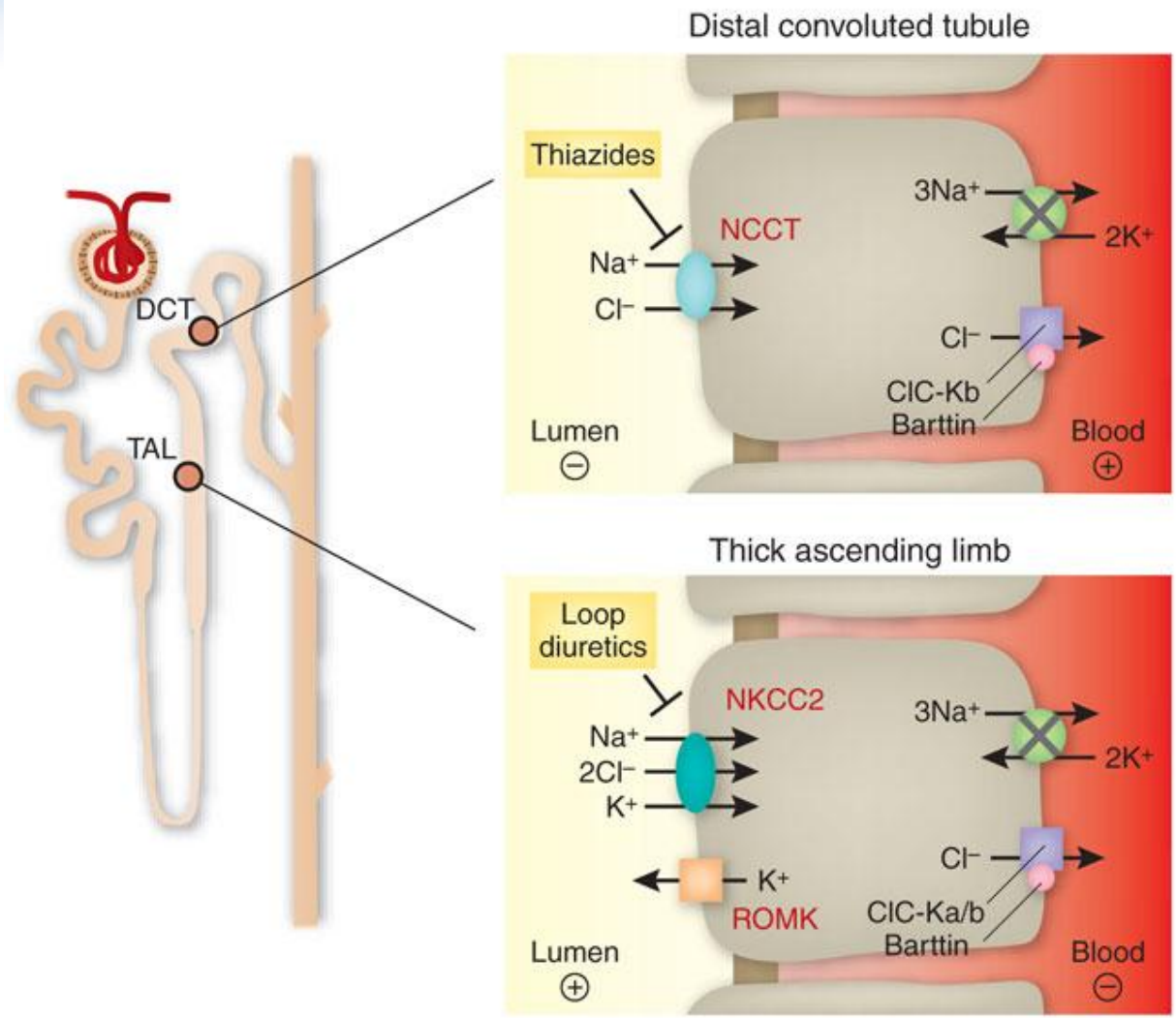
Types of Diuretics

- High ceiling vs. low ceiling diuretics
- Thiazides
- Potassium-sparing diuretics
- Calcium-sparing diuretics
- Osmotic diuretics

High ceiling (loop) diuretics

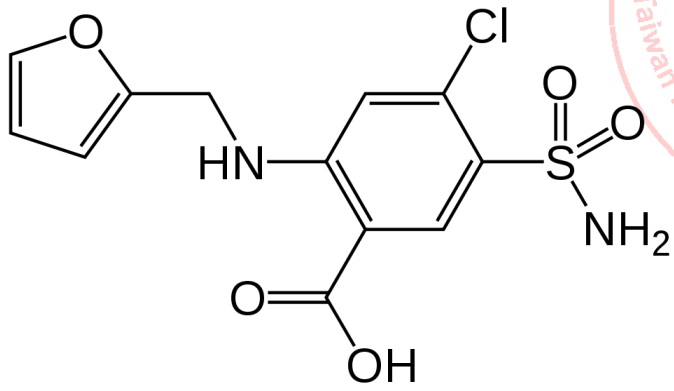
- May cause a substantial diuresis – up to 20% of the filtered load of NaCl and
- Loop diuretics: often synonymous with high ceiling diuretics
  - Furosemide
  - Ethacrynic acid
  - Torsemide
  - Bumetanide

