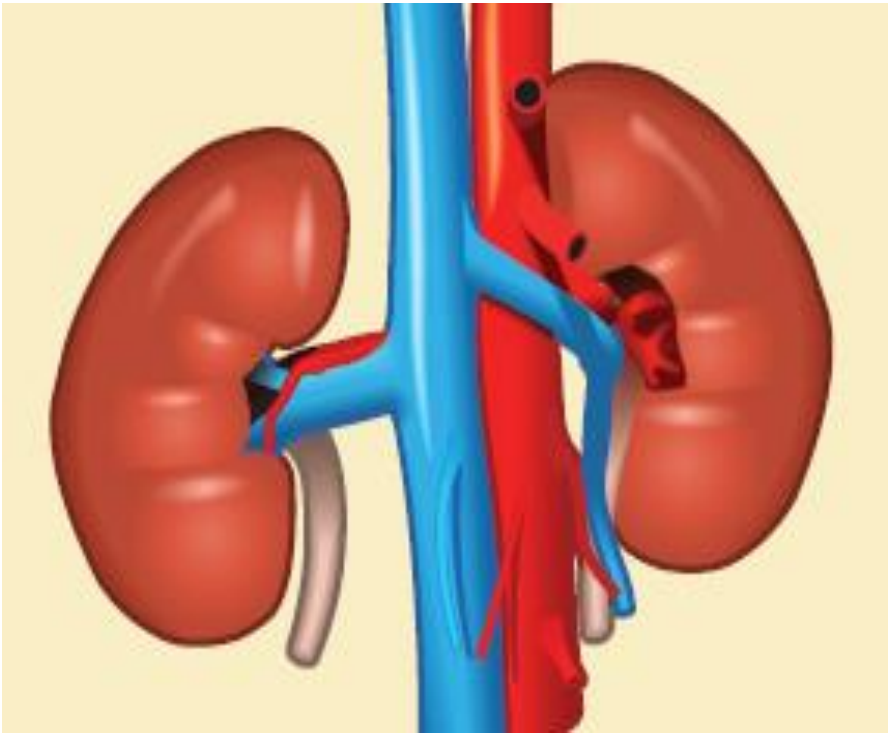
# 신장환자 약물처방

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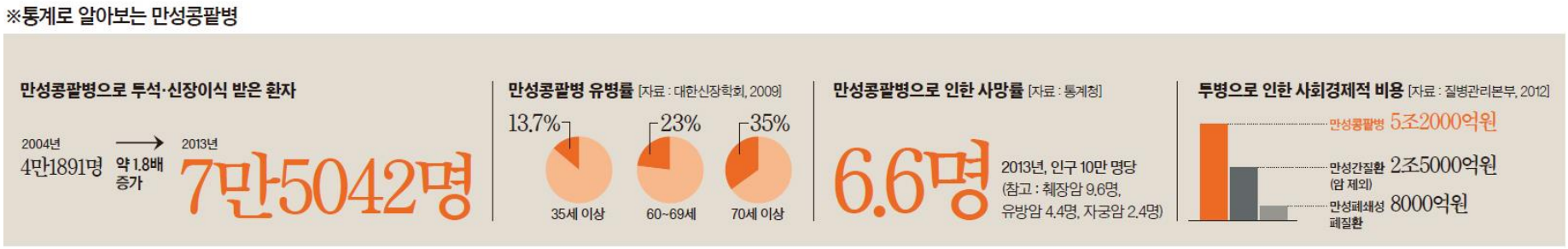
신장내과학교실
이수미

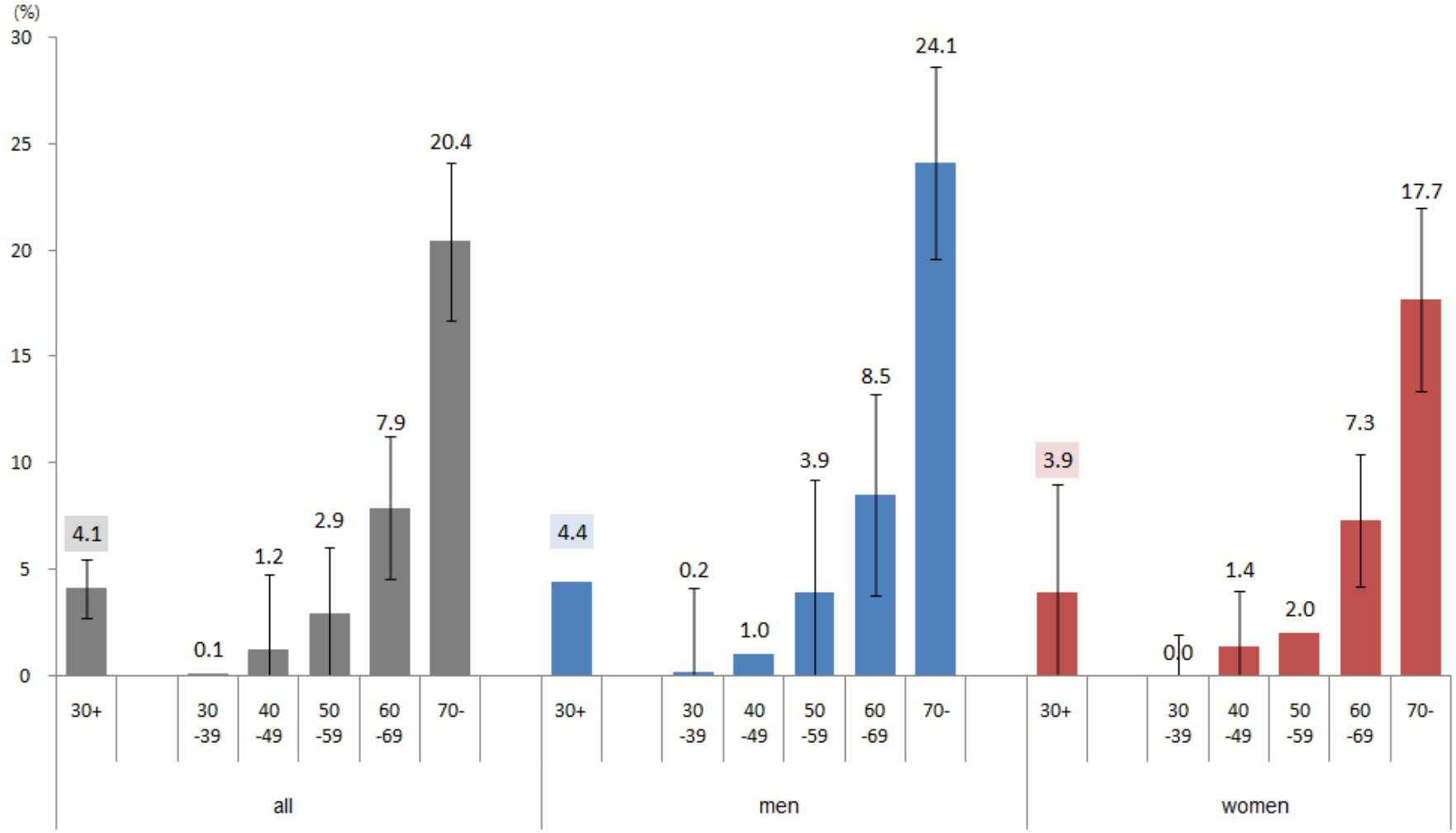
# Contents

# Epidemiology of CKD

- Changes in the demographics of  the population
- Under-recognition of earlier stages of CKD
- Improved survival from nonrenal disease (particularly CVD)

