Managing Complications in Chronic Kidney Disease Patients

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Objectives

1. Identify common complications of the CKD patients
2. Apply pharmacokinetic and pharmacodynamics principles in the dosing of medications in CKD
3. Interpret lab results in the management of anemia of CKD
4. Assess therapeutic options for osteoporosis in the CKD patient
5. Compare and contrast anticoagulation

No Disclosures

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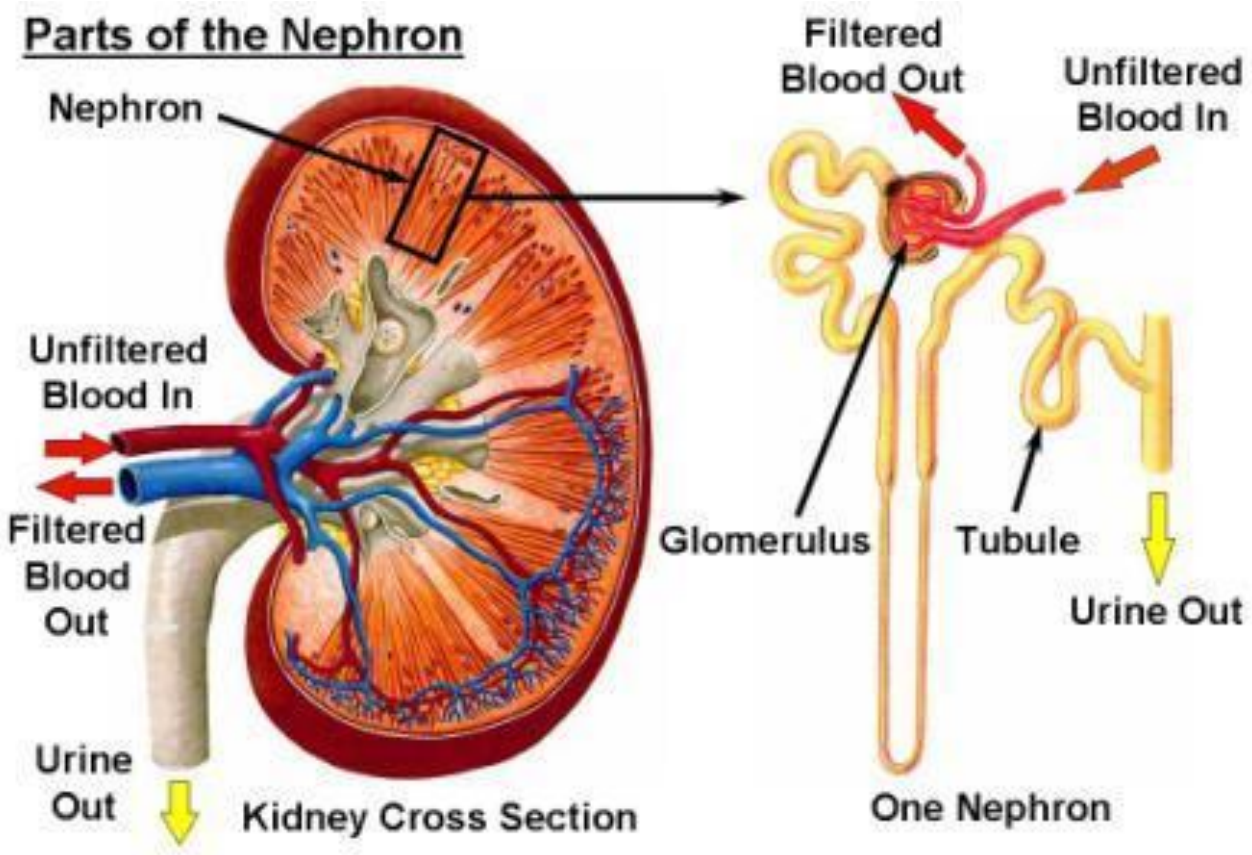
Outline

- The Kidney 101
- Evaluating Kidney Function and Drug Dosing
- Complications of CKD
  - Dialysis
  - Anemia
  - Bone Disease
  - Anticoagulation in CKD

The Kidney 101



Kidney Functions: Metabolic

- Metabolic functions of the kidney:
  - Controls blood pressure
  - Maintenance of body fluid compartments
  - Regulation of serum electrolytes
  - Maintenance of acid-base homeostasis
  - Excretion of toxins/drugs/metabolic byproducts

Kidney Functions: Endocrine

- Secretion of hormones that :
  - Regulate systemic and renal hemodynamics (renin, PGs, bradykinins)
  - Stimulate RBC production (erythropoietin)
  - Control calcium, phosphate and bone metabolism (through 1,25-dihydroxyvitamin D3)

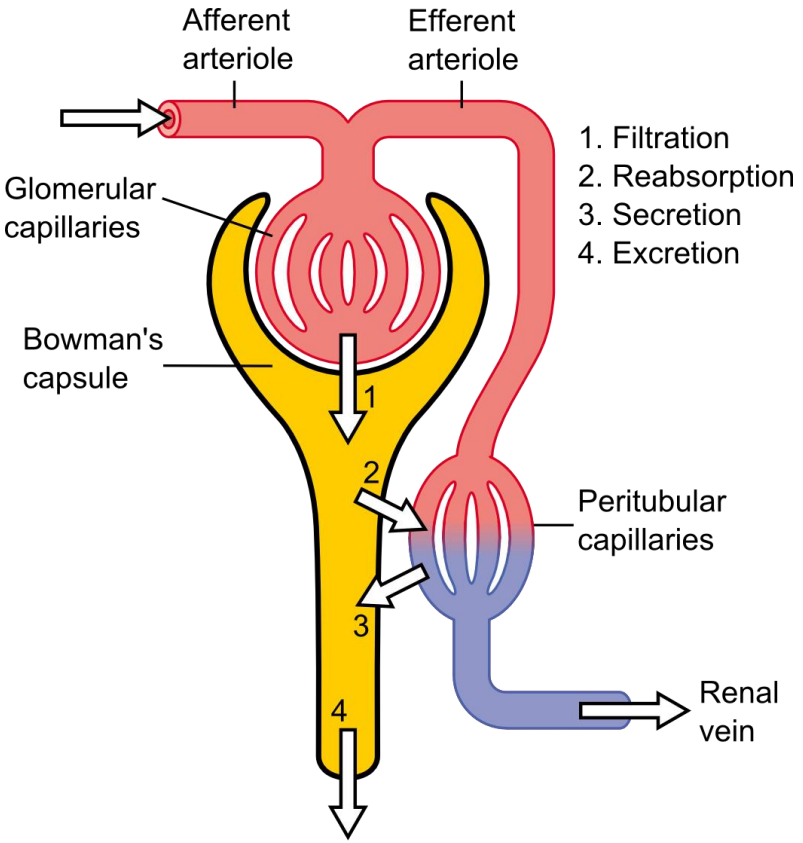
How is kidney function measured?

Glomerular filtration rate (GFR)

How to assess kidney function: GFR

- **Glomerular filtration rate (GFR)**:

  is the volume of fluid filtered from the renal glomerular capillaries into Bowman's space per unit time.



Excretion = Filtration – Reabsorption + Secretion

GFR

- Best overall index of kidney function
- Normal varies according to age, sex, body size
- In young adults, normal is approximately 120-130 ml/min/1.73 m^2 and declines with age

How can we practically measure GFR?

Gold Standards for Measuring GFR

- Inulin Clearance
- Iothalamate Clearance
- DPTA radionucleotide scan
- Cystatin C

What are more feasible options?

(1) Serum creatinine

(2) 24 hour urine collection for Creatinine Clearance (CrCl)

(3) Estimating with an equation based on the level of serum creatinine:
- Cockcroft-Gault
- Modification of Diet in Renal Disease (MDRD)
- CKD-EPI

What Measurement of Kidney Function do you use for Drug Dosing?

Limitations of ALL Drug Dosing Studies

- No gold standard comparison
- No clinical outcomes
- No drug level outcomes

Annals of Pharmacotherapy 2010; 44:439-446.

American Journal of Kidney Diseases 2009;54:33-42

American College of Cardiology 2008;51:991-996

Pharmacotherapy 2008; 28:1125-1132.

Annals of Pharmacotherapy 2006;40:1248-1253

American Journal of Kidney Diseases 2009;54:33-42

Nephrology Dialysis Transplantation 2007;22:2894-2899

Case Example

- HR, a 72 yr female with osteoporosis. Her family MD wants to start her on alendronate 10mg daily.
  - MDRD = 33ml/min/1.73m^2
  - CKD-EPI= 34ml/min/1.73m^2
  - CrCL= 29 ml/min
- Literature suggest to avoid in patient with CrCL < 30ml/min
- How do you dose?

Dosing Adjustments

- Many medications are excreted by the kidneys and require adjustment when GFR is reduced
- Most pharmacokinetic studies and recommendations are based on CG eq'n
- In most cases, the GFR estimates from MDRD & CKD-EPI and the CG equations fall within the same interval for dose adjustment.

Clinical Pearls for Dose Adjustments

Balance efficacy and toxicity

- Type of infection (CNSA vs MRSA)
- Location of infection (CNS vs. blood)
- Severity (Outpatient vs. ICU)
- Pharmacokinetics (concentrate in urine (UTI) vs. crossing blood brain barrier (meningitis)
- Pharmacodynamics (concentration vs. time dependent killing)
- Toxicity (penicillin vs. AMG)
- Ability to monitor levels (vancomycin vs. cefazolin)
- Prophylaxis vs Treatment

Dosing Adjustments

- Published guidelines suggest: dose reduction, lengthening the dosing interval or both.
- Dose reduction (while maintaining the normal dosing interval)
  - More constant drug concentrations but associated with higher risk of toxicities
- Normal Dose but increasing interval
  - Associated with fewer toxicities but higher risk of subtherapeutic drug concentration