Mechanisms of Action: Loop diuretics

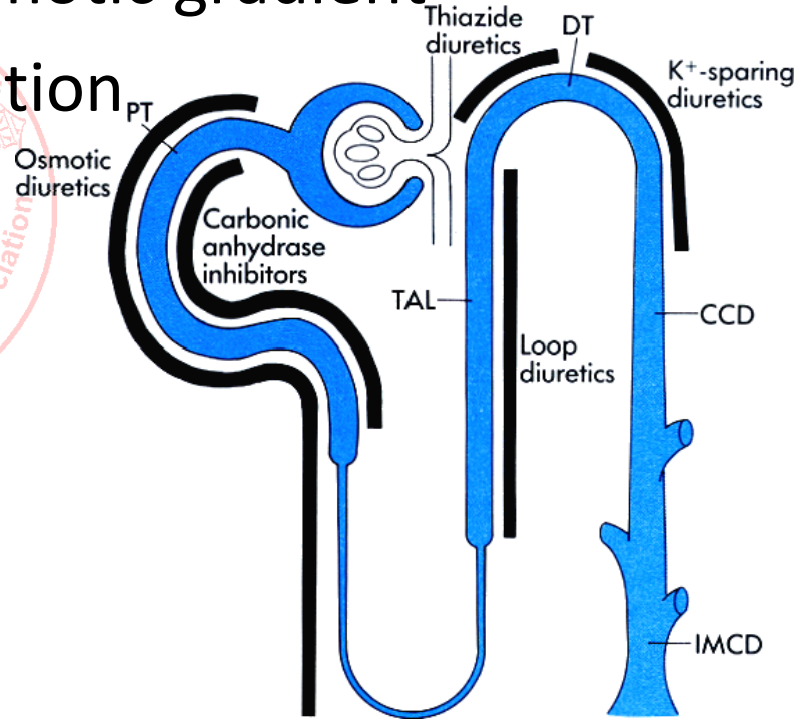


Furosemide

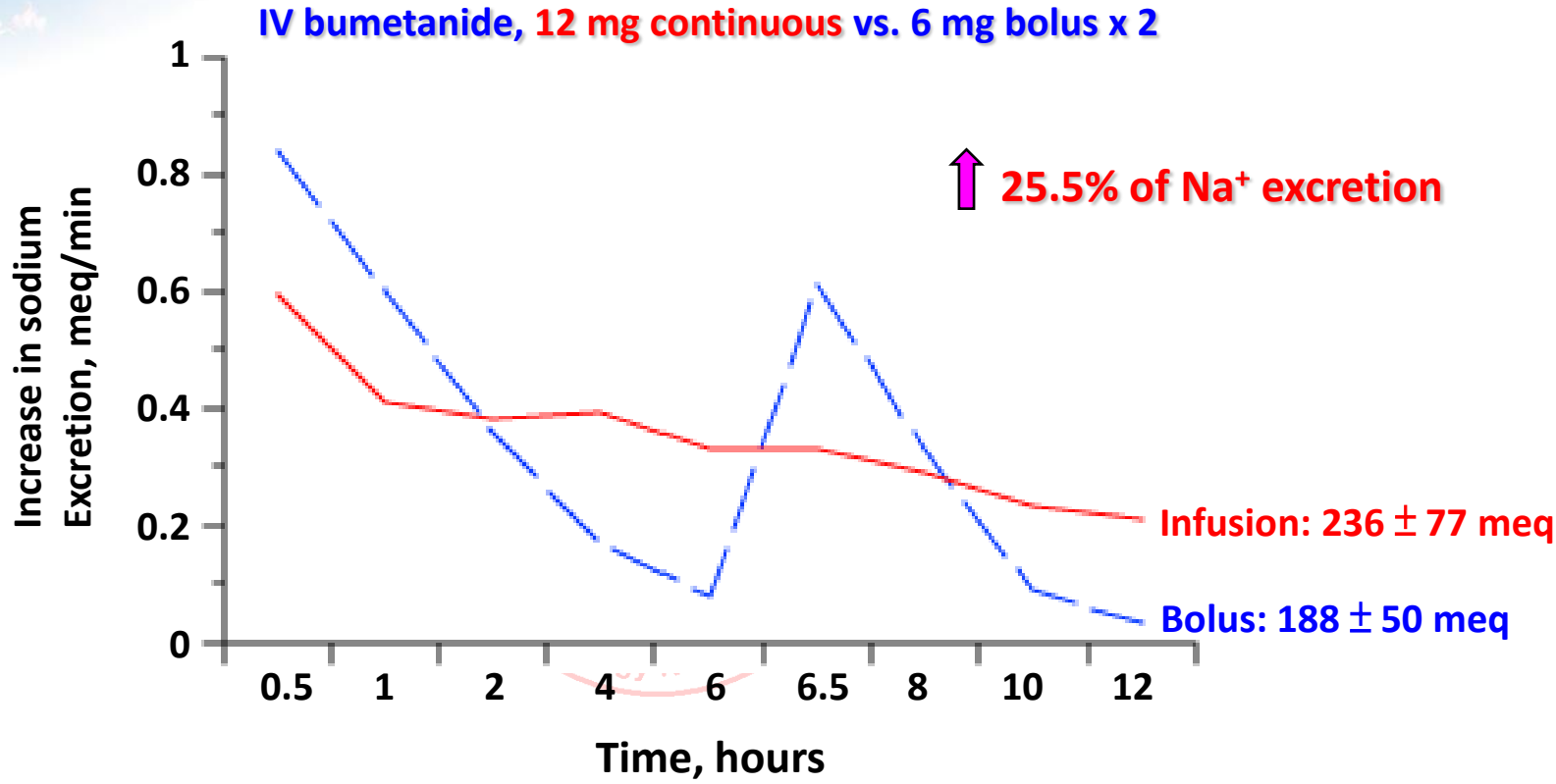
- The name Lasix derived from the phrase "**la**sts **six** (hours)"
- Inhibiting Na-K-2Cl symporter in the thick ascending limb
- Abolishes the corticomedullary osmotic gradient
- Increase in K^+, Mg^{++} and Ca^{++} excretion



Furosemide



Peak diuresis after first dose of loop diuretic



8 patients, mean CCr 16.8 (range 9.0~28.2 ml/min), Indiana, U.S.A.