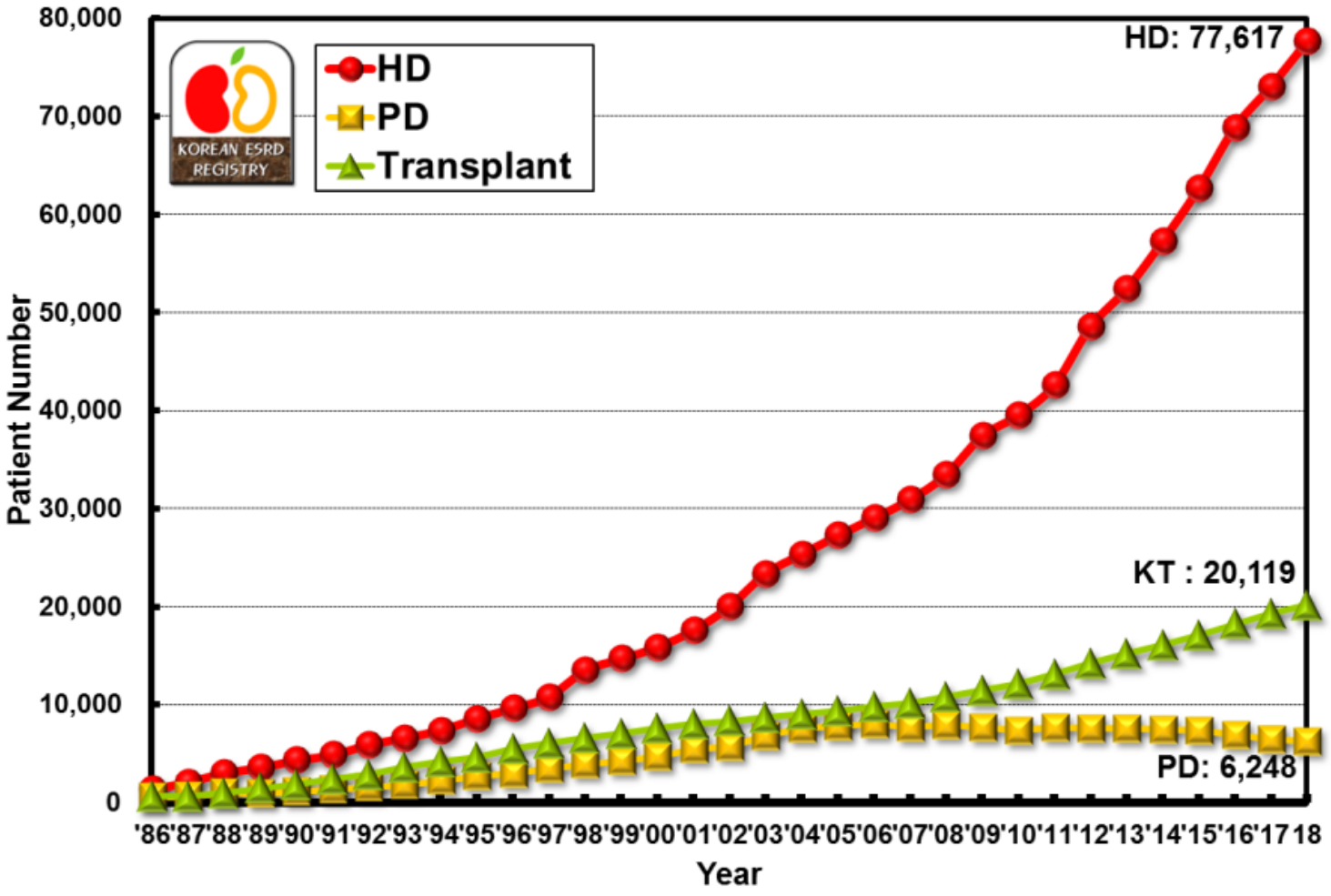


# Prevalence of CKD (Stage 3 to 5) by Sex and Age, 2013



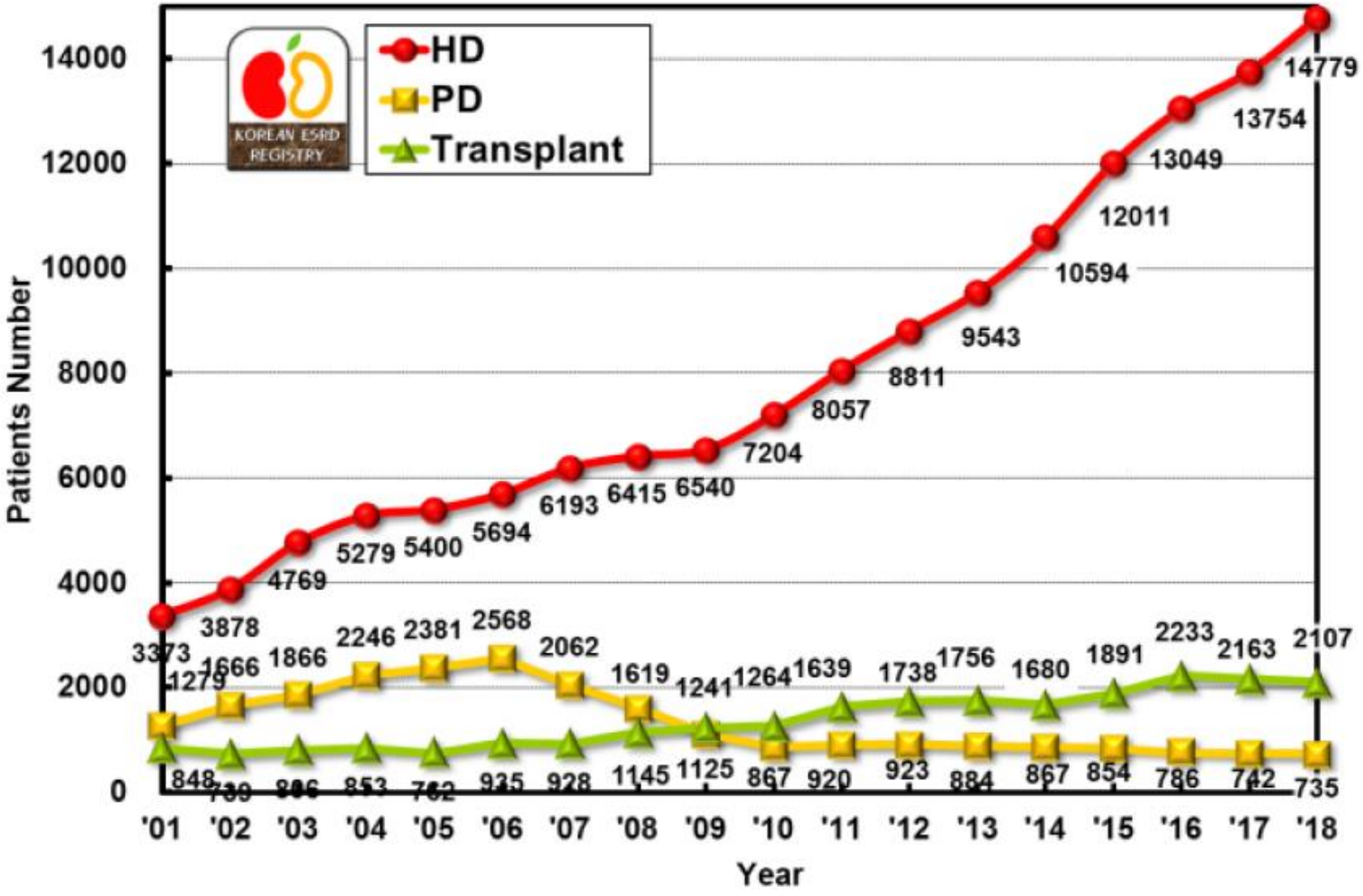

*CDC*, 2013

# Prevalence of Renal Replacement Therapy



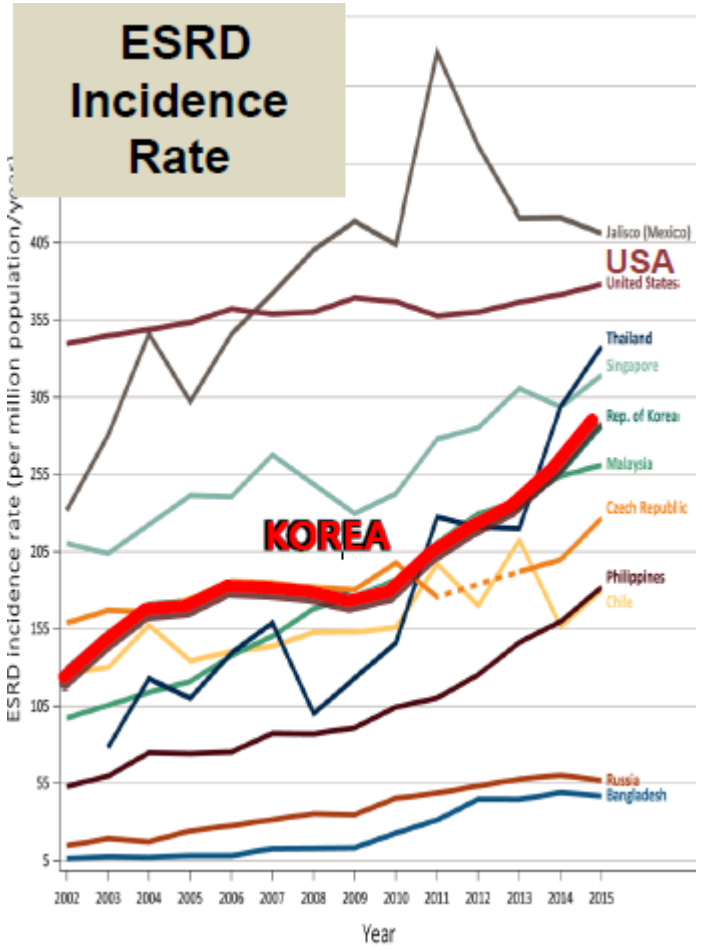

*KSN*, 2019

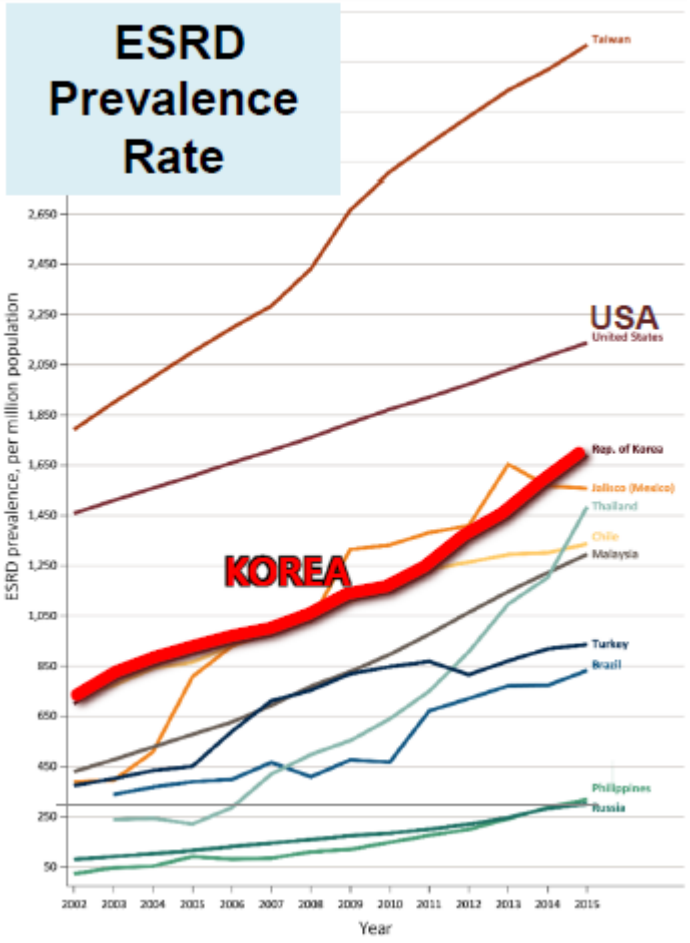
# Incidence of Renal Replacement Therapy