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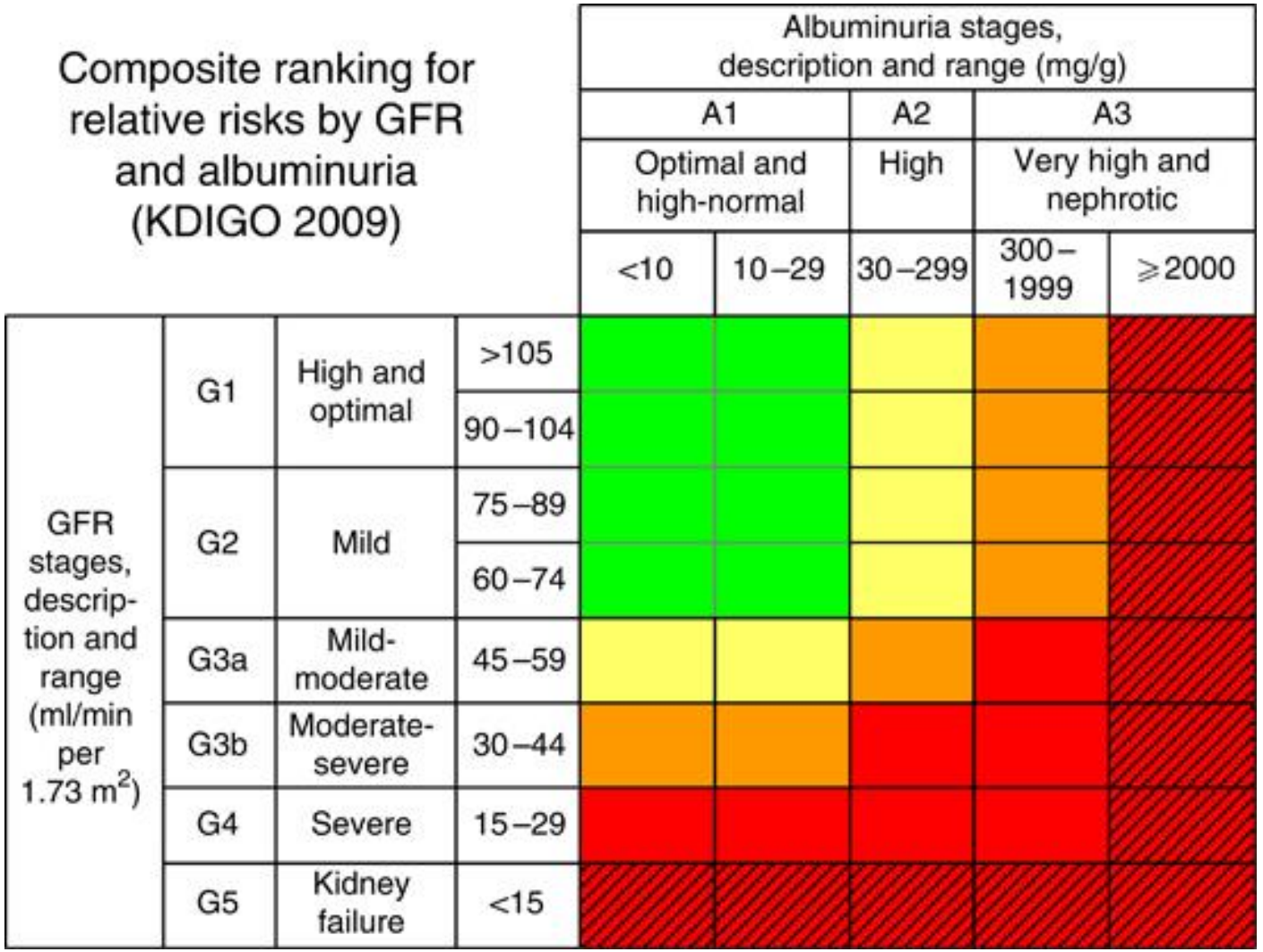
CKD and Definition

- Chronic kidney disease (CKD) is defined by:
  - The presence of kidney damage* or an eGFR < 60 ml/min/1.73 m2 and
  - Present for ≥ 3 months and
  - Not treated with dialysis or transplant

*Hematuria, proteinuria, or anatomic abnormalities

Composite ranking for relative risks by GFR and albuminuria (KDIGO 2009)



KDIGO. Summary of recommendation statements. Kidney Int 2013; 3(Suppl):5.

CKD and Classification

- Classification of the type of kidney disease is based on pathology, etiology and clinical history

- The most common causes of chronic kidney disease include:
  - Diabetic glomerulosclerosis (30%)
  - Vascular diseases (hypertension, renal artery stenosis) (20%)
  - Glomerular diseases (primary or secondary) (20%)

CKD and Consequences

- Cardiovascular disease
  - CAD
  - Hypertension
  - Pericarditis
- Volume overload
- Anemia
- Bone and mineral metabolism
  - Hypocalcemia
  - Hyperphosphatemia
- Electrolyte abnormalities
  - Hyperkalemia
  - Metabolic acidosis
- Uremia
  - Nausea, vomiting
  - Pruritus
  - Encephalopathy
- Dialysis
  - Hemodialysis
  - Peritoneal Dialysis

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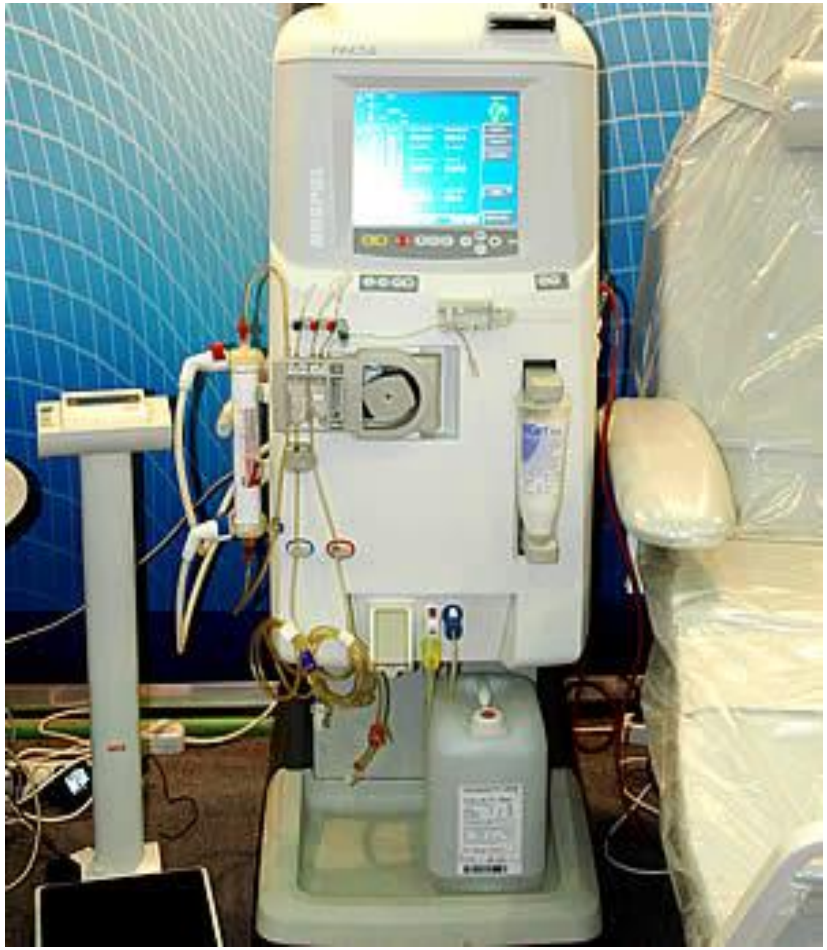
CKD and Indications for dialysis

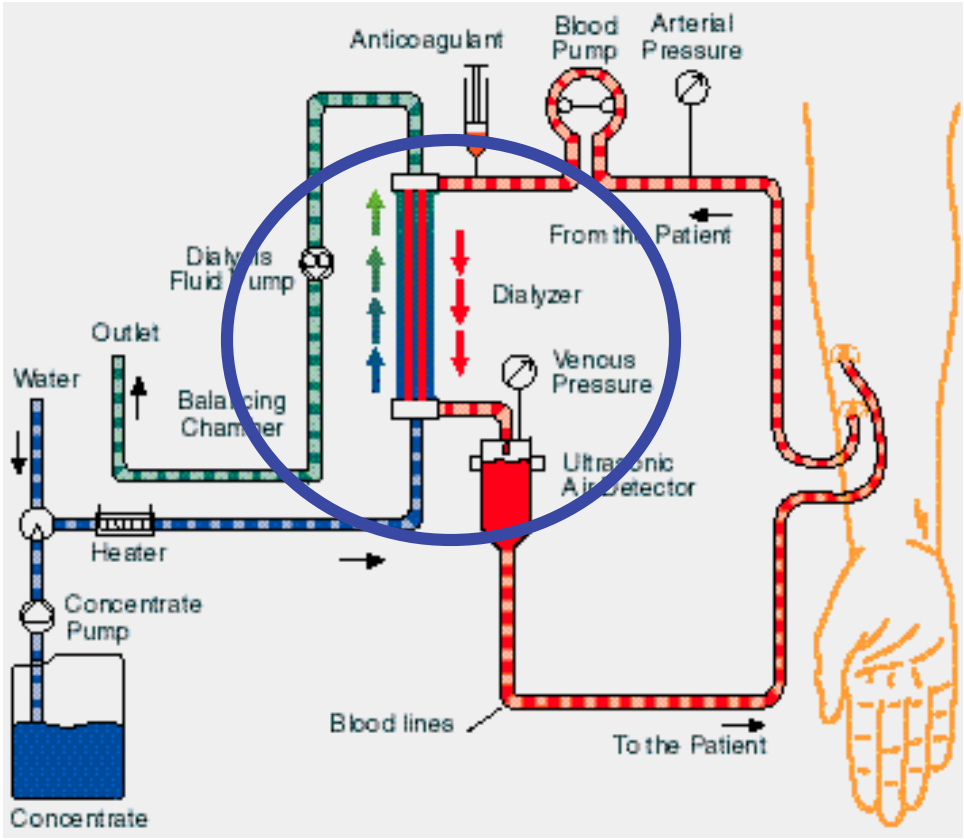
- Persistent metabolic disturbances refractory to medical therapy
  - Hyperkalemia
  - Metabolic acidosis
- Fluid overload refractory to diuretics
- Progressive uremia
  - Encephalopathy
  - Persistent nausea and vomiting
  - Evidence of malnutrition

CKD and Dialysis

- 2 types of dialysis:
  - Hemodialysis (HD)
  - Peritoneal dialysis (PD)
- No major outcome difference demonstrated for either
- Modality driven largely by patient choice

Hemodialysis





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Drug Properties

Case on HD

- You are working on the inpatient medicine unit and a patient with DM nephropathy and neuropathy has been admitted to start hemodialysis (HD).
- Among the many medications being taken by this patient is duloxetine. You are asked to provide information regarding the appropriate dosing of duloxetine around the HD schedule.
- Your review of the standard drug information resources reveals no specific information on drug dialyzability.

What do you advise?

What determines Drug Dialyzability

- Molecular Size
- Protein Binding
- Volume of Distribution
- Water Solubility
- Plasma Clearance
- Technical Aspects of Dialysis

Molecular Weight

Size of the drug is Important!