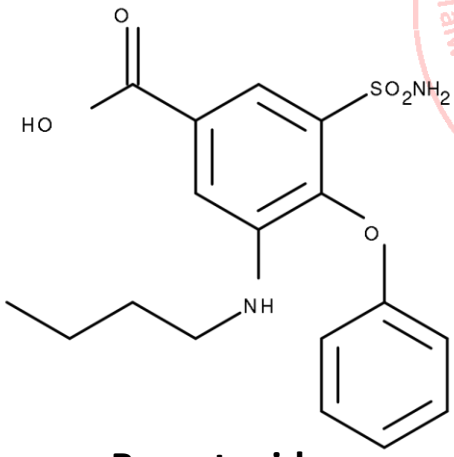
Continuous infusion: 30% greater increase in Na^+ excretion

Peak natriuretic response: 25% less than the first bolus

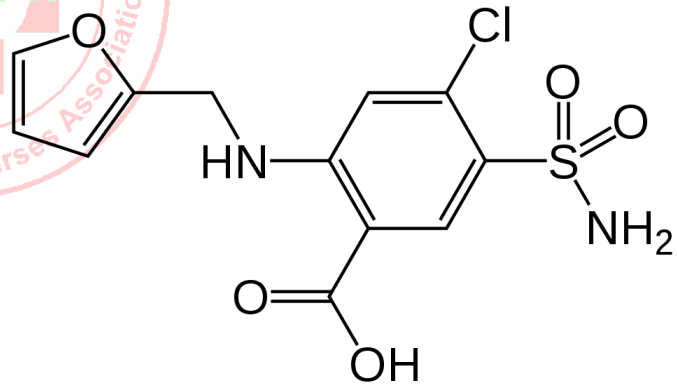
Rudy DW, et at., *Ann Intern Med* 115(5): 360-66, 1991

Bumetanide

- Often used when high doses of furosemide are ineffective
- 40 times more potent than furosemide (normal renal function)
- Dosage: PO 0.5 to 2 mg/day as a single dose;
  IV 0.5 to 1 mg over 1 to 2 minutes, MAX dose 10 mg/day



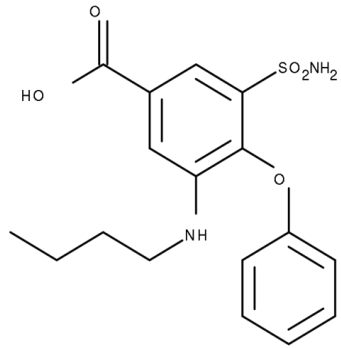
Bumetanide



Furosemide

Furosemide vs. Bumetanide

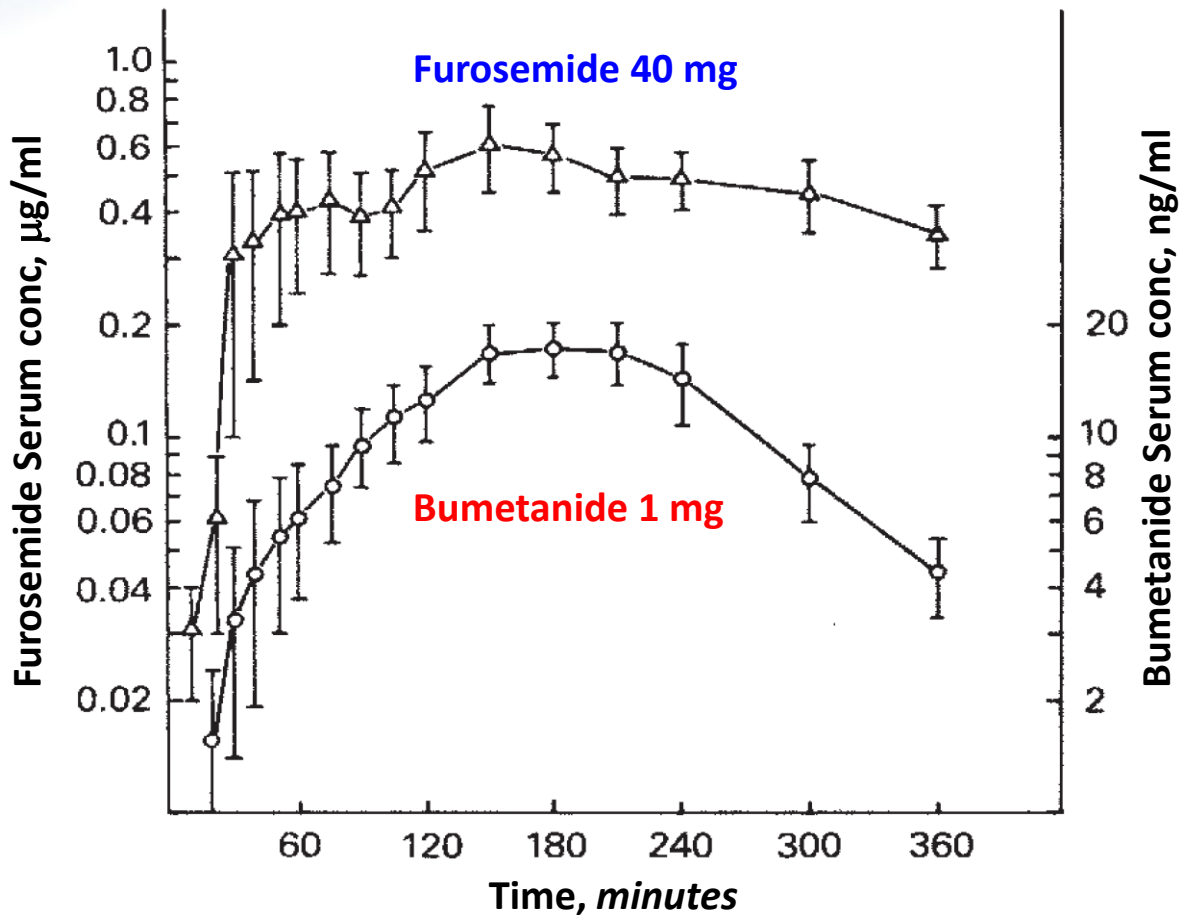
- Furosemide:
  - incompletely absorbed in the intestine (60%)
  - Inter- and intraindividual differences in bioavailability (10-90%)
- Bumetanide:
  - completely absorbed (80%)
  - absorption not altered when taken with food
  - predictable absorption, more predictable effect



Bumetanide

Brunton, Laurence et al. Goodman & Gilman's The Pharmacological Basis of THERAPEUTICS. 11th ed. 2006. 749-753