*KSN*, 2019

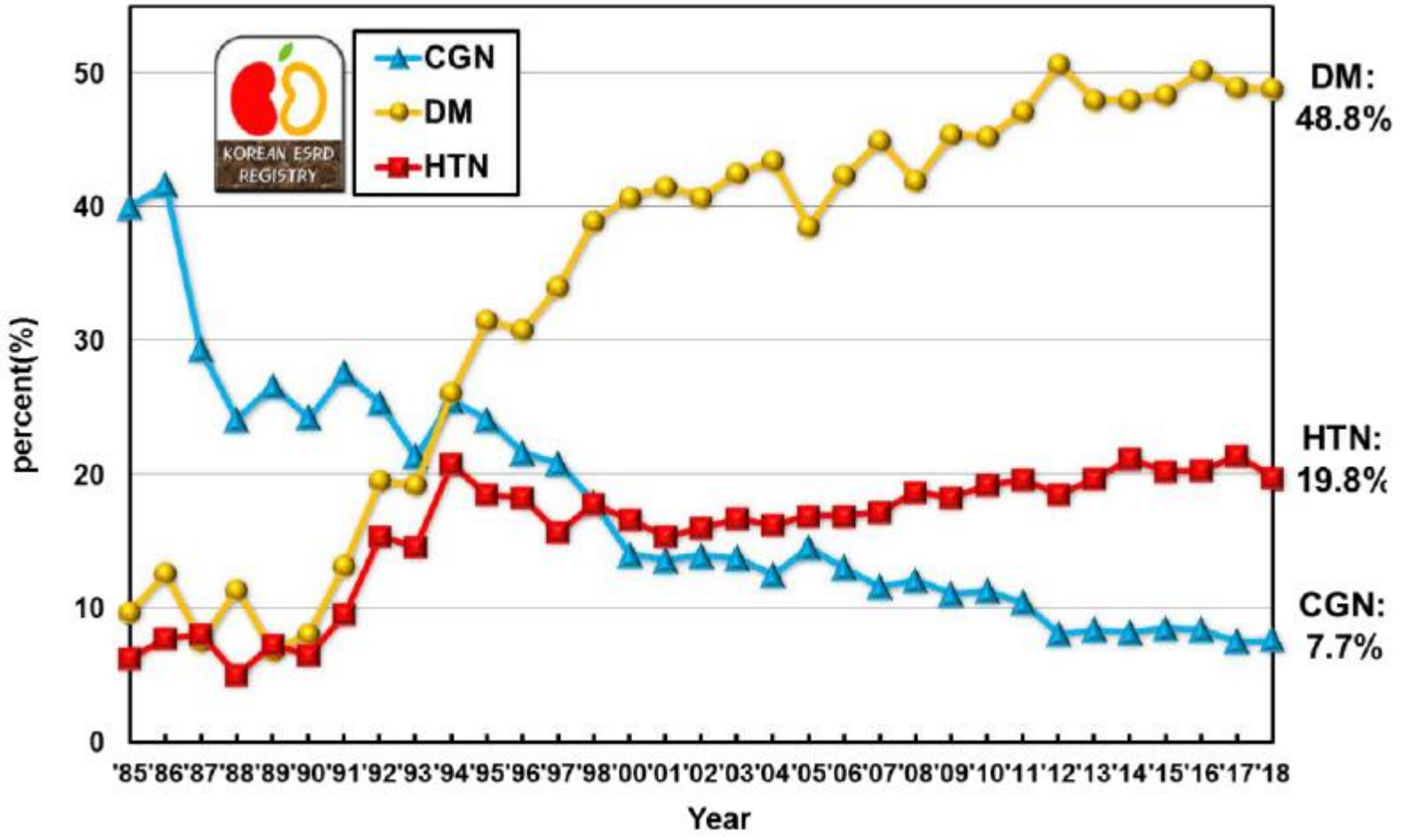
# International Comparison




*USRDS*, 2018

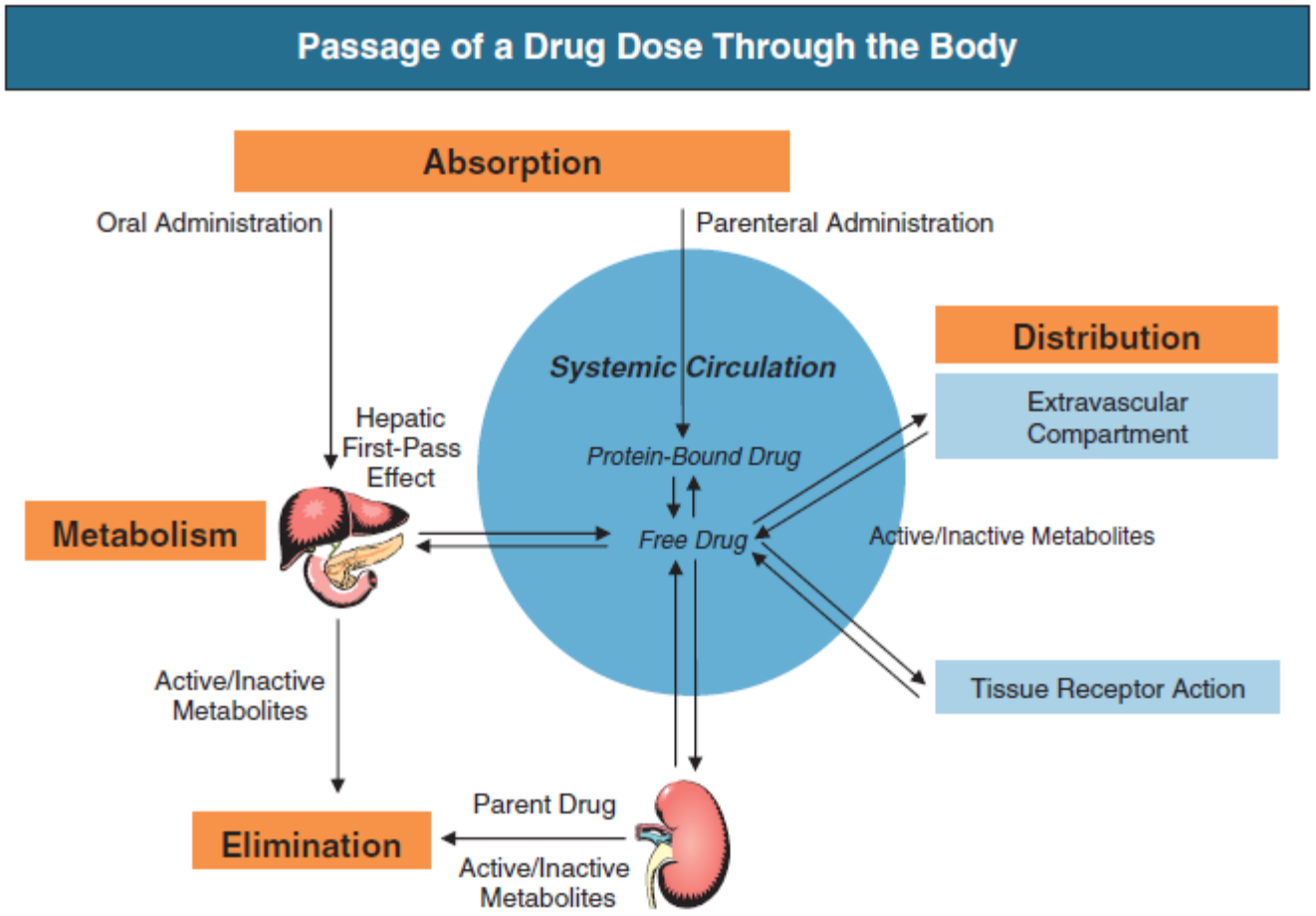
# Three Major Causes of ESRD




*KSN*, 2019

# Contents

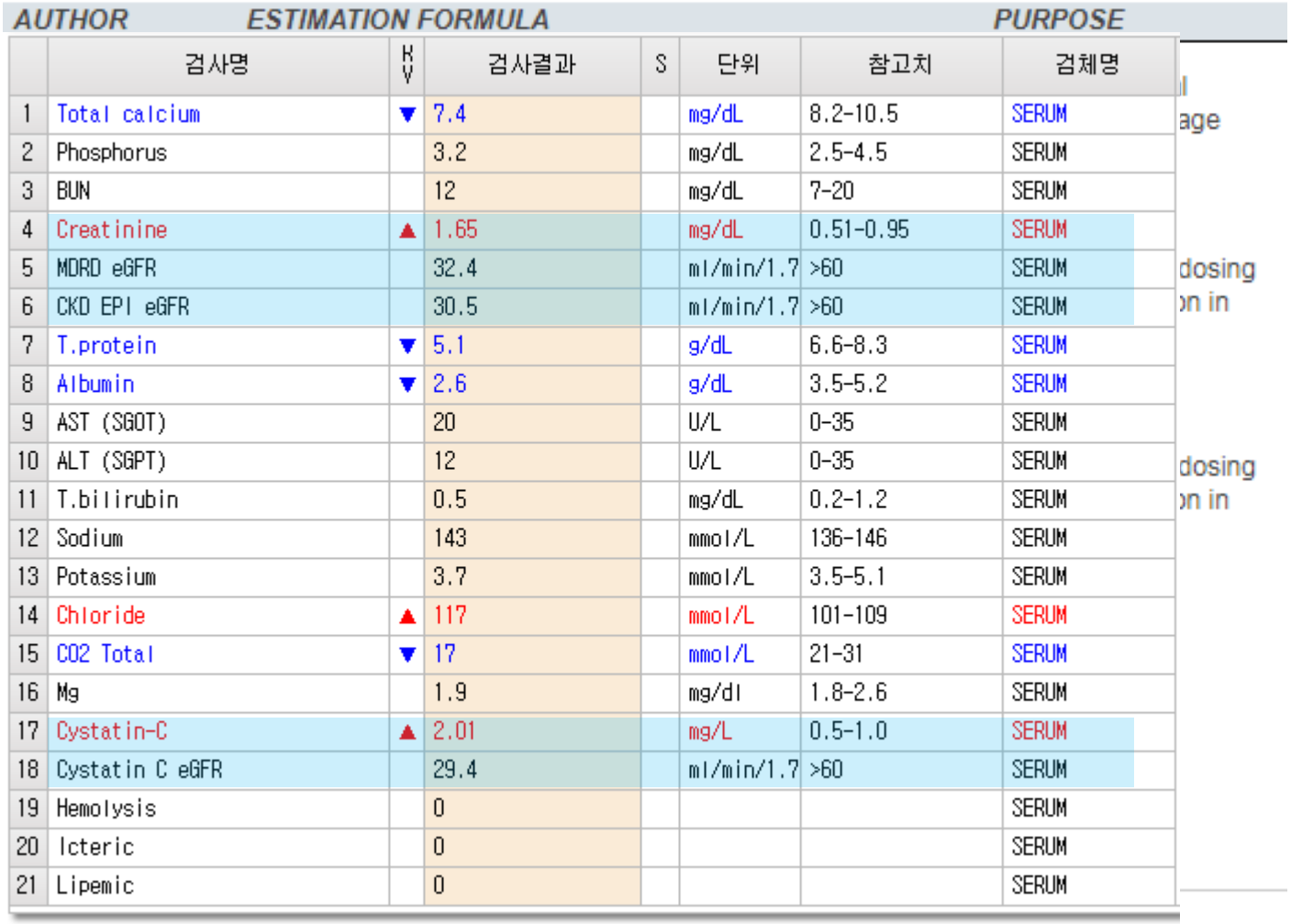
# Pharmacokinetic Principles



# Estimating Renal Function for Drug Dosage

- Creatinine
- Creatinine based estimation of renal function for prescription medication dosage (adult)
  - ✓ Creatinine clearance : Cr excretion in 24-hour urine collection, age/gender/weight/race
  - ✓ Cockcroft-Gault equation : most widely used
  - ✓ Estimated glomerular filtration rate (eGFR) by Modification of Diet in Renal Disease (MDRD) formula
  - ✓ Mild (30-60 ml/min), moderate (10-30 ml/min), severe (dialysis)

# Formulas to Assess Renal Function



AUTHOR ESTIMATION FORMULA PURPOSE

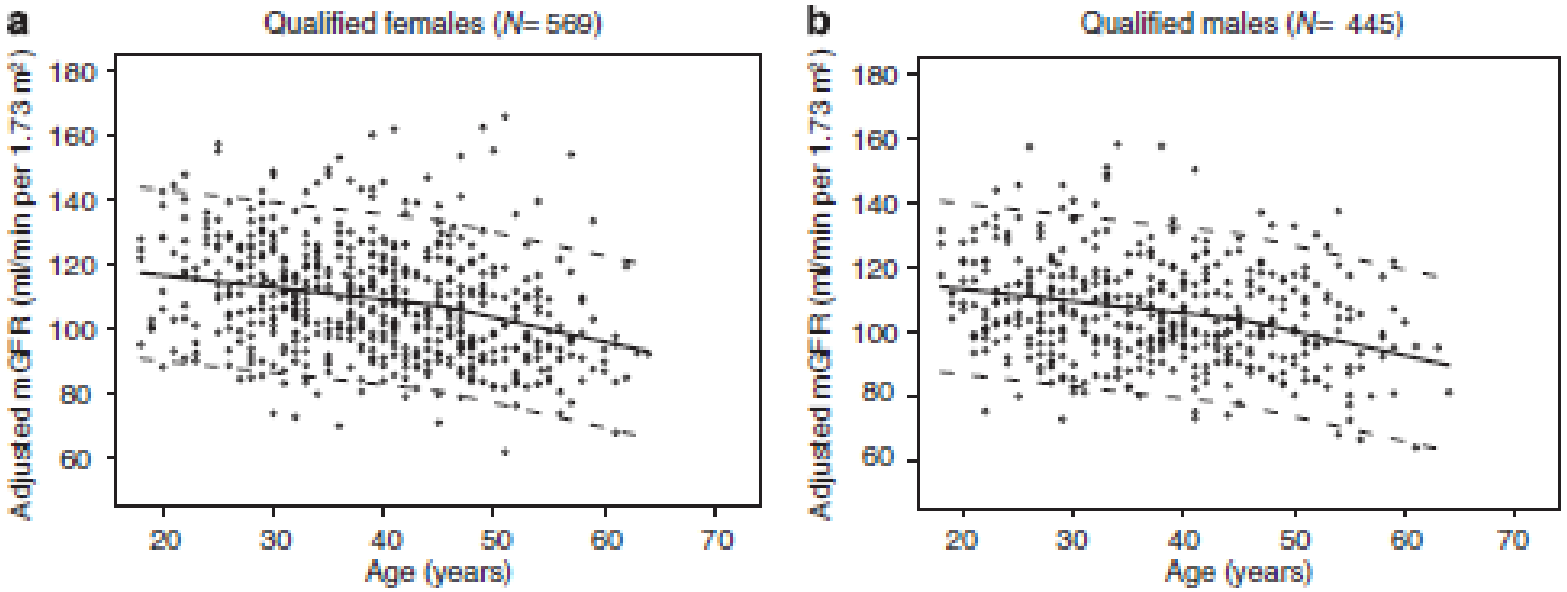
| | 검사명 | H/V | 검사결과 | S | 단위 | 참고치 | 검체명 |
|---|---|---|---|---|---|---|---|
| 1 | Total calcium | ▼ | 7.4 | | mg/dL | 8.2-10.5 | SERUM |