- Up to 13, 000 daltons removed by High Flux/High Efficiency Dialyzers

Can you predict dialyzability on the basis of these molecular weights in Daltons

- Duloxetine (MW 334)
- Vancomycin (MW 1,485)
- Iron dextran (MW 96,400)

Protein Binding

- Primary drug binding proteins are albumin and α_1-acid glycoprotein.
- MW albumin: 69,000.
- MW α_1-acid glycoprotein: 44,100.
- Only unbound drug is dialyzable.

Protein Binding

Can you predict dialyzability on the basis of these protein binding values?

- Duloxetine (MW 334, PB 95%)
- Cefotaxime (MW 477, PB 13-38%)

Volume of Distribution

- An indicator of dialyzer membrane exposure to drug molecules (amount of drug in blood).
- Drugs with large Vd exhibit less dialyzability as compared to those with small Vd.
- Highly lipid soluble drugs tend to have large volumes of distribution and minimal dialyzability in aqueous dialysate.

Volume of Distribution

Can you predict dialyzability on the basis of these volume of distribution values?

- Duloxetine (Vd 1640L; 23L/kg)
- Cefotaxime (Vd 18 L; 0.26 L/kg)

Plasma Clearance

- Inherent metabolic clearance
  $Cl_M = Cl_{renal} + Cl_{nonrenal}$
- In dialysis patients, Cl_{renal} is largely replaced by dialysis clearance (Cl_{dial}).
- If $Cl_{nonrenal}$ is large compared to Cl_{renal}, Cl_{dial} of a drug may be minimal.
- If Cl_{dial} increases Cl_M by 30% or more, Cl_{dial} is considered to be clinically important

Plasma Clearance

Can you predict dialyzability on the basis of these clearance data?

- Duloxetine (renal excretion: <1%- minimally removed
  - 77% of metabolites of the metabolites are removed

Case on HD

- You are working on the inpatient medicine unit and a patient with DM nephropathy and neuropathy has been admitted to start hemodialysis (HD).
- You are asked to provide information regarding the appropriate dosing of duloxetine around the HD schedule.
- Your review of the standard drug information resources reveals no specific information on drug dialyzability.

What do you advise?

a) Duloxetine is dialyzed- give post HD

b) Duloxetine is not dialyzed – give any time

c) Duloxetine is contraindicated- do not give

d) Duloxetine is not dialyzed but is not indicated

Case on HD

- MW is small to permit drug removal by HD
- High Protein binding
- Large Vd
- High Non Renal Clearance

Clinically insignificant amounts of duloxetine removed

Dulextine can be dosed without regard to the effects of dialysis

But remember the metabolites – so start low and go slow

My Approach

Clearance > Size > Protein Binding > Vd

Other Principles in Hemodialysis

- **Membrane Technology**
  - High Flux membranes/High Efficiency Dialyzers:
    - Up to 13,000 daltons (D)
- **Blood Flow Rates**
  - 300-400ml/min
  - High blood flow rates will present more drug to membrane
- **Dialysate Flow Rates**
  - 750ml/min
  - High dialysate flow rates will maximize drug concentration gradient across the membrane
- **Frequency/Duration of Dialysis**

Frequency and Duration of Dialysis

What is Frequent Hemodialysis?

- Short daily hemodialysis (SDHD):
  - 2hrs of HD, 6 days/week - high blood and dialysate flow rates
- Nocturnal Hemodialysis (NHD):
  - Mainly at home, 6-8 hrs/day, 5-7 nights per week at slower blood and dialysate flows
- Slow Long Efficiency Dialysis (SLED)
  - Done in the ICU, Daily for 8-12hrs at slower blood and dialysate flows

SDHD, NHD and SLED

What does this mean clinically and for drug removal?

Drug Dosing in SDHD or NHD or SLED

- Very little in the literature with respect to dosing of drugs in daily dialysis
- Dialyzers (pore size, SA) are similar in daily dialysis to IHD
- What is Different?
  - Blood flow rates
  - Dialysate Flow rates
  - Frequency of Dialysis
  - Duration of Dialysis

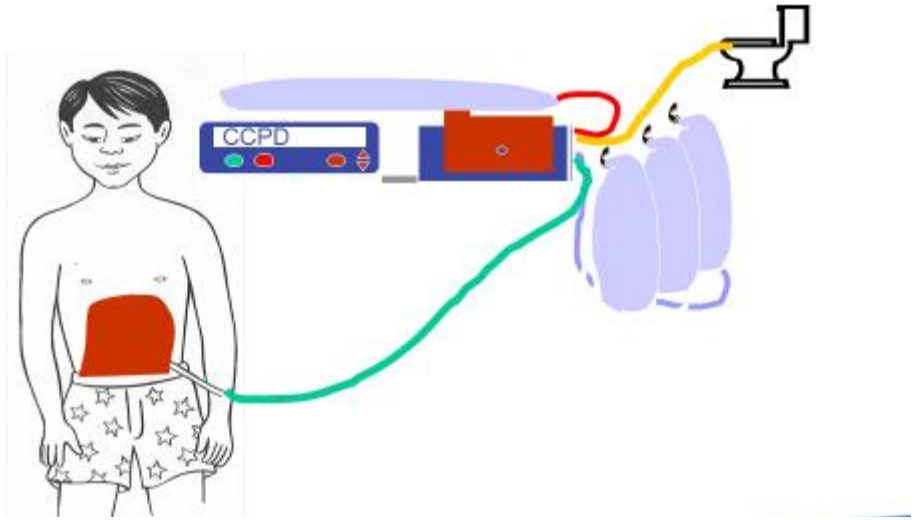
Solute clearance in dialysis

	Small Solute Clearance	Large Solute Clearance	
Increasing frequency	↑	—	SDHD
Increasing time	↑	↑	
Time and Frequency	↑ ↑	↑	NHD & SLED

Peritoneal Dialysis

Ambulatory Peritoneal Dialysis

Continuous Cyclic Peritoneal Dialysis



Practical Tips for Dosing In PD patients

- Systemic Drugs vs Intraperitoneal Drugs
- Treatment of Peritonitis
- Dosing Based on CrCl of 10ml/min

CKD and Consequences

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ANEMIA CASES

Case 1

- RW is a 68 yr old male (70 kg) on HD for the past 5 years secondary to DM. He states he has been feeling tired over the past month
- Other comorbidities:
  - HTN
  - Dyslipidemia
  - CAD

Case 1

- **Labs:**
  - Hgb- 99g/L (last 2 months: 105 and 101g/L)
  - Tsat: 0.16; Ferritin: 242; (3 months ago: Tsat 0.20, Ferritin 550)
  - Ret Count: 108 bil/L
  - Vitamin B: 336; Red cell Folate: 1059
- **Medications:**
  - Darbepoietin 50mcg iv weekly-
  - Iron Sucrose 100mg iv once monthly
  - Amlodipine 10mg po daily
  - Ramipril 10mg daily
  - Atorvastatin 20mg po qhs

- Replavite 1 tab po daily
- $CaCO_3$ 1250mg-2 tabs tid with food.
- Insulin: Humulin 30/70 12 u bid

Case 1

How do we treat his anemia?

A) Increase darbepoeitin

B) Iron Load

C) Both

D) Do nothing

Case 2

- RJ is a 60 year old male on hemodialysis secondary to his DM-2. He started dialysis 2 years ago. He was recently admitted with cellulitis in which he received cefazolin 2 g with each HD and ciprofloxacin 500mg po daily. His labs, past medical history and medications are as follows:

Case 2

Labs (this month)

- Hgb 91g/L (previous 101g/L; 103g/L)
- Ferritin 789ug/L (previous 320ug/L; 333ug/L)
- Tsat 0.16 (previous 0.23; 0.25)
- P 1.45 mmol/L (previous 1.54mmol/L; 1.48mmol/L)
- Ca 2.45 mmol/L (previous 2.42mmol/L; 2.39umol/L)
- PTH 58pmol/L (previous 52pmol/L; 48pmol/L)

History:

- Private Insurance
- Drinks alcohol: 3-4 drinks per week
- No smoking

Case 2

Medications:

- Ramipril 10mg od
- Amlodipine 10mg od
- Replavite 1 tablet daily
- Lantus 24 u sc qhs; Lispro 9 u with each meal
- Atorvastatin 20mg qhs
- Venofer 100mg iv monthly
- Darbepoietin 10mcg iv weekly
- CaC03 1250mg tid with food

- **For his anemia, what would you recommend?**

  A) Increase his darbepoietin to 20mcg iv weekly

  B) Increase iv iron to 100mg iv twice monthly

  C) Increase darbepoietin to 20mcg iv weekly and increase iv iron to 100mg twice monthly

  D) Do nothing

CKD and Consequences

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- Dialysis
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Cases on CKD Bone Disease

Case 1

RR is a 70 year old male on hemodialysis for 3 years now. His reason for ESRD is DM and HTN which he has had for 20 years. On rounds he complains of feeling generally unwell.

PMH

- HTN x 20 years
- DM 2 x 20 years

Family/Social History

- Alcohol: occasional socially; Does not smoke
- Exercise: cycles for 30 min 3x per week during Hemodialysis
- Wt; 72kg
- Has ODB coverage
- Allergies: NKDA

Case 1

Medications:

- NPH 22u sc bid
- Amlodipine 10mg od
- Atorvastatin 20mg qhs
- Ramipril 10mg od
- Metoprolol 50mg bid
- Replavite 1 tab daily
- Lorazepam 1mg qhs prn
- Darbepoietin 40mcg iv weekly
- CaCO3 1250mg 1 tab with lunch and supper
- Calcitriol 0.25mcg 3x/week

Labs:

- Hgb 115g/L (140-180)
- Ferritin 289ug/L (22-275)
- Tsat 29% (0.25-0.5)
- B12 and Folate: normal
- Calcium 2.19mmol/L (2.2-2.6)
- P 2.11mmol/L (0.8 – 1.40)
- PTH 90pmol/L (1.3—7.6)
- Albumin 39 g/L (38-50)
- ALP 50 u/L (40-150)
- Sr Cr 889 umol/L (65-110)
- A1C 6.8%
- BP 130/ 80; HR 72 Bpm

Case 1

What do we do for managing his CKD Bone Disease

A) Nothing- talk to patient re: medications

B) Change binder to sevalemer

C) Change binder to lanthanum

D) Increase Calcitriol

Case 2

JB is a 67 year old female on hemodialysis for 5 years now. Her reason for ESRD is vasculitis.