Serum conc. versus time of bumetanide & furosemide



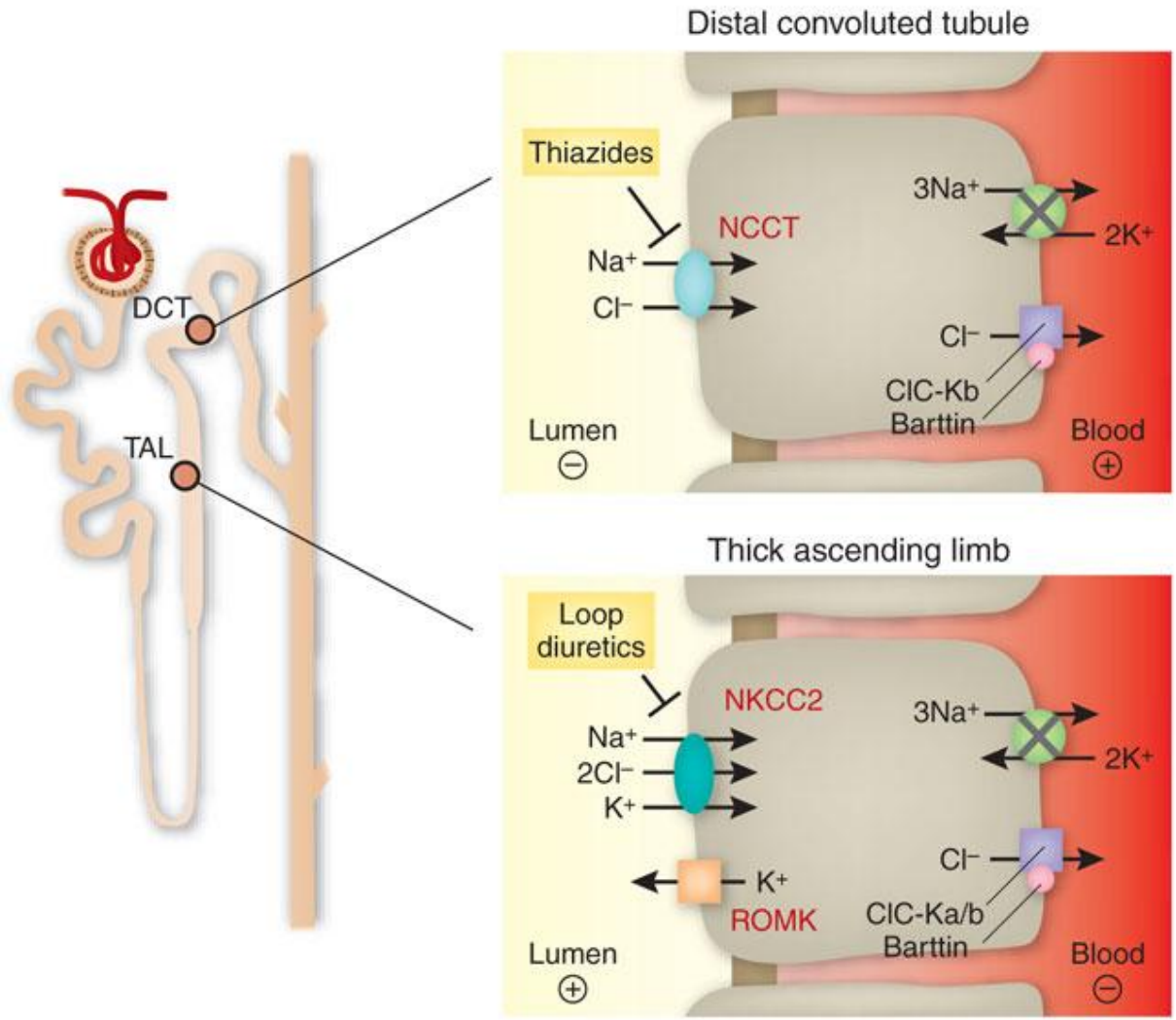
20 stable, compensated CHF patients, Texas, U.S.A.