| 2 | Phosphorus | | 3.2 | | mg/dL | 2.5-4.5 | SERUM |
| 3 | BUN | | 12 | | mg/dL | 7-20 | SERUM |
| 4 | Creatinine | ▲ | 1.65 | | mg/dL | 0.51-0.95 | SERUM |
| 5 | MDRD eGFR | | 32.4 | | ml/min/1.7 | >60 | SERUM |
| 6 | CKD EPI eGFR | | 30.5 | | ml/min/1.7 | >60 | SERUM |
| 7 | T.protein | ▼ | 5.1 | | g/dL | 6.6-8.3 | SERUM |
| 8 | Albumin | ▼ | 2.6 | | g/dL | 3.5-5.2 | SERUM |
| 9 | AST (SGOT) | | 20 | | U/L | 0-35 | SERUM |
| 10 | ALT (SGPT) | | 12 | | U/L | 0-35 | SERUM |
| 11 | T.bilirubin | | 0.5 | | mg/dL | 0.2-1.2 | SERUM |
| 12 | Sodium | | 143 | | mmol/L | 136-146 | SERUM |
| 13 | Potassium | | 3.7 | | mmol/L | 3.5-5.1 | SERUM |
| 14 | Chloride | ▲ | 117 | | mmol/L | 101-109 | SERUM |
| 15 | CO2 Total | ▼ | 17 | | mmol/L | 21-31 | SERUM |
| 16 | Mg | | 1.9 | | mg/dl | 1.8-2.6 | SERUM |
| 17 | Cystatin-C | ▲ | 2.01 | | mg/L | 0.5-1.0 | SERUM |
| 18 | Cystatin C eGFR | | 29.4 | | ml/min/1.7 | >60 | SERUM |
| 19 | Hemolysis | | 0 | | | | SERUM |
| 20 | Icteric | | 0 | | | | SERUM |
| 21 | Lipemic | | 0 | | | | SERUM |