Family History: None
Social: Has ODB coverage
Allergies: None
Medical History:

- Appendix removed 10 years ago
- Parathyroidectory 3 years ago

Case 2

Medications

- Ramipril 5mg daily
- Atorvastatin 20mg daily
- Replavite 1 tab daily
- Darbeopoieitn 20mcg iv weekly
- CaCO3 1250mg 2 tabs tid with food
- Calcitriol 0.25mcg po daily

Labs

- Hgb 110g/L (140-180)
- Ferritin 489ug/L (22-275)
- Tsat 25% (0.25-0.5)
- B12 and Folate: normal
- Calcium 2.68mmol/L (2.2-2.6) last 2 months: 2.75 and 2.65
- P 2.11mmol/L (0.8 – 1.40) last 2 months: 1.95 and 2.15
- PTH 90pmol/L (1.3—7.6) last month 67
- Albumin 39 g/L (38-50)
- ALP 50 u/L (40-150)
- Sr Cr 889 umol/L (65-110)
- A1C 6.8%
- BP 130/ 80; HR 72

Case 2

How do you manage his CKD Bone Disease?

A) Change Calcium to Sevelamer

B) Change Calcium to Lanthanum

C) Increase calcitriol

D) Decrease the calcium in the dialysate bath

Case 2b

After 3 months we control her P (<1.8mmol/L) and Calcium still at 2.65mmol/L. Her PTH is now 150pmol/L.

What can we do?

A) Increase sevelamer

B) Increase lanthanum

C) Increase calcitriol

D) Start cinacalcet

Case 3

- LL is a 61 yr postmenopausal woman with Lung Tx in 1992 and on NHD (5x/week) since 2003 (2° to cyclosporin toxicity)
- Meds: prednisone, azathioprine, cyclosporin, Aranesp, simvastatin, septra, irbesartan
- Labs are N range except PTH < 1.0
- Recent BMD scores:
  - Lumbar spine: –2.8
  - Femoral neck: -3.0
  - Total Hip: -2.6
- Fracture of left ankle and compression fracture of thoracic spine

Case 3

- How do we manage her osteoporosis?
- A) Do nothing
- B) Start alendronate
- C) Start Denosumab
- D) Start Calcium and Vitamin D

Case on Anticoagulation in CKD

Case

Mrs V. is a 55 year old lady on HD since 2007. She has ESRD from unknown origin.

- PMH:
  - CAD- MI and ischemic cardiomyopathy
  - PAF- right occipital infarct in 2015
  - PVD
  - Hepatitis C (treated with interferon)
- Medications:
  - rosuvastatin, ramipril, metoprolol, clopidogrel, ASA, **warfarin**, pantoprazole, replavite, cinacalcet, Aranesp, Venofer

- She is admitted with calciphylaxis of her left foot

Case

What do we do about her anticoagulation for AF?

A) Continue warfarin

B) D/C warfarin and start a DOAC

C) D/C warfarin and start a LMWH

D) D/C warfarin

Case– Part B

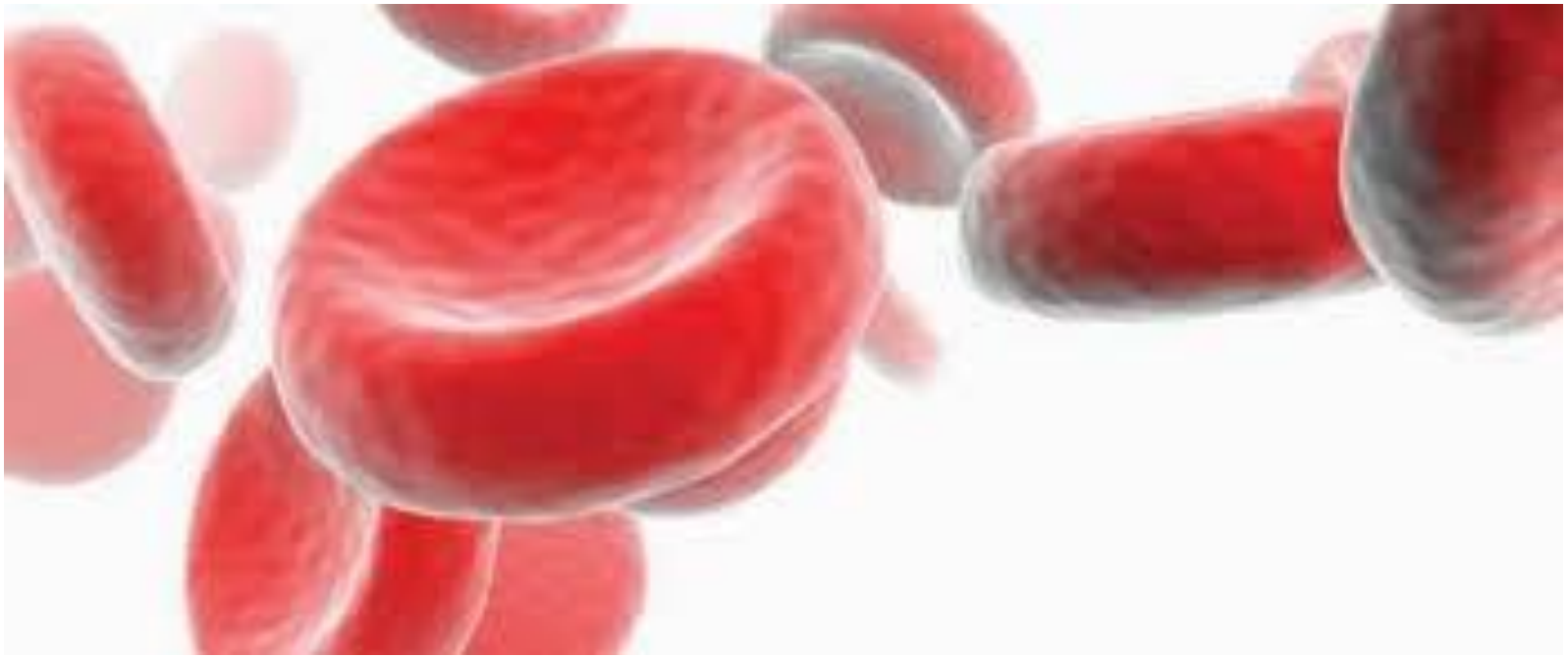
Which DOAC?

a) Rivaroxaban
b) Dabigatron
c) Apixaban
d) Endoxaban

Background Information for Cases

- Anemia
- CKD Bone Disease
- Anticoagulation

Anemia of CKD



Definition Of Anemia

- Reduction of hemoglobin or a decrease in the circulating red blood cell mass to below age-specific and gender-specific limits

- Anemia should be considered a sign, not a disease

Presentation

- **Recent Onset:** tachycardia, lightheadedness, SOB, HA

- **Chronic Onset:** fatigue, decreased exercise tolerance, weakness, vertigo, sensitivity to cold, pallor, palpitations

Laboratory Evaluation

Initial Evaluation involves a **CBC**:

- RBC count
- WBC count
- Hgb
- Hct
- RBC indices (MCV, MCH, MCHC)
- Reticuloctye count
- RBC distribution width (RDW)
- Platelet Count