Brater DC, Day B, et at, *Kidney Int* 26(2): 183-9, 1984

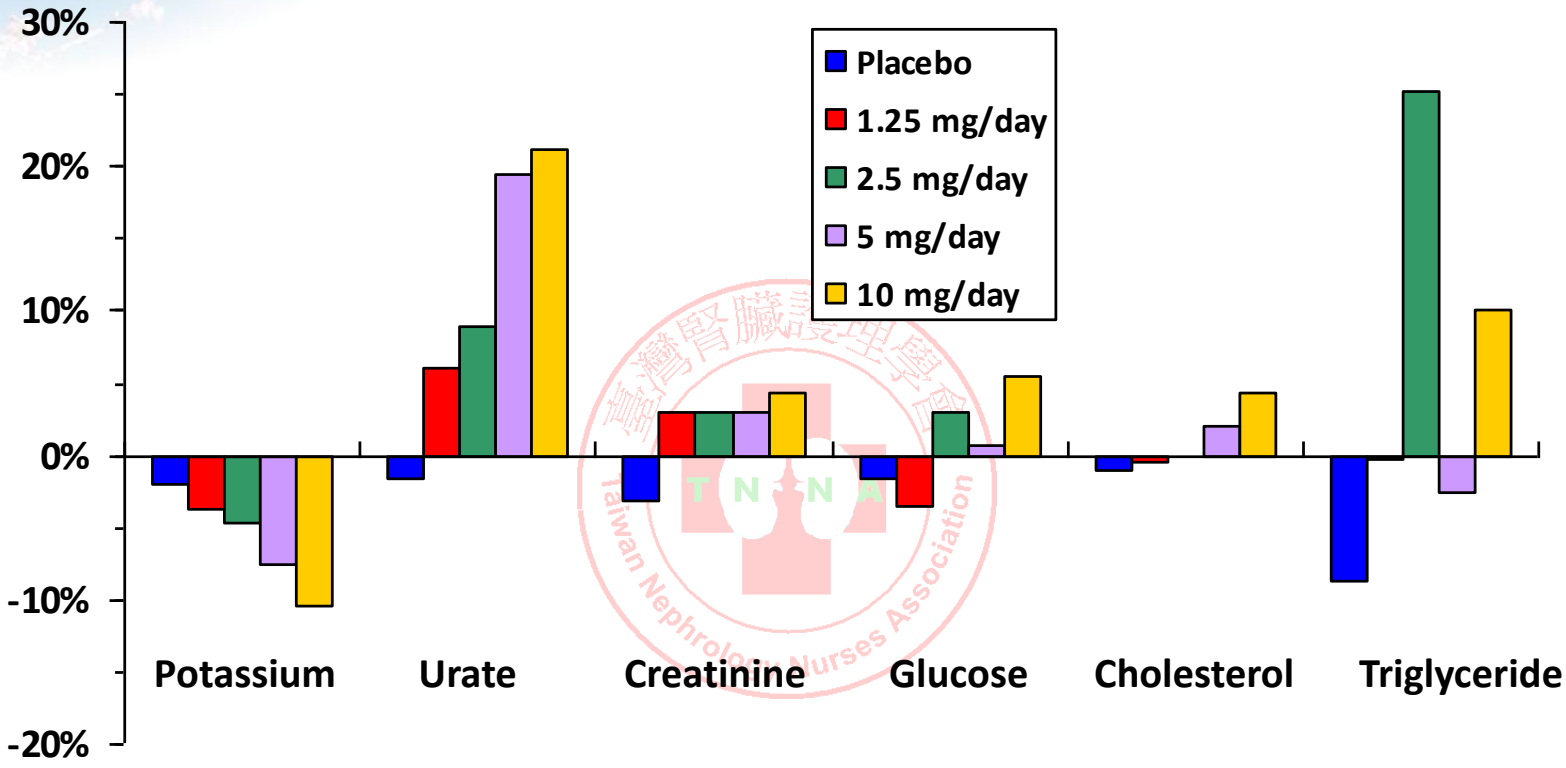
Thiazide diuretics

- Lower BP by inducing sodium and fluid loss
- Have a greater antihypertensive effect than the loop diuretics in normal renal function; maybe related to the longer duration of action
- Promote calcium retention

  (Loop diuretics enhance urinary calcium loss)
- Also cause loss of potassium & increase in serum uric acid
- Ineffective among patients with GFR < 30 mL/min


Distal convoluted tubule
Thiazides
NCCT
Na+
Cl−
3Na+
2K+
Cl−
ClC-Kb
Barttin
Lumen
Blood
Thick ascending limb
Loop diuretics
NKCC2
Na+
2Cl−
K+
3Na+
2K+
Cl−
K+
ROMK
ClC-Ka/b
Barttin
Lumen
Blood
DCT
TAL

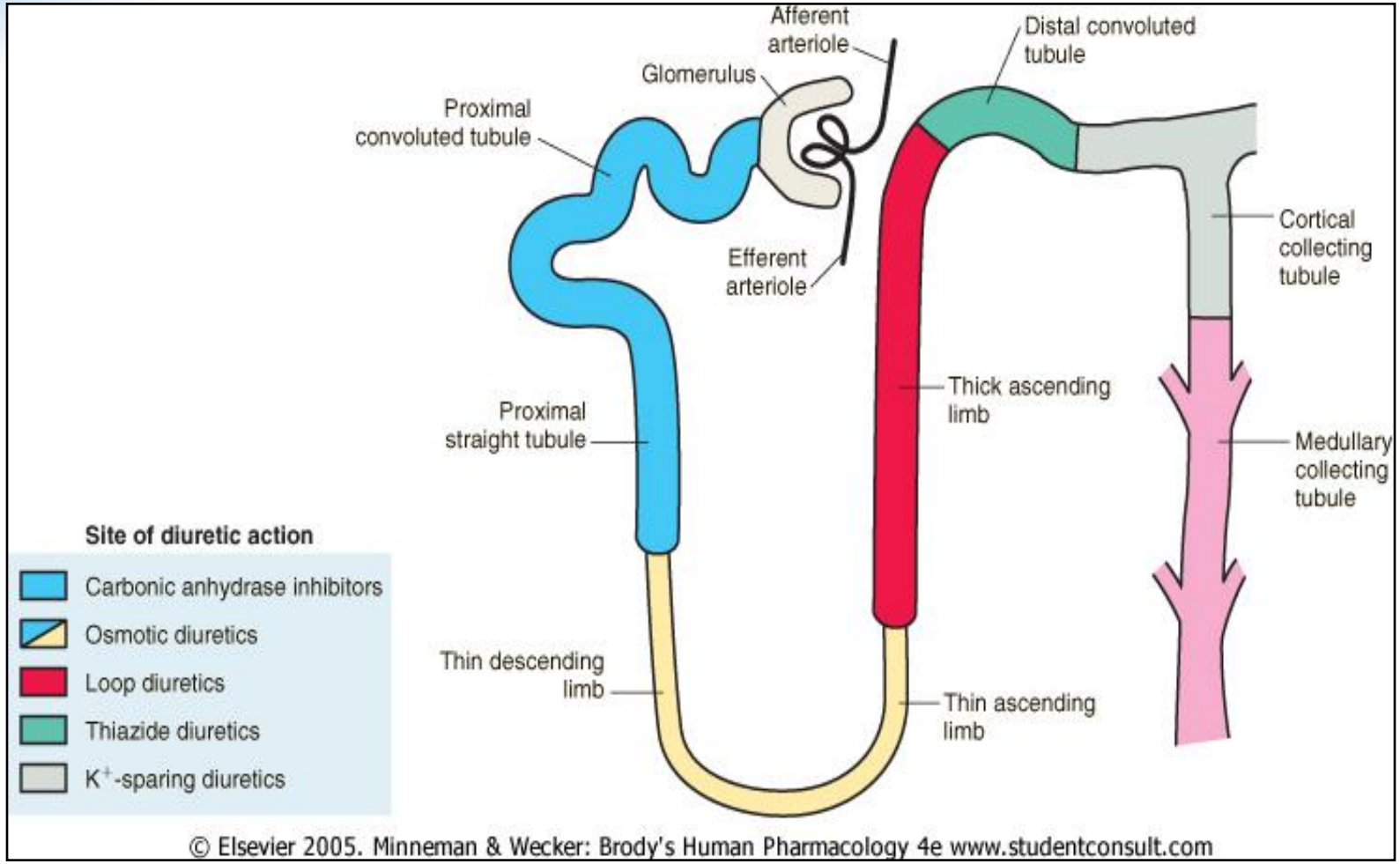
Dose-dependence of thiazide-induced side effect