Am Fam Physician 2008; 78: 743–750

# Factors Affecting Serum Creatinine Levels

| Factors Affecting Serum Creatinine Concentration | | |
|---|---|---|
| **Factors** | **Effect on Creatinine** | **Mechanism/Comment** |
| Age | Decrease | Reduced creatinine generation caused by age-related decline in muscle mass |
| Female gender | Decrease | Reduced creatinine generation caused by reduced muscle mass |
| **Race** | | |
| African American | Increase | Higher creatinine generation caused by higher average muscle mass in African Americans; not known how muscle mass in other races compares with that of African Americans or Caucasians |
| **Diet** | | |
| Vegetarian | Decrease | Decrease in creatinine generation |
| Ingestion of cooked meats and creatinine supplements | Increase | Transient increase in creatinine generation, although this may be blunted by transient increase in GFR |
| **Body Habitus** | | |
| Muscular | Increase | Increased muscle generation caused by increased muscle mass and/or increased protein intake |
| Malnutrition, muscle wasting, amputation | Decrease | Reduced creatinine generation caused by reduced muscle mass and/or reduced protein intake |
| Obesity | No change | Excess mass is fat, not muscle mass, and does not contribute to increased creatinine generation. |
| **Medications** | | |
| Trimethoprim, cimetidine, fibric acid derivatives other than gemfibrozil | Increase | Reduced tubular secretion of creatinine |
| Keto acids, some cephalosporins | Increase | Interference with alkaline picrate assay for creatinine |

# Effects of Age on Renal Function




Kidney Int 2009; 75: 1079–1087

# Definition of CKD

**Criteria for CKD (either of the following present for >3 months)**

| | |
|---|---|
| Markers of kidney damage (one or more) | Albuminuria (AER ≥30 mg/24 hours; ACR ≥30 mg/g [≥3 mg/mmol])<br>Urine sediment abnormalities<br>Electrolyte and other abnormalities due to tubular disorders<br>Abnormalities detected by histology<br>Structural abnormalities detected by imaging<br>History of kidney transplantation |
| **Decreased GFR** | GFR <60 ml/min/1.73 $m^2$ (GFR categories G3a–G5) |

Abbreviations: CKD, chronic kidney disease; GFR, glomerular filtration rate.

*KDIGO*, 2012

# Staging of CKD

■ S.O.A.P.

# CKD G4A3
- h/o edema 20170103 171124 180206 180513 180525
- solondo 60 171207

# DM (1997) - lantus, repaglinide, 올메텍 20, 트리메부틴 (prof.서성환)
# DMR/DMN
# UA s/p stent (prof.김무현) 2017
- R/O cardiac LC (2018), ascites tapping

■ S.O.A.P.

# CKD G3bA3
# s/p Fx, femur neck, Rt (2018, prof.김현준)
# DM (2008)
# DMR (2018)
# HTN
# Pancreatitis (prof.노명환)

| mment |
| --- |
| st common patient in the low clearance clinic |
| mmon cause of nephrotic syndrome in childhood |
| st outcome after kidney transplantation |
| st common disease caused by a mutation in a single ne |
| mmon condition in children |
| e genetic disorder |

# Contents

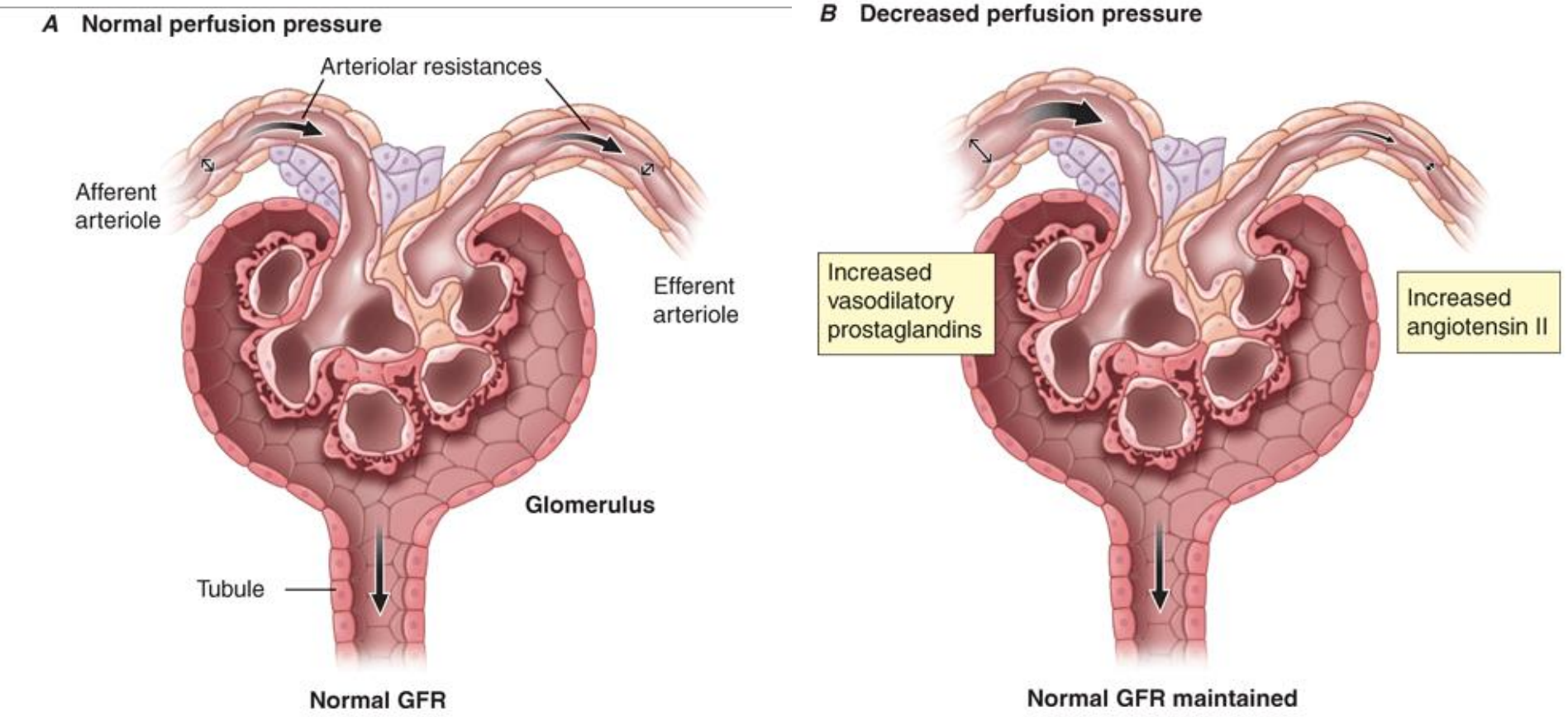
# Some Samples of Nephrotoxic Drugs

- ACE inhibitors, ARBs
- Aminoglycosides (Amikacin, Gentamicin, Tobramycin)
- Antifungals (Amphotericin)
- Antivirals (Acyclovir, Cidofovir, Foscarnet, Indinavir)
- Calcineurin inhibitors (Cyclosporine, Tacrolimus)
- Chemotherapeutics (Cisplatin, Ifosfamide)
- Lithium
- NSAIDs
- Proton pump inhibitors
- Radiocontrast media

# Risk Factors for Drug-Induced Nephrotoxicity

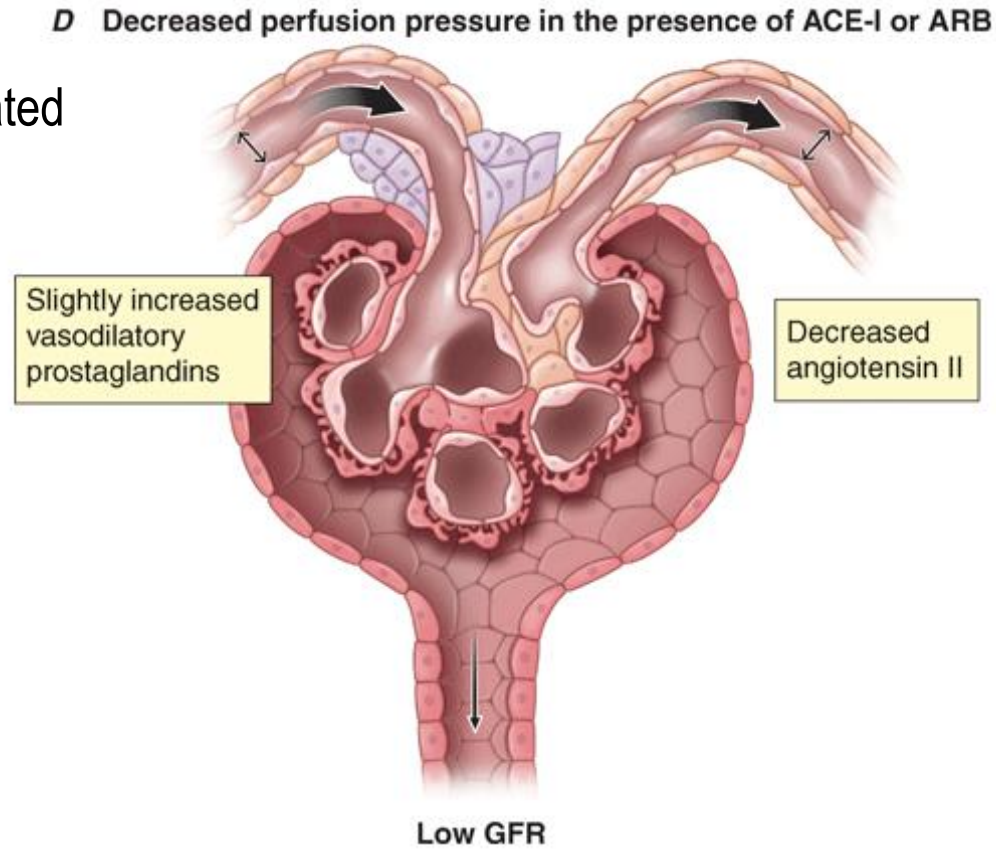
- “Absolute” or “effective” intravascular volume depletion
- Age older than 60 years
- Diabetes
- Exposure to multiple nephrotoxins
- Heart failure
- Sepsis
- Underlying renal insufficiency