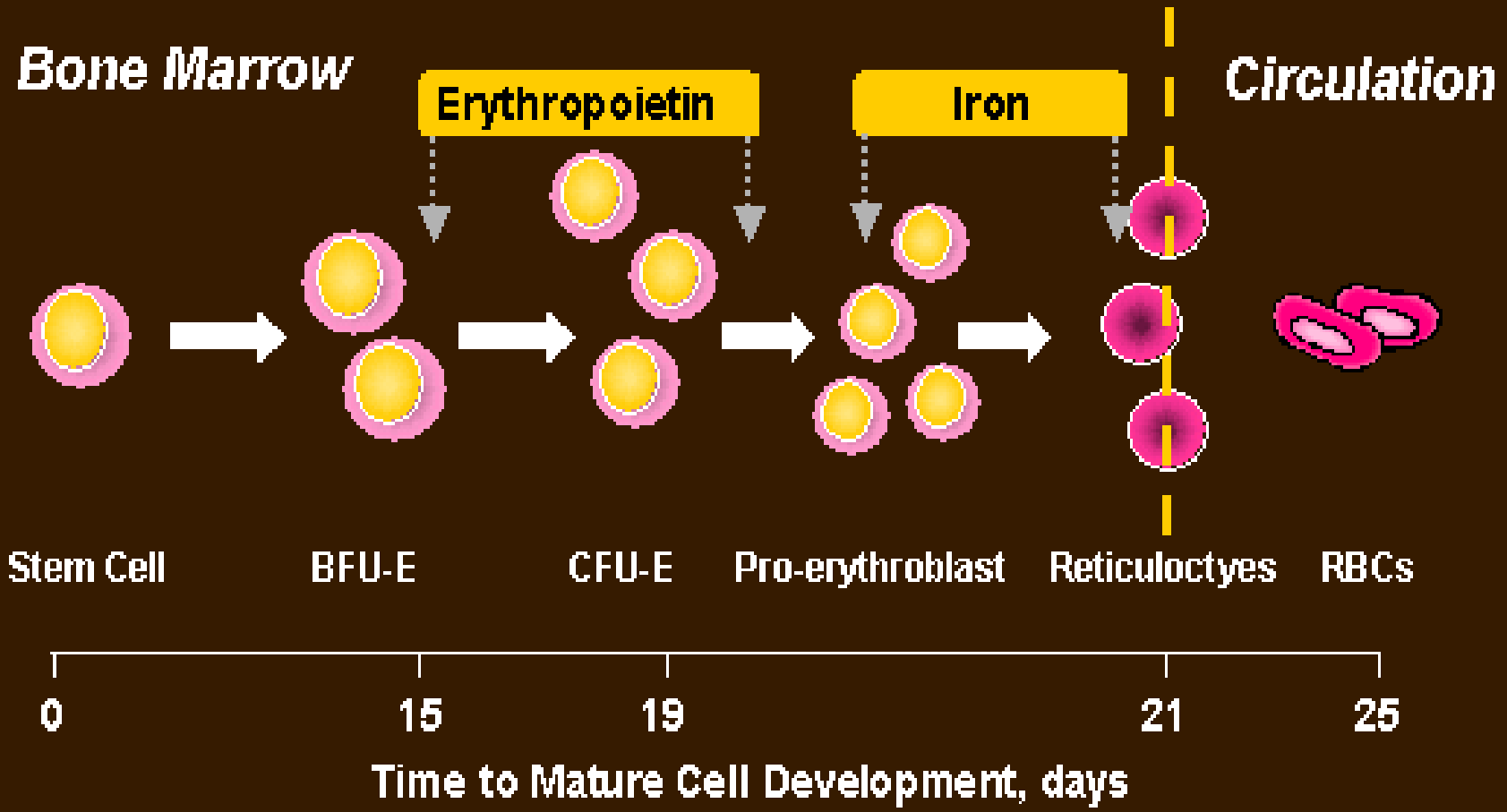
Anemia of CKD

- Very common co morbidity in these patients

Mechanism

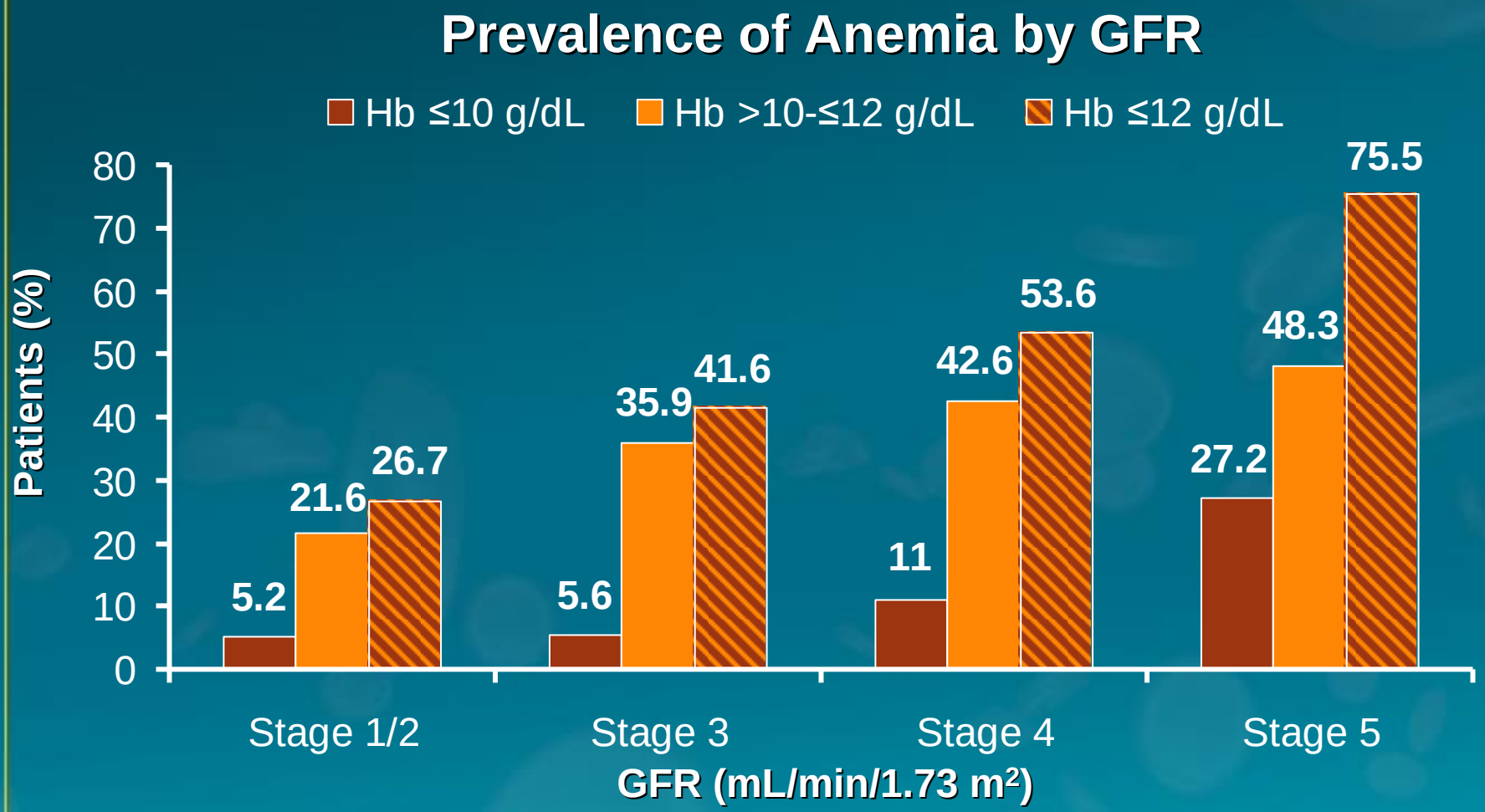
- decreased production of EPO by kidneys
- decreased life span of RBC due to uremia
  - 60 days vs 120 days
- iron losses: blood loss in hemodialysis machine (5mg/dialysis)
- folic acid thru dialysis
- frequent labs

Healthy RBC Production Requires EPO *and* Iron



Brock. *Iron Metabolism in Health and Disease*. W.B. Saunders Co; 1994.

Anemia Occurs Early and Its Prevalence Increases as Renal Function Declines



Anemia=Hb ≤12 g/dL

N=5,222

McClellan et al. *Curr Med Res Opin.* 2004;20:1501-1510.

The Pathophysiologic Consequences of Untreated Anemia

Cardiac function[1]
Cognitive function[2]
Exercise and physical performance[3]
Health-related quality of life[4]

Increased cardiac output requirement[1,5]
LVMI[1,5]
Transfusion requirements[6]
Hospitalization[7,8]
Mortality[9,10]
Expenditures[8]

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2. Nissenson. *Am J Kidney Dis.* 1992;20(1suppl1):S21-S24.
3. Mancini et al. *Circulation.* 2003;107:294-299.
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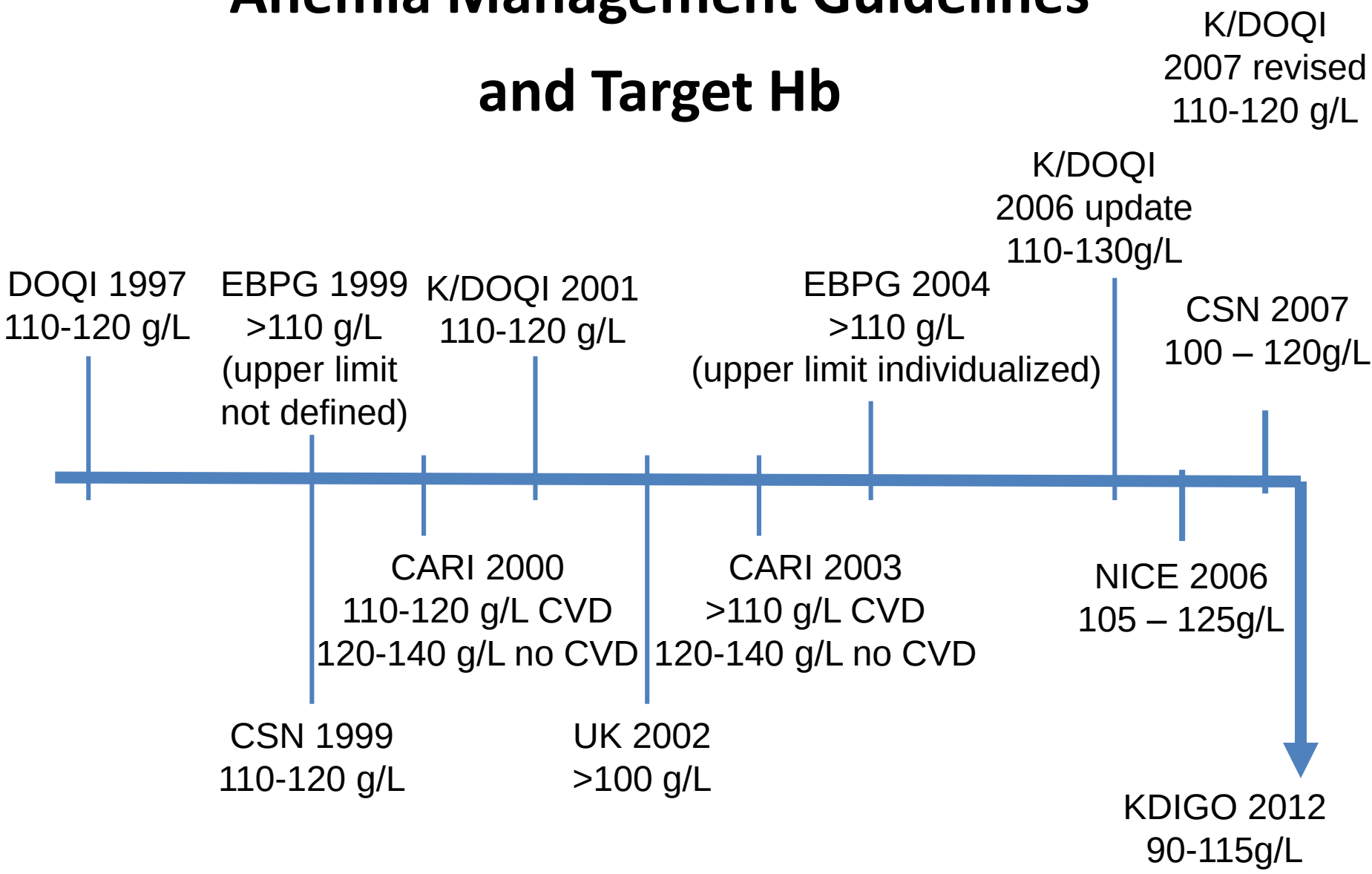
Study	Study Population	HCT/ Hb Target	CV Outcome	Quality of Life
Besarab *NEJM* 339:1998	HD + CHF/CAD	30 42	No difference	Improved
Foley *KI* 58:2000	HD-CHF/CAD	95-105 130-140	No difference	Improved
Roger *JASN* 15:2004	Stage 3-5	90-100 120-130	No difference	Improved
Parfrey *JASN* 16:2005	HD-CHF/CAD	95-115 135 -145	No difference	Improved
Levin *AJKD* 46:2005	Stage 2-5	90-105 12-14	No difference	Improved
Singh *NEJM* 355: 2006	Stage 4-5	110-115 130-135	Worse in high Hb	No difference
Druecke *NEJM* 355: 2006	Stage 4-5	110-115 130-150	No difference	Improved
Pfeffer NEJM 2009	Stage 3-5	130 vs 90	No difference (Increased stroke)	No difference

Anemia Management Guidelines and Target Hb



CVD=cardiovascular disease

Anemia of CKD- Treatment

- **Erythropoietin (Eprex®)**
  - initial dose: 50units/kg 2-3 x /week
  - maintenance dose varies widely
  - sc vs iv dosing
  - 2-3 x/week vs 1x/week
- **Darbepoietin (Aranesp®)**
  - initial dose: 0.45mcg/kg 1x week
  - sc vs iv dosing
  - q1w or q2w and up to qmonthly

Anemia of CKD

Monitoring

- **Efficacy Endpts**
  - Hgb: 90-115g/L
  - Improved QofL
- **Safety Endpts**
  - HTN
  - Pure red cell aplasia