Bendrofluazide (multiply by 10 to get equivalent doses of hydrochlorothiazide)
257 hypertension patients for 12 weeks in Zealand, Denmark

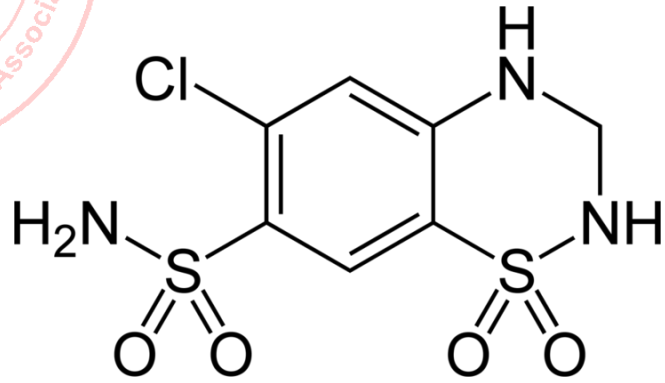
Carlsen JE, Kober L, et al, *BMJ* 300: 975-78, 1990

Hyponatremia: thiazide vs. loop diuretics



Hydrochlorothiazide

- A first line diuretic drug of the thiazide class
- Used in the treatment of hypertension, congestive heart failure, symptomatic edemas
- Calcium-sparing diuretic: prevention of kidney stones

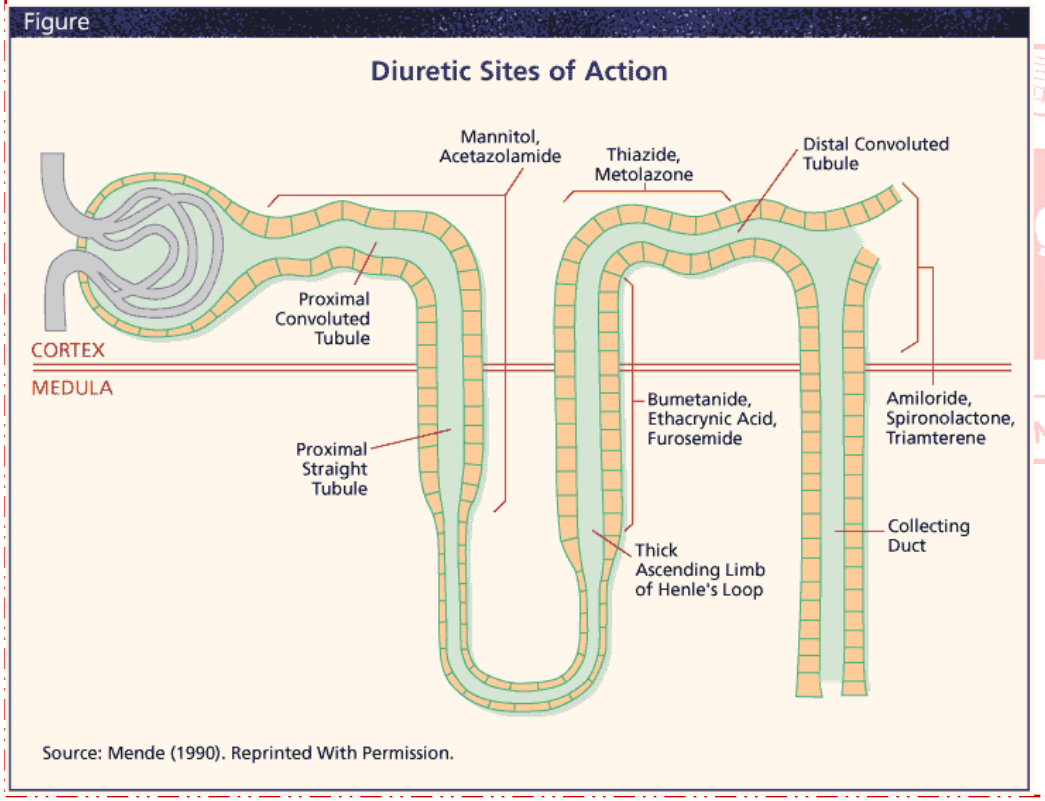


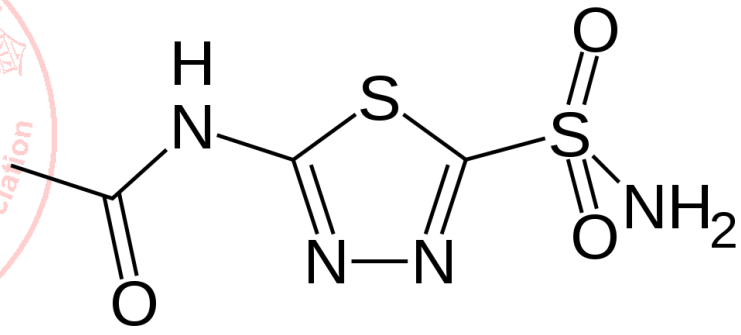
Potassium-sparing diuretics

- Aldosterone antagonists: Spironolactone
  - Competitive antagonist of aldosterone
  - Prevents aldosterone from entering the principal cells
  - Preventing sodium reabsorption
- Epithelial sodium channel blockers (ENaC)
  - Amiloride
  - Triamterene.