# GFR Autoregulation



# Mechanisms of Drug Nephrotoxicity : ACEi/ARBs

- Mechanism
  - Impairment of angiotensin II-mediated efferent arteriole vasoconstriction during renal hypoperfusion
- Prevention and management
  - Withdraw in renal hypoperfusion

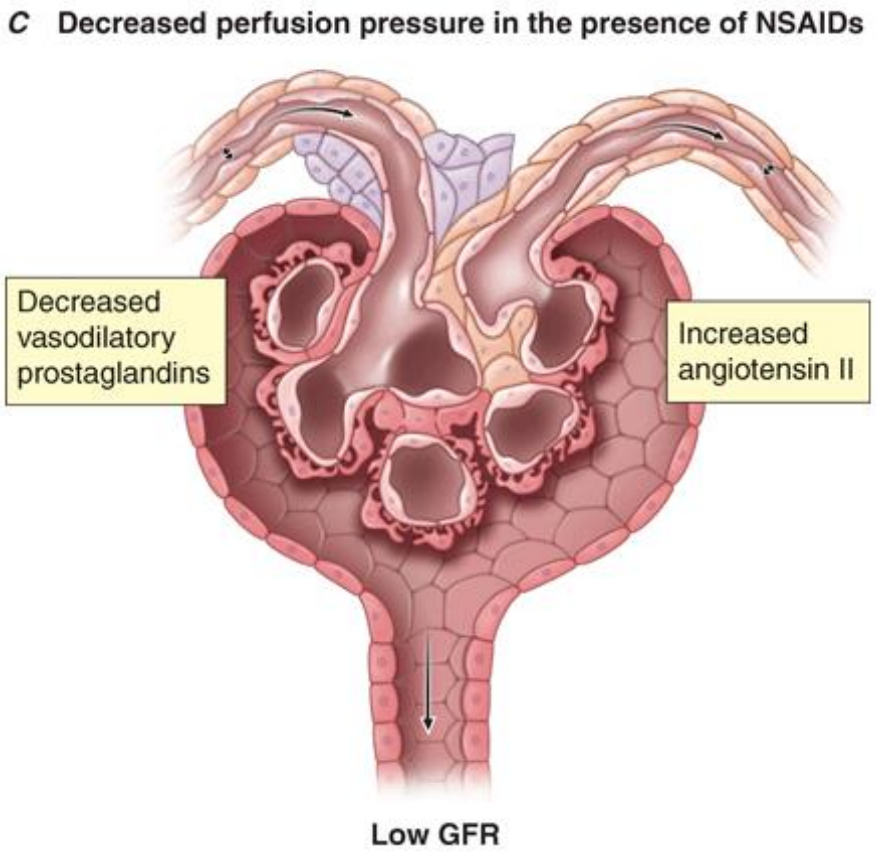


# Mechanisms of Drug Nephrotoxicity : NSAIDs

- Mechanism
  - Hemodynamically induced AKI caused by vasoconstriction via reduced prostaglandin production
  - Recruitment and activation of lymphocytes

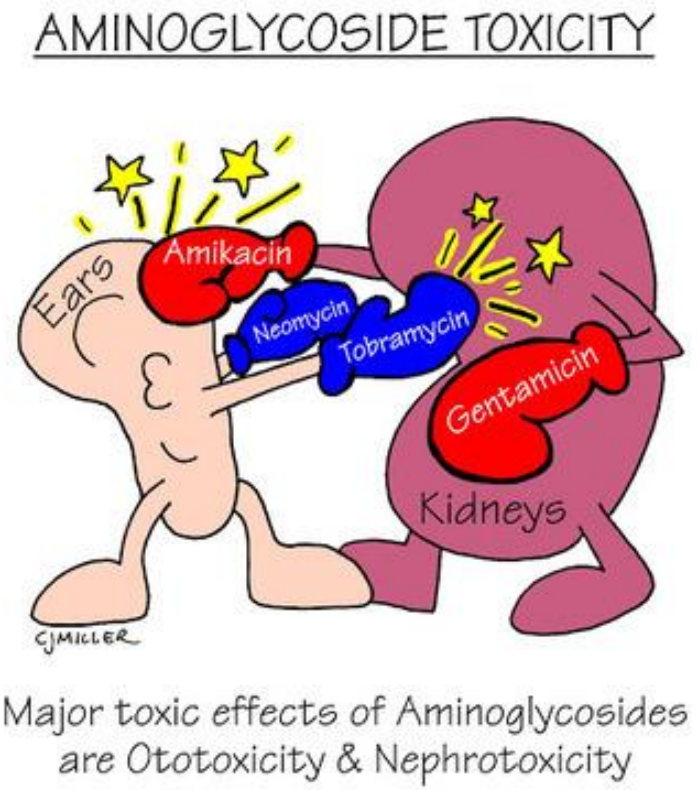
  → acute and chronic TIN, with or without nephrotic syndrome

- Prevention and management
  - Avoid use
  - Withdraw during hypoperfusion



# Mechanisms of Drug Nephrotoxicity : Aminoglycosides

- Incidence of AKI : 10-25%
- Mechanism
  - In proximal tubule, aminoglycosides bind to anionic phospholipid, are delivered to megalin, are taken up into the cell, accumulate, and cause direct toxicity
- Prevention and management
  - Alternative if possible
  - Monitor drug concentrations
  - Avoid multiple daily doses
  - Withdraw if Cr rises



# Contents

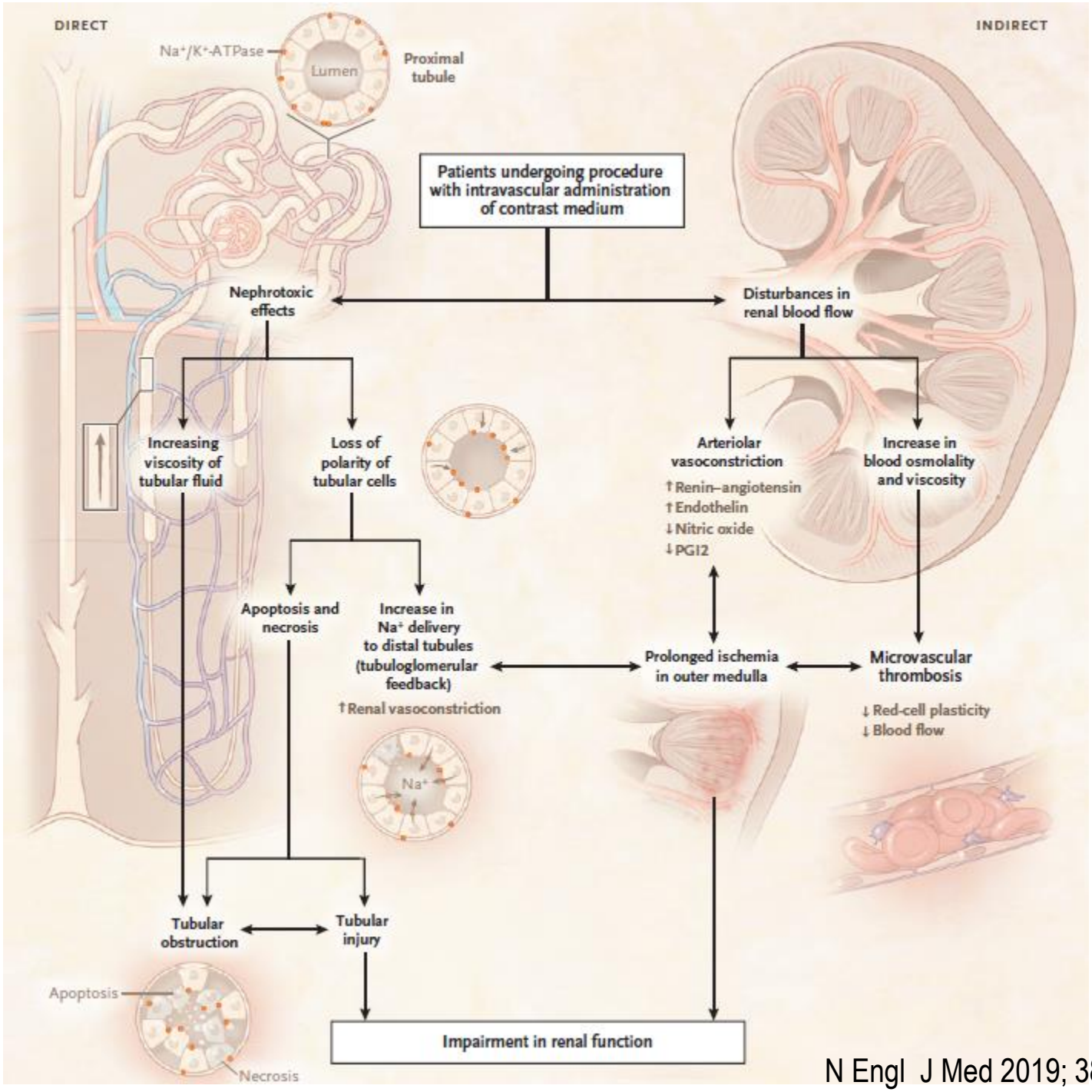
# Contrast induced nephropathy

- Definition
- Pathophysiology
- Risk factors
- Prognosis
- Preventive strategies