Anemia of CKD

Hyporesponse to EPO

- Consider:
  - iron deficiency
  - GI blood loss
  - infection/inflammation
  - hyperparathyroidism
  - malignancy
  - other anemias

Anemia of CKD

Hyporesponse to EPO

- Consider:
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  - infection/inflammation
  - hyperparathyroidism
  - malignancy
  - other anemias

Anemia of CKD

- **When do we add iron?**
  - TSAT <20% (<30%- new KDIGO)
  - Ferritin < 200 (< 500 –new KDIGO)
- **How do we administer iron?**
  - Oral iron is tried first and usual practice for CKD 3-4
  - Iv iron preferred for HD pts
- **Which iron product?**

IRON REPLACEMENT THERAPY

Oral preparations

- Iron salts
- Newer forms of oral iron

Intravenous preparations

- Iron dextran
- Iron saccharate/sucrose
- Iron gluconate
- Ferrumoxytol

ORAL IRON PRODUCTS

Brand	Strength (elemental iron)	Quantity	Cost (cost/tab)	Cost/100mg elemental iron	Coverage
Ferrous sulfate 300mg	60mg drops 15mg/mL 6mg/mL	100 50mL 250mL	$6.49 ($0.07/tab) $19.99 $19.99	$0.12 $2.68 $1.34	No
Ferrous gluconate 300mg	35mg	100	$5.99 ($0.06/tab)	$0.17	Yes
Palafer (ferrous fumarate 300mg)	100mg 20mg/mL	30 100mL	$12.49 ($0.42/tab) $19.99	$0.42 ($0.15) $1.00	Yes
Proferrin (heme iron polypeptide)	12mg	100	$0.39/tab	n/a	No
Triferex (polysaccharide iron complex)	150mg	100	$66 ($0.66/tab)	n/a	No

ORAL IRON PREPARATIONS

Advantages

- Easy to administer
- Convenient
- Hypersensitivity reaction is less likely
- Inexpensive

Disadvantages

- Gastrointestinal side effects
- Drug interactions
  - Calcium
  - H_2-blockers/PPIs
- Poor absorption

	Iron Dextran	Iron Sucrose	Iron Gluconate	Ferrumoxytol
Chemical description	Ferric oxyhydroxide-dextran complex	Iron (III) hydroxide sucrose complex	Sodium ferric gluconate complex in sucrose	carbohydrate-coated, superparamagnetic iron oxide nanoparticle
Availability	Infulfer® 50mg/mL in 2mL and 5mL vials	Venofer® 20mg/mL in 5mL vials	Ferrlecit® 12.5mg/mL in 5mL vials	Ferraheme® 510mg vials (17ml vials)
Indication	Treatment of patients with iron deficiency where oral form is unsatisfactory or impossible	Treatment of patients with dialysis-associated anemia	Treatment of iron deficiency in dialysis-associated anemia	Treatment of iron deficiency in dialysis-associated anemia
Contraindications/ Precautions	•Hypersensitivity to product •Anemia unrelated to iron deficiency •Acute kidney infection •Concomitant use of oral iron products •History of asthma •History of allergies, liver dysfunction	•Hypersensitivity to product •Anemia unrelated to iron deficiency •Patients with iron overload	•Hypersensitivity to product •Anemia unrelated to iron deficiency •Patients with iron overload •Formuation contains benzyl alcohol—not for use in neonates	•Hypersensitivity to product •Anemia unrelated to iron deficiency •Patients with iron overload May interfere with MRI for up to 3 months (max effects 1-2 days post dose) due to it's superparamagnetic properties
Test dose	•IM/IV: 0.5mL (25mg) one hr before rest of dose	•Not required	•A one time test dose: 2mL (25mg) diluted in 50mL NS over 1hr	•Not required

	Iron Dextran	Iron Saccharate/ Sucrose	Iron Gluconate	Ferumoxytol
Administration	IM or IV	IV	IV	IV push
Adverse effects	•Life-threatening anaphylactoid reaction in 0.6-0.7% of patients •Increased risk of adverse effects with TDI •Symptoms: arthralgia, backache, chills, dizziness, fever, headache, malaise, myalgia, nausea & vomiting, subsiding in 3-4 days •Other effects seen: chest pain, hypotension,, pruritus, abdominal pain	•Post-marketing anaphylactoid reactions 0.006% •Life-threatening reactions 0.002% •Hypotension (36%) may be related to rate and total dose administered •Cramps 23% •Effects >5%: nausea, vomiting, diarrhea, headache	•Life-threatening reaction 0.1% •Others: hypotension, flushing, hypertension, syncope, tachycardia, cramps, dizziness, pruritus, nausea, vomiting, myalgia, arthralgia, dyspnea, chest pain, asthenia, headache, abdominal pain, fatigue	•diarrhea (4.0% vs. 8.2%), nausea (3.1% vs. 7.5%), dizziness (2.6% vs. 1.8%), hypotension (2.5% vs. 0.4%), constipation (2.1% vs. 5.7%) and peripheral edema (2.0% vs. 3.2%)
Drug interactions	Do not mix any medications	No studies	No studies	No studies
Approximate cost	$	$$	$$	$$

INTRAVENOUS IRON PREPARATIONS

Advantages

- Better efficacy to replace & maintain iron stores compared to PO preparations
- No dependence on GI absorption

Disadvantages

- Potential for anaphylaxis-type reactions
- Requires IV access
- Controversies:
  - Oxidative stress
  - Risk of infections
- Requires multiple hospital visits by patient

ADMINISTRATION OF IV IRON

- IV iron has been administered in different doses & dosing intervals
  - Iron dextran 1g IV in a single infusion
  - Iron sucrose 1g load usually given as 100mg IV each hemodialysis session x10 doses
  - Iron gluconate 125mg IV each session x 8 doses
- Large doses of IV iron sucrose given over 4-6 hours have been well-tolerated

Anemia of CKD

- **When to monitor**
  - do not draw iron studies until 2 weeks after loading dose
  - For oral replacement it will take 3-6months to see storage indices to increase
- **What to monitor**
  - **Efficacy Endpts**
    - Ferritin > 200
    - Tsat > 0.2
  - **Safety Endpts**
    - Infusion Related (IV)
    - GI side effects

Anemia of CKD

Hyporesponse to EPO

- Consider:
  - iron deficiency
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  - infection/inflammation
  - hyperparathyroidism
  - malignancy
  - other anemias

Anemia of CKD

Hyporesponse to EPO

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  - iron deficiency
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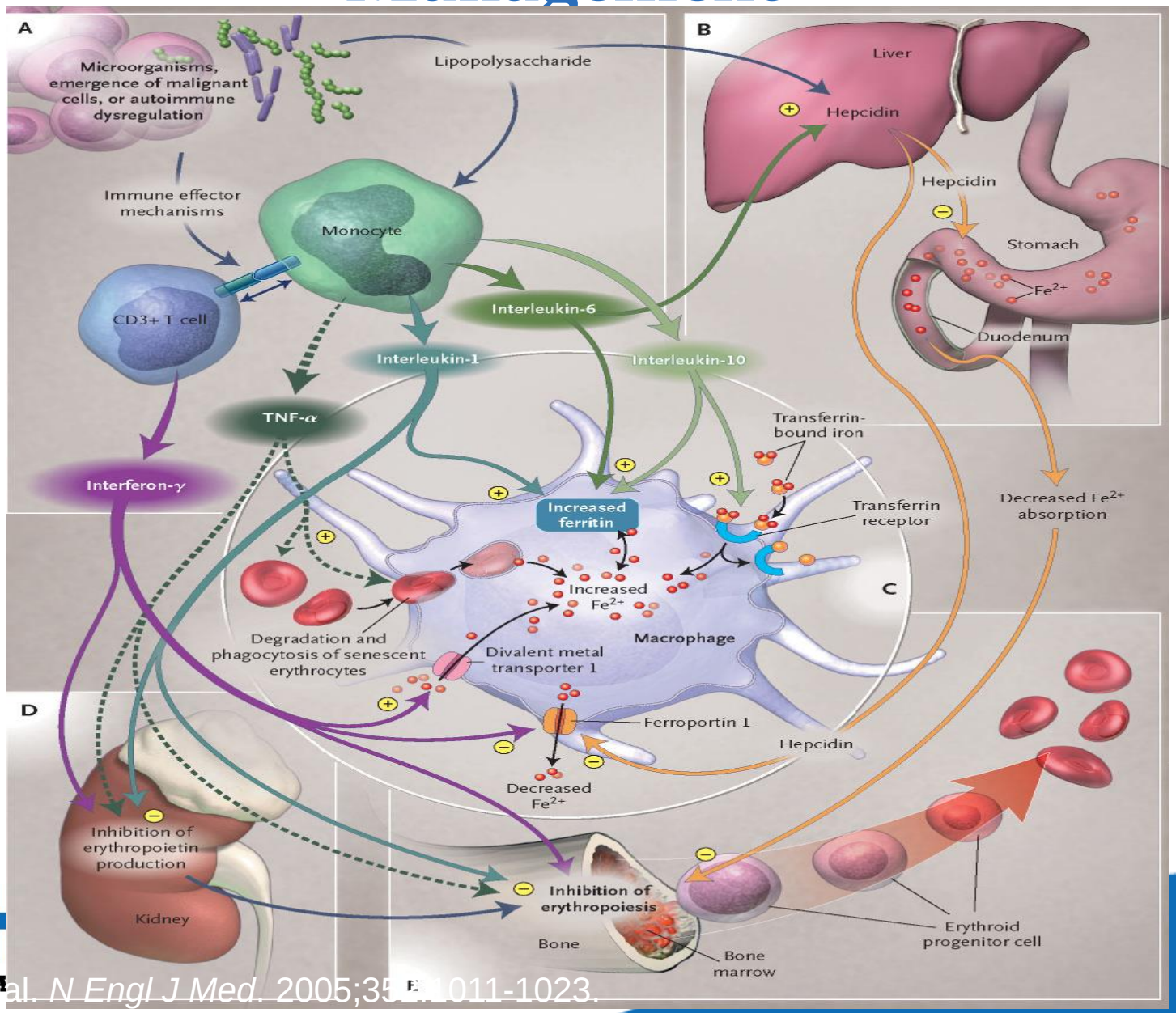
  - malignancy
  - other anemias

Infection & Inflamation in Anemia Management



al. *N Engl J Med*. 2005;35[illegible]1011-1023.