Acetazolamide

- Trade name: Diamox
- Carbonic anhydrase inhibitor





Acetazolamide

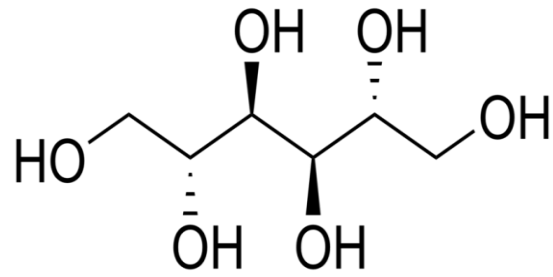
- Glaucoma:
  - Decreases fluid formation in the eye resulting in lower intraocular pressure.
- Neurologic: epilepsy
- Decrease CSF generation (idiopathic intracranial hypertension)
- Hyperkalemic periodic paralysis
- Sleep apnea (Off-label uses)
  - lowering blood pH and encourage respiration

Acetazolamide

- Acute mountain sickness (Prophylaxis, Not an immediate fix)
  - Dose: 125 to 500 mg QD a few days before going high
  - Indications:
    - Sea level to 3000 M in a day / 600 M per day when above 2500 M
    - Significant history of acute mountain sickness
  - Mechanism: acidemia, stimulates ventilation

Mannitol

- Indications:
  - Reduce acutely raised intracranial pressure
  - Treatment of oliguric renal failure (* with controversy)
  - Treatment of acute glaucoma in veterinary medicine
  - Prevention of dialysis dysequilibrium syndrome

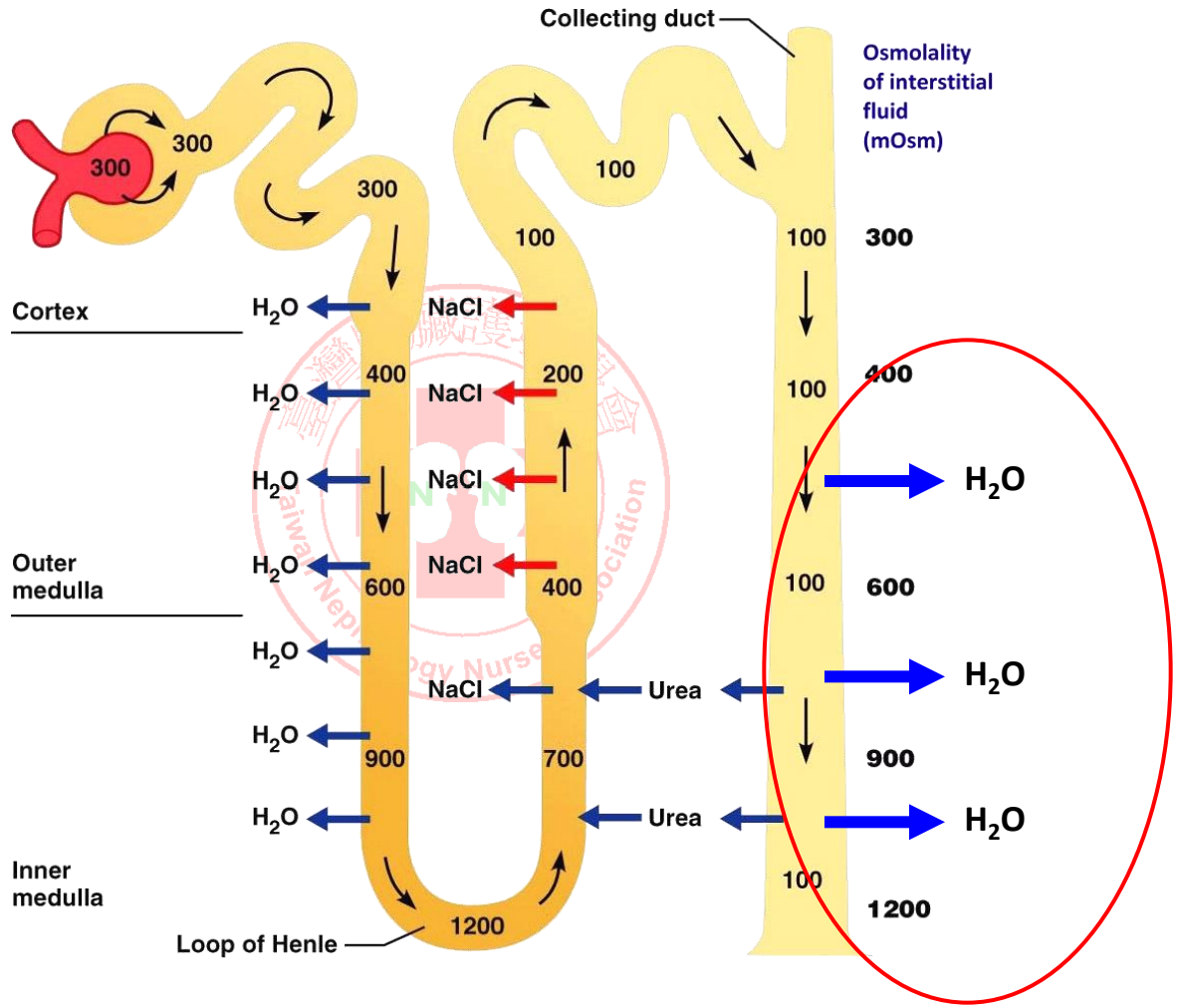


Smith MN, et al, Anaesthesia 63: 701, 2008
Yallop KG, et al, Anaesthesia 63: 576, 2008

Fluid & electrolyte complications

- Loop or thiazide-type diuretics:
  - Volume depletion / Azotemia
  - Hypokalemia
  - Metabolic alkalosis
  - Hyponatremia, hyperuricemia, and hypomagnesemia
- K^+-sparing diuretics (amiloride, triamterene, spironolactone)
  - Hyperkalemia
  - Metabolic acidosis

水通道 (Water channel) 的作用

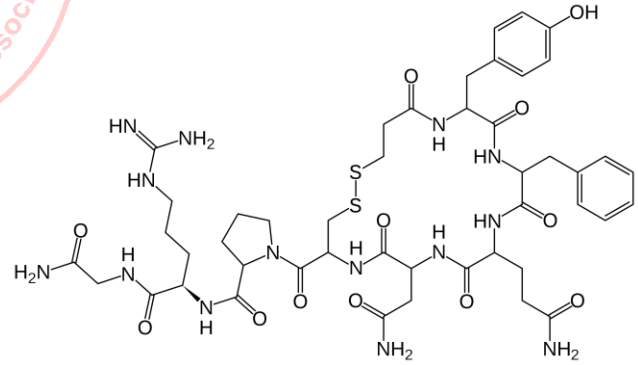


作用於水通道 (Water channel) 藥物

- ADH agonist: Desmopressin
- ADH antagonist: Conivaptan, Tolvaptan, lithium

Desmopressin (DDAVP, Stimate, Minirin)