# Contrast induced nephropathy

- ***At 48 hrs*** after a radiological procedure with iodine based contrast media
- Elevation of serum ***Cr ≥ 25%  or 0.5 mg/dL of baseline***
- ***Exclusion*** of other explanations (other nephrotoxic agents, prerenal, cardiorenal syndrome …)

*KDIGO*, 2012




N Engl J Med 2019; 380: 2146–2155

# Risk factors

| Associated with the patient |
| --- |
| - Concomitant acute kidney injury of other origins |
| - Reduced GFR (<45 ml/min/1.73m$^2$ or <60 ml/min/1.73 m$^2$ for intravenous or intra-arterial administration) |
| - Previous AKI or CKD |
| - Diabetic nephropathy |
| - Dehydration |
| - Anaemia |
| - Poor haemodynamic status |
| - Age > 70 years |
| - Concurrent nephrotoxic drug treatment |
| **Associated with the procedure** |
| - Large doses of contrast medium |
| - Multiple administrations of contrast medium |
| - Use of contrast medium with excessive osmolality or viscosity |
| - intra-arterial administration |

Nat Rev Nephrol 2017; 13: 169–180

# Prognosis

- The 3rd most common cause of AKI in hospital
- Most : self-limited
  - ✓ Increase over 12h to 48h, peak at 4 to 5 days
  - ✓ Return to baseline value within 1 to 2 weeks
- <1% : need dialysis (3% in CKD, 12% in CKD with diabetes)
- Associated with increased in-hospital morbidity and mortality

# Prevention

- Avoid volume depletion and NSAIDs
  - Avoid ACEi/ARB – insufficient data
- Dose and type of contrast agent
  - Use lowest effect dose and avoid repeated studies (within 48 to 72 hrs)
  - Use Iso-osmolal agent or nonionic low-osmolal agents
- Fluid administration
  - Volume supplementation
  - Isotonic saline vs. Hypotonic saline
  - Sodium bicarbonate vs. Sodium chloride

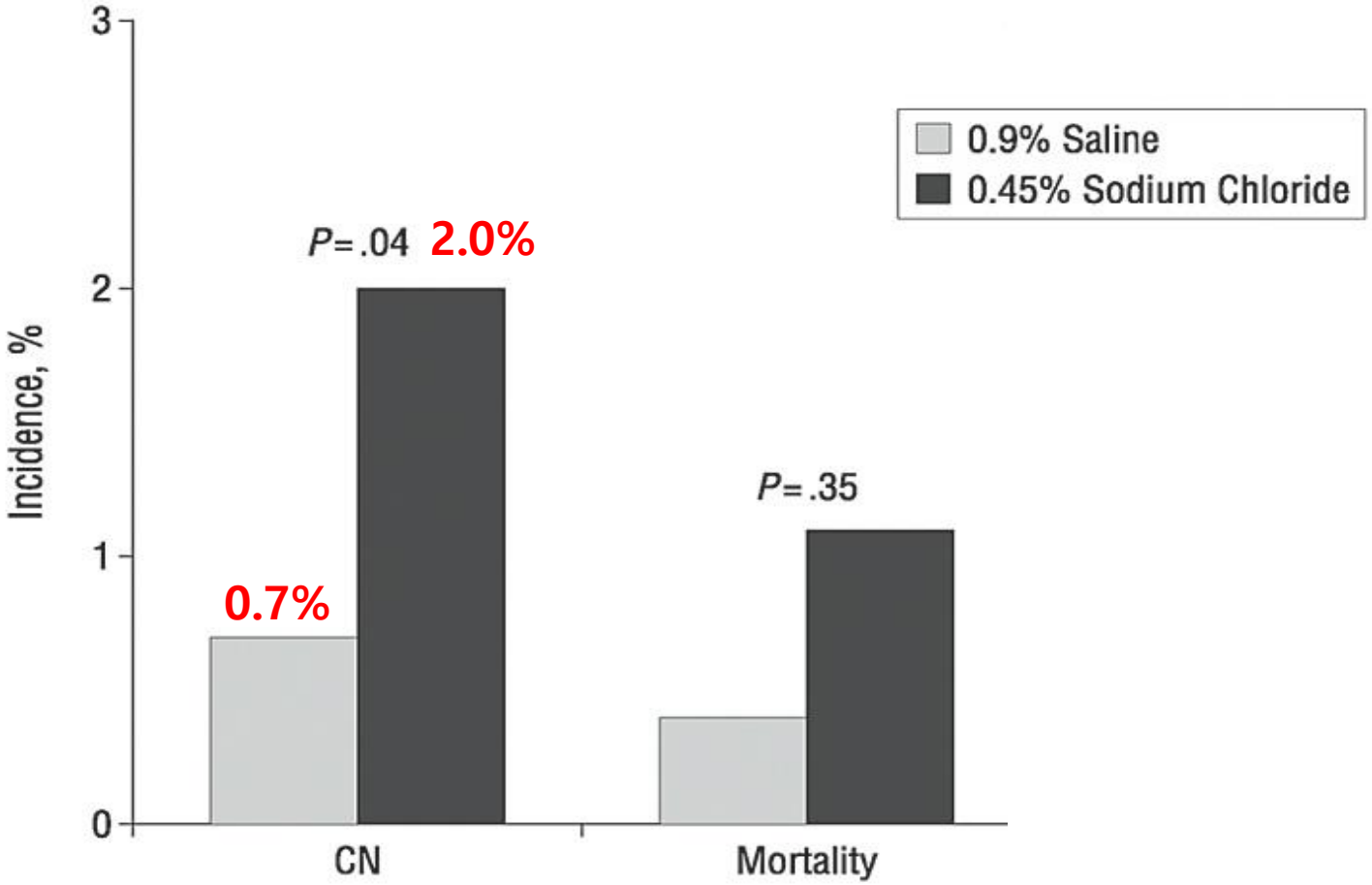
# Fluid administration : Volume Supplementation

| Study | Number of patients | Baseline serum creatinine | Duration of infusion before contrast | Duration of infusion after contrast | Infusion rate | Infusate | CIN rate |
|---|---|---|---|---|---|---|---|
| Solomon *et al.*[1] | 78 | 2.1 mg/dl | 12 h | 12 h | 1 ml/kg per h | 0.45 Saline versus 0.45 saline+mannitol versus 0.45 saline+furosemide | 11 versus 28 versus 40% |
| Taylor *et al.*[2] | 36 | 1.74 mg/dl | 12 h versus $\frac{1}{2}$ –1 h | 12 h versus 6 h | 75 versus 300 ml/h | 0.45 Saline | 11.1 versus 5.6% |
| Mueller *et al.*[4] | 1383 | 0.93 mg/dl | Started at 0800 hours | 12 h | 1 ml/kg per h | 0.9 Saline versus 0.45 saline | 0.7 versus 2.0% |
| Trivedi *et al.*[5] | 53 | 106 $\mu$mol/l | 12 h versus none | 12 h versus none | 1 ml/kg per h | 0.9 Saline | 3.7 versus 34.6% |
| Bader *et al.*[6] | 39 | 0.9 mg/dl | 12 h versus bolus only | 12 h versus none | 2000 ml/24 h | 0.9 Saline | 5.3 versus 15% |
| Krasuski *et al.*[15] | 63 | 2.1 mg/dl | 12 h versus 20 min | 12 h | 1 ml/kg per h versus 250 ml/20 min | 0.45 Saline | 0 versus 10.8% |
| Merten *et al.*[16] | 119 | 1.80 mg/dl | 1 h | 6 h | 3 ml/kg per h before 1 ml/kg per h after | Sodium bicarbonate versus saline | 1.7 versus 13.6% |

CIN is defined as an increase in serum creatinine of at least 0.5 mg/dl within 48 h,[1,2,4,5] an increase in serum creatinine of 25% or more within 48 h,[16] or a decrease in glomerular filtration rate of more than 50% within 48 h.[6]

Kidney Int 2006; 100: S16-S19

# Fluid administration
# : Isotonic saline vs. Hypotonic saline




Arch Intern Med 2002; 162: 329-336

# Fluid administration
# : Sodium bicarbonate vs. Sodium chloride

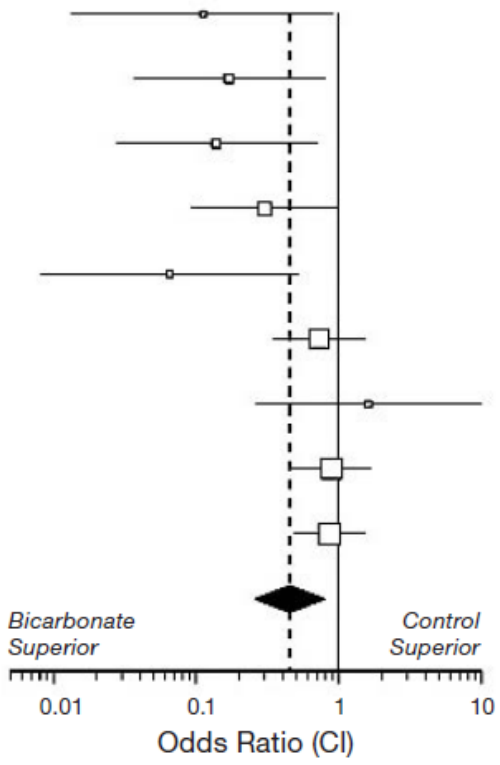
- Sodium bicarbonate
  - ✓ Alkalizing the tubular urine
    - ➢ ↓ free radical formation
    - ➢ ↓ oxidant injury