Hyporesponsiveness: Infection/Inflammation

- Inflammation/infection may be a common cause of hyporesponse to ESAs in patients with CKD anemia.
- Clinical data indicate that CRP levels and ESA dose requirements may remain elevated until the underlying condition is corrected.
- When an underlying inflammatory condition affects Hb, consider the following when clinically appropriate:
  - Temporarily increasing the ESA dose in 25% increments to mediate the effect on Hb.
  - Permanently increasing the ESA dose in 25% increments when the underlying condition cannot be completely controlled.

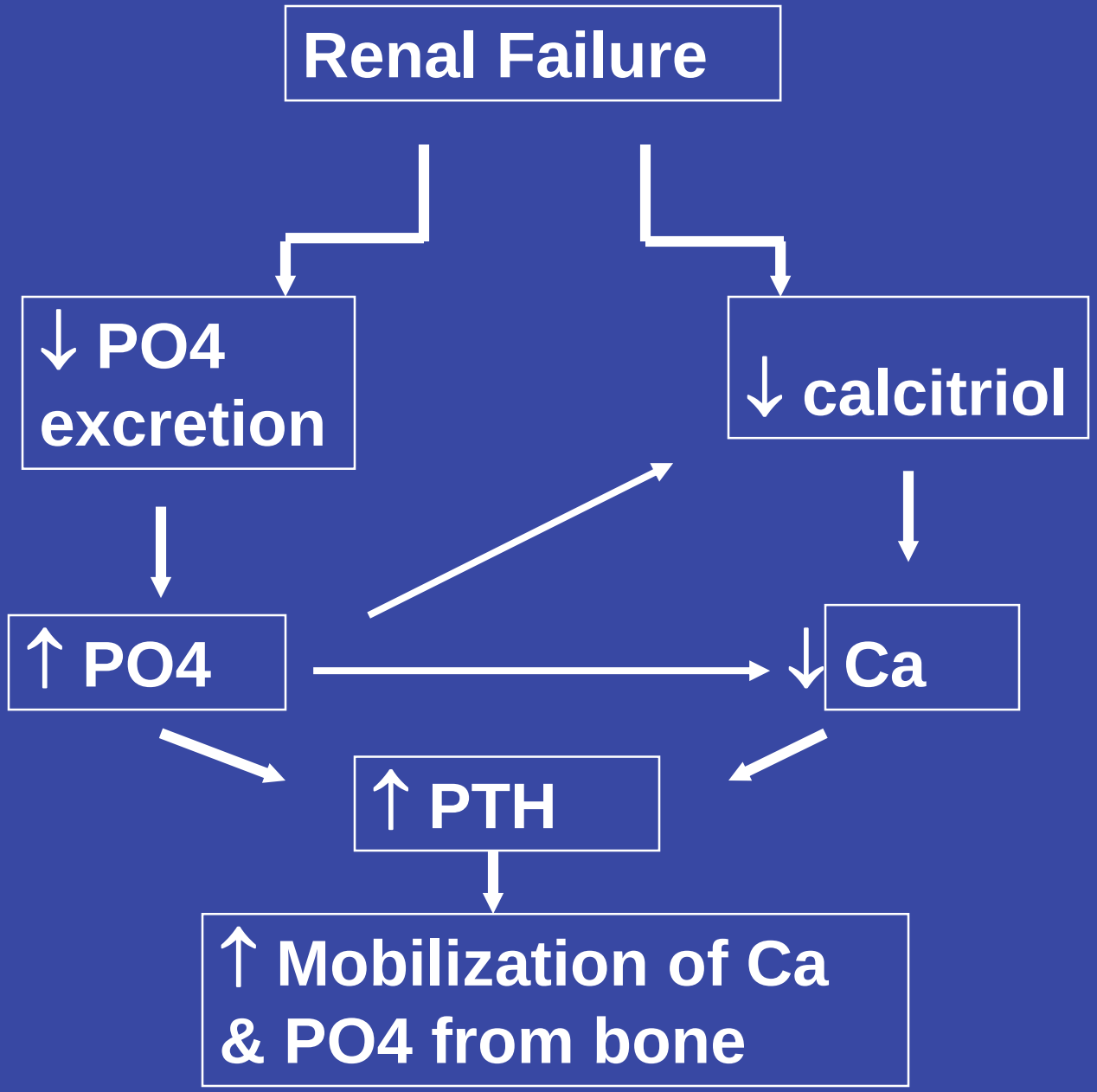
Summary

- Treatment of renal anemia with ESA has evolved over the past 20 years.
- Adverse outcomes have been observed when the level of hemoglobin *targeted* is > 130 g/L.
- Recommended target is 90 – 115g/L.
- Iron replacement is key for erythropoiesis

CKD and Consequences

- Cardiovascular disease
  - CAD
  - Hypertension
  - Pericarditis
- Volume overload
- Anemia
- Bone and mineral metabolism
  - Hypocalcemia
  - Hyperphosphatemia
- Electrolyte abnormalities
  - Hyperkalemia
  - Metabolic acidosis
- Uremia
  - Nausea, vomiting
  - Pruritus
  - Encephalopathy
- Dialysis
  - Hemodialysis
  - Peritoneal Dialysis

Bone Mineral Metabolism in CKD


Renal Failure
↓ PO4 excretion
↓ calcitriol
↑ PO4
↓ Ca
↑ PTH
↑ Mobilization of Ca & PO4 from bone

Implications

- Increased mortality
- Calcification
- Bone Disease

Implications

- Increased mortality
- Calcification
- Bone Disease

Increased Mortality

- Poor phosphorous control
- Increased PTH levels

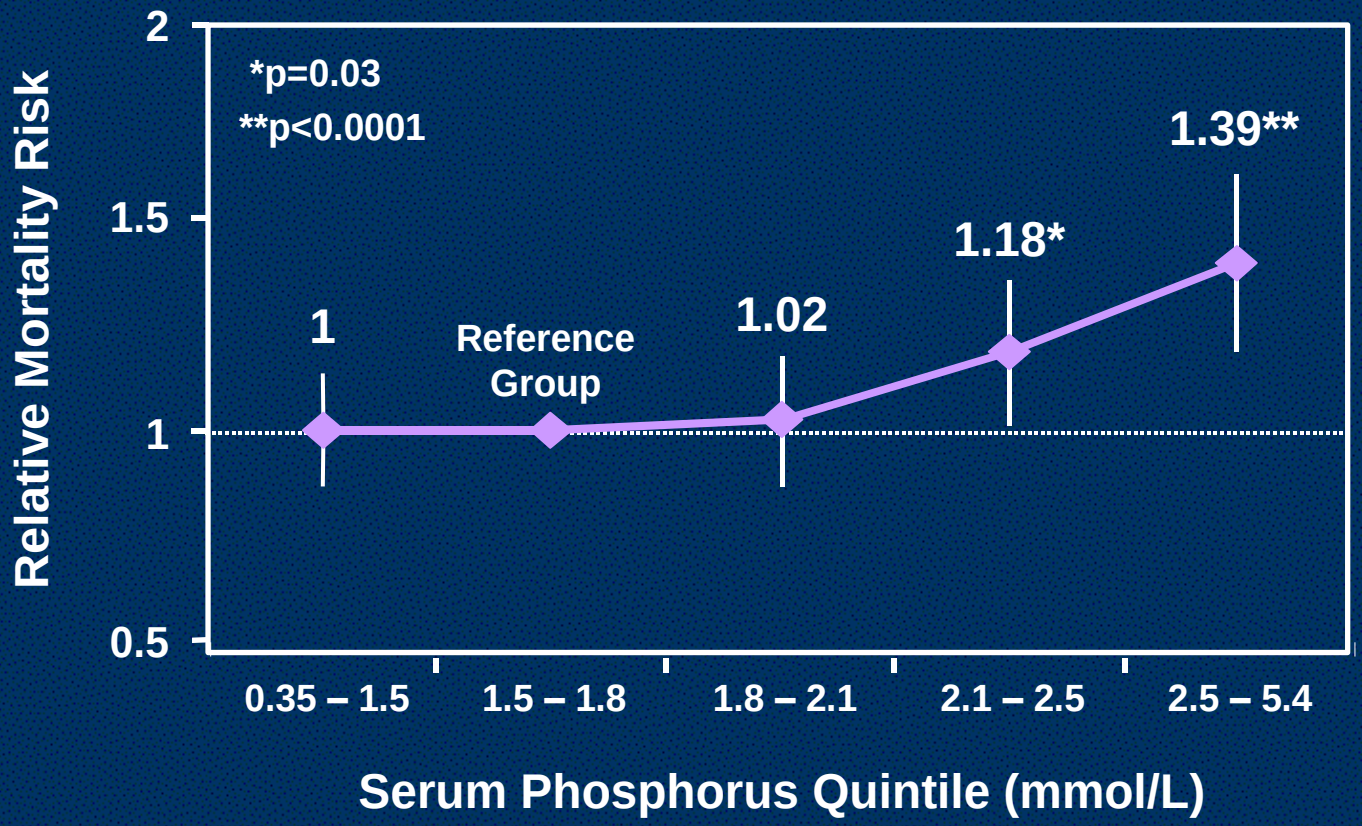
both independently associated with an increased mortality risk and cardiac death

What is considered a high P value in CKD patients and is it common?

Current International Guidelines

Guideline	Target Intact PTH	Target Calcium	Target Phosphorous
Europe (2000)	9.35-18.7 pmol/L	2.1-2.7 mmol/L	1.49-1.81 mmol/L
Australia (2000)	2-3 times upper limit of normal	2.1-2.6 mmol/L	<2.20, preferably <1.81 mmol/L
K/DOQI (2003)	16.5-33 pmol/L Stage 3: 3.85-7.7 Stage 4: 7.7-12.1	2.1-2.4 mmol/L Stage 3&4: 2.2-2.6	1.13-1.78 mmol/L Stage3&4: 0.84-1.49
KDIGO/CSN	< 50pmol/L	Normal range	Normal Range

Elevated Serum Phosphorus Levels Are Associated with Increased Mortality Risk



Vertical bars indicate 5% to 95% confidence intervals; n=6407

Block GA et al. *Am J Kidney Dis* 1998;31:607-617.