- Synthetic replacement for vasopressin
- Taken nasally, intravenously, or as a pill
- Indications:
  - diabetes insipidus
  - coagulation disorders: promote von Willebrand factor release
  - Bedwetting
- Major side effect: Hyponatremia



Nephrotoxic Agents

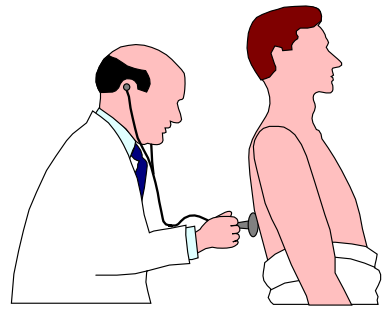
Nephrotoxic Drugs

- Radiocontrast Agents
- Aminoglycosides
- Nonsteroidal Anti-Inflammatory Drugs (NAIDs)
- Angiotensin-Converting Enzyme Inhibitors (ACEIs)
- Lithium
- Crystal-Induced Acute Renal Failure
- Calcineurin inhibitors (Cyclosporine, Tacrolimus)
- Amphothericin B
- Chemotherapy

Nephrotoxic Drugs

Patient- Related Risk Factors

- Age, Sex
- Previous renal disease
- Diabetes, Multiple myeloma, Lupus, Proteinuric disease
- Salt retaining diseases (Chirrosis, Heart Faiure, Nephrosis)
- Acidosis, potassium or magnesium depletion
- Hyperuricemia, Hyperuricosuria
- Kidney transplant



Nephrotoxic Drugs

Drug - Related Risk Factors

- Inherent nephrotoxic effects
- Dose
- Duration, frequency and form of administration
- Repeated exposure
- Drug interaction (synergistic toxic effects)

Radiocontrast agents: Pathogenesis

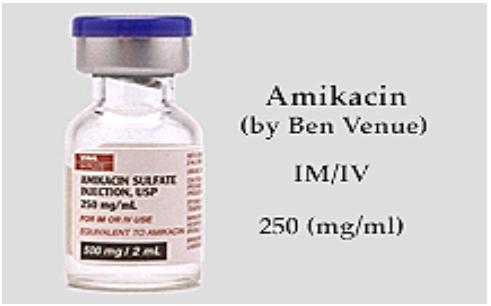
- Renal Vasoconstriction
  (Adenosine, Endothelin)
- Tubular Injury
  (Oxidative stress induced damage)

Radiocontrast agents: Risk Factors

- Underlying renal disease (Cr >1.5mg/dL)
- Diabetic nephropathy, Heart Failure, i.e. Hypovolemia
- Multiple Myeloma
- Dose (lower doses safer but not necessarily safe)

Aminoglycosides

- Amikacin [AMIKIN ®]
- Gentamicin [GARAMYCIN ®]
- Neomicin
- Netilmicin [NETROMYCIN ®]
- Kanamicin [KANTREX ®]
- Streptomycin
- Tobramycin [TOBREX, NEBCIN ®]



Aminoglycosides

Drug - Related Risk Factors

- Inherent nephrotoxic effects

  Gentamicin > Amikicin & Tombamycin
- Prolonged high trough levels (> 2.0 ng/ml)
- Dose; Duration; Frequency

  Single daily dose; “Post-antibiotic” effect
- Drug interaction: Cephalothin Cyclosporin A; Cisplatin, Cephalosporins, NSAIDs, ACEIs, Diuretics

Nonsteroidal Anti-Inflammatory Drugs (NSAIDs)

Chemical Structure / Activity	Generic Name
Acetic acids:	Diclofenac, Indomethacin, Sulindac,
Fenamates:	Meclofenamate, Mefenamic acid
Napthylalkanones:	Nabumetone
Oxicams:	Meloxicam and Piroxicam
Propionic acids:	Fenoprofen, Flurbiprofen, Ibuprofen, Ketoprofen, Naproxen, Oxaprozin
Pyranocaboxylic acid:	Etodolac
Pyrrolizine carboxylic acid:	Ketorolac
Selective COX-2 inhibitors:	Celecoxib, Rofecoxib, Valdecoxib,

Nonsteroidal Anti-Inflammatory Drugs (NSAIDs)

- Hemodynamically- Induced ARF
- Acute Interstitial Nephropathy + Proteinuria
- Papillary necrosis and chronic renal failure
  (Analgesic nephropathy)
- Salt and water retention; Hyperkalemia;
  Hypertension

ACE Inhibitors-Induced Acute Renal Failure

- First group of antihypertensive drugs shown to be renoprotective
- “High renin” patients are at risk:
  - Bilateral (>70%) renal artery stenosis
  - Moderate to Severe congestive hart failure
  - Volume deleted (excessive use of diuretics)

Calcineurin Inhibitors

- Cyclosporin A [Sandimmune®, Neoral®]
  Tracolimus [Pro-GRAF®]
- Mechanism or action
- Cyclosporin vs. Tracolimus

Calcineurin Inhibitors

Acute nephrotoxicity

- Azotemia: renal vasoconstriction, reduced RBF and GFR; Oliguric ATN with high doses
- Relatively more dose-dependent
- Largely reversible; Calcium channel blockers (+/-)
- Difficult to differentiate from acute rejection (renal biopsy)

Nephrotoxic Drugs

Prevention: General Rules

- Be aware of nephrotoxic potential of specific drugs
- Identify patients at risk
- Be aware of increased risk in elderly
- Asses the benefit/risk ratio for Rx of potentially nephrotoxic drug

Nephrotoxic Drugs

Prevention: General Rules

- Avoid dehydration/Be aware of volume depletion
- Limit dose and duration of treatment
- Adjust the dose based on changes in GFR
- Avoid a combination of potentially nephrotoxic drugs

Thanks for your attention

謝謝您的聆聽