**Lower rate of CIN**

- Sodium bicarbonate is alternative ?
  - ✓ Systemic review of RCTs – mixed results

# Fluid administration
# : Sodium bicarbonate vs. Sodium chloride

| Trial | Contrast-Induced Nephropathy | | | | Odds Ratio (CI) | % Weight |
|---|---|---|---|---|---|---|
| | Bicarbonate | | Control | | | |
| | *Yes* | *No* | *Yes* | *No* | | |
| Merten et al. 2004 | 1 | 68 | 8 | 60 | 0.11 (0.01–0.91) | 5.4 |
| Briguori et al. 2007 | 2 | 115 | 11 | 107 | 0.17 (0.04–0.78) | 8.5 |
| Masuda et al. 2007 | 2 | 29 | 10 | 20 | 0.14 (0.03–0.70) | 7.9 |
| Ozcan et al. 2007 | 4 | 84 | 12 | 76 | 0.30 (0.09–0.97) | 11.6 |
| Recio-Mayoral et al. 2007 | 1 | 55 | 12 | 43 | 0.07 (0.01–0.52) | 5.5 |
| Shaikh et al. 2007 | 14 | 145 | 19 | 142 | 0.72 (0.35–1.49) | 16.9 |
| Adolph et al. 2008 | 3 | 69 | 2 | 74 | 1.61 (0.26–9.92) | 6.8 |
| Brar et al. 2008 | 21 | 154 | 24 | 154 | 0.88 (0.47–1.64) | 18.2 |
| Maicli et al. 2008 | 25 | 225 | 29 | 223 | 0.85 (0.49–1.50) | 19.2 |
| *Pooled* | 73 | 944 | 127 | 899 | 0.45 (0.26–0.79) | 100.0 |




Wien Klin Wochenschr 2008; 120: 742–748

# Fluid administration
# : Sodium bicarbonate vs. Sodium chloride

| Outcome | Sodium Bicarbonate (N=2511) | Sodium Chloride (N=2482) | Odds Ratio (95% CI) | P Value | Acetylcysteine (N=2495) | Placebo (N=2498) | Odds Ratio (95% CI) | P Value |
|---|---|---|---|---|---|---|---|---|
| | *no. of patients (%)* | | | | *no. of patients (%)* | | | |
| Primary end point* | 110 (4.4) | 116 (4.7) | 0.93 (0.72–1.22) | 0.62 | 114 (4.6) | 112 (4.5) | 1.02 (0.78–1.33) | 0.88 |
| Secondary end points | | | | | | | | |
| Contrast-associated acute kidney injury† | 239 (9.5) | 206 (8.3) | 1.16 (0.96–1.41) | 0.13 | 228 (9.1) | 217 (8.7) | 1.06 (0.87–1.28) | 0.58 |
| Death by 90 days | 60 (2.4) | 68 (2.7) | 0.87 (0.61–1.24) | 0.43 | 67 (2.7) | 61 (2.4) | 1.10 (0.78–1.57) | 0.59 |
| Need for dialysis by 90 days | 32 (1.3) | 29 (1.2) | 1.09 (0.65–1.81) | 0.73 | 30 (1.2) | 31 (1.2) | 0.97 (0.58–1.60) | 0.90 |
| Persistent kidney impairment by 90 days | 28 (1.1) | 25 (1.0) | 1.10 (0.64–1.91) | 0.71 | 26 (1.0) | 27 (1.1) | 0.96 (0.56–1.66) | 0.89 |
| Hospitalization with acute coronary syndrome, heart failure, or stroke by 90 days | 272 (10.8) | 251 (10.1) | 1.08 (0.90–1.29) | 0.40 | 244 (9.8) | 279 (11.2) | 0.86 (0.71–1.04) | 0.11 |
| All-cause hospitalization by 90 days | 1071 (42.7) | 1052 (42.4) | 1.01 (0.90–1.13) | 0.85 | 1069 (42.8) | 1054 (42.2) | 1.03 (0.91–1.15) | 0.64 |

N Engl J Med 2018; 378: 603–614

# Pharmacological Prevention: Hydration

| Fluid | Timing of administration | Recommendation |
|---|---|---|
| **Optimum hydration protocol** | | |
| Normal saline | 12 hrs before procedure | 1ml/kg/h for 12hrs before and after contrast administration |
| **When not practical (i.e. for outpatients)** | | |
| Isotonic saline or $NaHCO_3$ solution | 1-3 hrs before procedure | 3ml/kg/h for 1-3 hrs before and 1ml/kg/h for 6 hrs after contrast administration |

* Post-procedure hydration may be more important than pre-procedure fluids.

# Pharmacological Prevention: N-acetylcysteine


- Muteran ® (1cap =200mg)
  - Used orally
  - 600mg-1200mg twice daily : day -1 and 0
- Plausible mechanism
  - Scavenge oxygen derived free radicals
  - Improving renal hemodynamics
  - Prevent direct toxic tissue damage
- Conflicting data
- Little adverse effects (nausea..) and inexpensive (1C=64 KRW)
- Benefit of iv remains uncertain

# Pharmacological Prevention

## 김 O 걸 (M/72)

# CKD G3bA3
- AKI d/t R/O postop
# Eso ca s/p VATS OP 160222 (prof.정상석)
# S-colon ca s/p LAR 160222 (prof.박기재)
# DM (2016)
# LC (unknown child A) prof.이성욱

| | 검사명 | K V | 검사결과 | S | 단위 | 참고치 | 검체명 |
|---|---|---|---|---|---|---|---|
| 1 | Total calcium | | 8.5 | | mg/dL | 8.2-10.5 | SERUM |
| 2 | Phosphorus | | 3.8 | | mg/dL | 2.5-4.5 | SERUM |
| 3 | Glucose | ▲ | 169 | | mg/dL | 74-106 | SERUM |
| 4 | BUN | ▲ | 33 | | mg/dL | 7-20 | SERUM |
| 5 | Creatinine | ▲ | 3.30 | | mg/dL | 0.67-1.17 | SERUM |
| 6 | MDRD eGFR | | 19[illegible] | | [illegible] | | SERUM |
| | | | | | | | SERUM |
| | | | | | | 7.2 | SERUM |
| | | | | | | 0 | SERUM |
| | | | | | | 8.3 | SERUM |
| | | | | | | 5.2 | SERUM |
| | | | | | | 1.52 | SERUM |
| | | | | | | | SERUM |
| | | | | | | | SERUM |
| | | | | | | 20 | SERUM |
| | | | | | | 1.2 | SERUM |
| | | | | | | 146 | SERUM |
| | | | | | | 5.1 | SERUM |
| | | | | | | 109 | SERUM |
| | | | | | | 1 | SERUM |

| | |
|---|---|
| - | [외래]2017-11-22 / 1 / NI / 이수미 |
| ☐ | N/S 500ml/bag 1BAG QD 1day IV5 MIX:1 원내[52] *Msg:- CT 찍기 전 1시간부터 80cc/hr 주세요 |
| ☐ | Sodium Bicarbonate 8.4% 20ml/amp 2AMP QD 1day IV5 MIX:1 원내[52] *Msg:- CT 찍기 전 1시간부터 80cc/hr 주세 |
| ☐ | Lasix 20mg/amp 1AMP QD 1day IV 원내[52] D/C 1회 *Msg:N/S 후 라식스 주세요 |
| ☐ | ㄴ[D/C] Lasix 20mg/amp D/C 1회 |
| + | [외래]2017-09-28 / 6 / NI / 이수미 |
| + | [외래]2017-09-28 / 5 / NI / 이수미 |
| + | [외래]2017-09-28 / 4 / NI / 이수미 |
| - | [외래]2017-09-28 / 2 / NI / 이수미 |
| ☐ | Ab Screening Test 1회 (Blood, Whole) D/C1일 |
| ☐ | Admission Profile 2 (LM1111-23) 1회 (Blood, Serum) |
| ☐ | Electrolyte Profile (LM1126-29) 1회 (Blood, Serum) |
| ☐ | CRP 1회 (Blood, Serum) |
| ☐ | Routine CBC (LM0131-38) 1회 (Blood, Whole) |
| ☐ | WBC Diff. Count (LM0141-54) 1회 (Blood, Whole) |
| ☐ | RBC (320mL) 1회 (Blood, Whole) Matching D/C1일 *Msg:3hour 주세요 |
| ☐ | Peniramin 4mg/amp 1AMP QD 1day IV 원내[52] *Msg:pre T/F |
| ☐ | Renamezin(S)/cap 2CAP BID 60day BH1 |
| ☐ | Muteran(L) 200mg/cap 3CAP BID 2day BP |

# Summary

- Estimating renal function is essential in renal drug dosage
  - Cockcroft-Gault equation or eGFR by MDRD formula
- Cautious use of potentially nephrotoxic agents and procedures
  - ACEi/ARB, NASIDs, Antibiotics, Radiocontrast …
- CIN is a common and potentially serious
  - The risk of CIN is elevated in patients with **CKD (particularly DM CKD)**
  - **Adequate IV volume expansion with** isotonic saline before/after the procedure can lessen the probability of CIN