Summary of Increased Mortality

- Elevated serum phosphorus levels are very common among hemodialysis patients
- Pts with a serum phosphorus level greater than 2.1 had a 41% higher risk of CAD

- Bottom line: CONTROL Serum Phosphorous

Implications

- Increased mortality
- Calcification
- Bone Disease

Pathogenesis

Promoters

Osteocalcin

Osteopontin

Cbfa-1

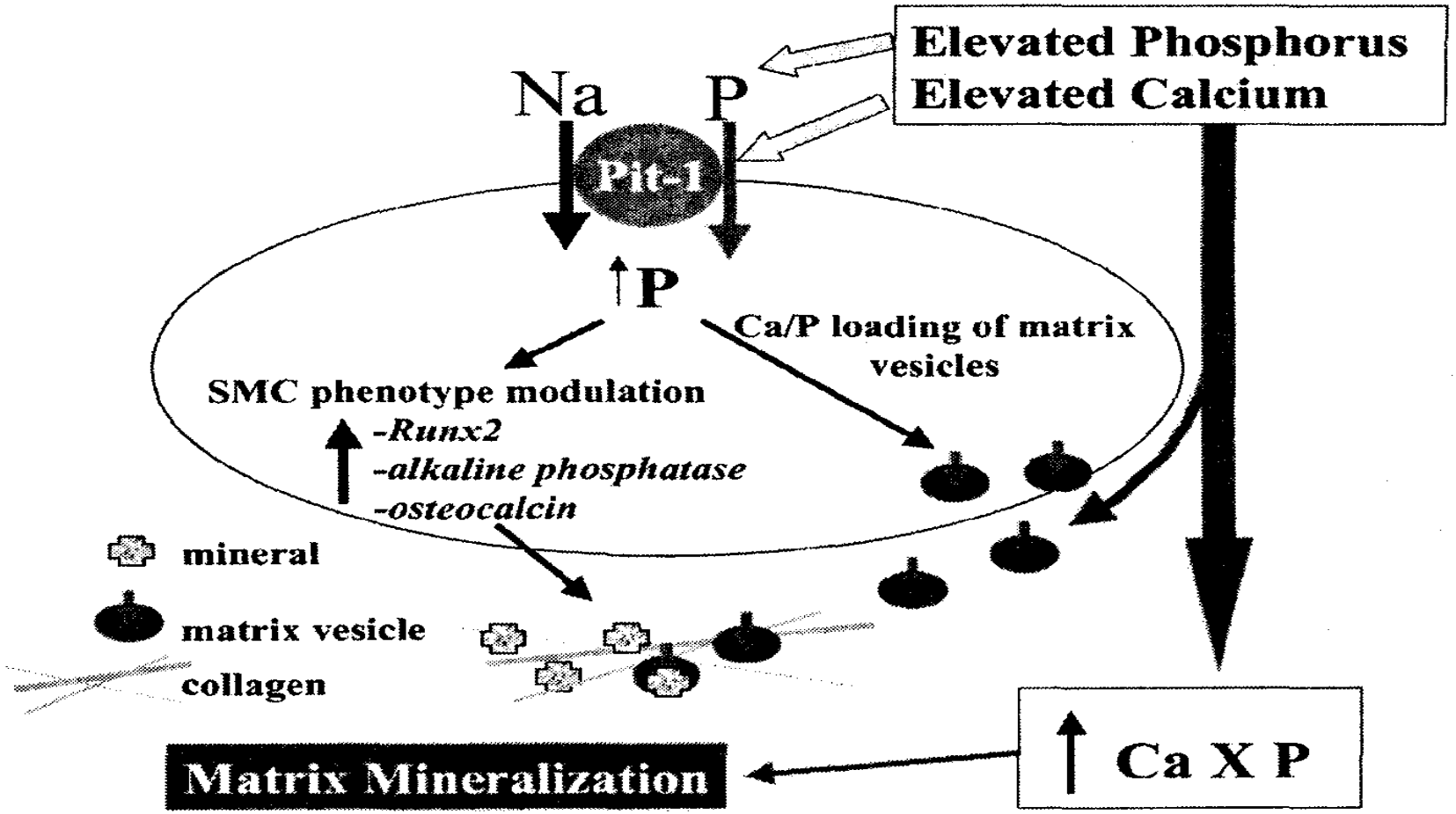
Inhibitors

MGP

Osteoprotegerin

Fetuin-A

Pathogenesis



Implications

- Increased mortality
- Calcification
- Bone Disease

Bone Disease of CKD

Osteitis fibrosa cystica

- High turnover bone disease
- Associated with ↑ PTH → stimulates osteoclast activity, bone breakdown, resorption

Osteomalacia

- Low turnover bone disease with abnormal mineralization
- Softening of bone
- Historically associated with aluminum toxicity

Adynamic bone disease

- Low turnover bone disease with normal mineralization
- Caused by excessive PTH suppression through vitamin D agents, calcimimetics, or phosphate binders

Tamasello, SR. PSAP 6th Edition. 2007; 55-67.

Goals of Treatment

- Correct or prevent hyperphosphatemia
- Normalize serum calcium levels
- Control PTH within target range

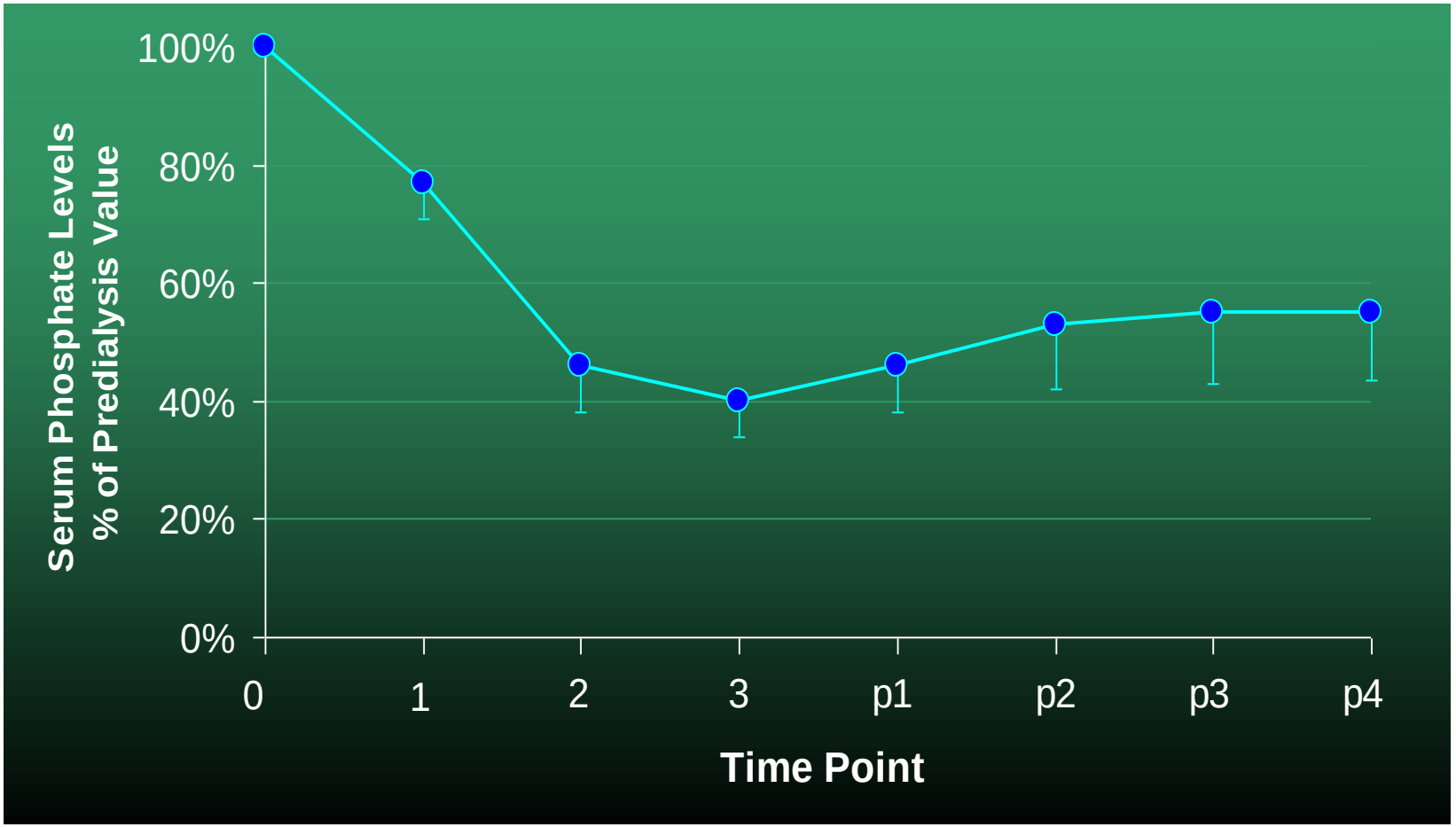
Phosphorous Management

- Dietary phosphate restriction
- Dialysis
- Phosphate-binding agents:
  - Aluminum based
  - Calcium based
  - Noncalcium, nonaluminum based

Diet

- Difficulty with long-term compliance
- Recommended protein intake (1.2 grams per kilogram body weight per day for adults)
- Phosphorus restrictions may compromise protein intake and nutritional status

Dialysis


Serum Phosphate Levels
% of Predialysis Value
100%
80%
60%
40%
20%
0%
0
1
2
3
p1
p2
p3
p4
Time Point

Aluminum-Containing P Binders

- Once the Gold Standard- excellent P binder
- 3rd line : aluminum accumulation
  - CNS toxicity, worsening anemia, constipation
  - Can interfere with bone mineralization, causing osteomalacia
- Usually used short-term with frequent monitoring
- Examples: Aluminum Hydroxide or Amphogel® 320mg/5mL
- Cost: $7 for 350mL (15ml/dose is $0.30)

Calcium-Containing P Binders

Calcium Carbonate:

- 1250mg contains 500mg elemental calcium
- Given at the start of a snack or meal
- Drug interactions (quinolones, iron, ranitidine)
- Inexpensive: $0.05/tab

Calcium-Containing P Binders

Calcium Acetate (PhosLo®):

- 669mg contains 169mg elemental calcium
- Enhanced potency- Binds 2x phosphorus as $CaCO_3$ but hypercalcemia similar between agents
- More expensive ($0.45/tab)

Calcium-Containing P Binders

Limitations

- SEs: GI disturbances
- Nonadherence
- Increased incidence of hypercalcemic episodes
- Continued calcium overload
- Drug Interactions

Nonmetal-Based P Binders

Sevelamer hydrochloride (Renagel®):

- Available as 800mg tablets
- Binds phosphate thru ion exchange
- Several trials comparing Sevelamer to calcium salts

Nonmetal-Based P Binders

Sevelamer hydrochloride (Renagel®)

- Limited long-term experience
- Pill burden (number of capsules)
- Cost ($1.57/800mg tab)
- EAP required:
  - Ca > 2.6
  - P > 1.8

Metal-Based P Binders

Lanthanum Carbonate (Fosrenal®)

- Well tolerated
- Effective binder

- Limitations:
  - No long term studies- worry about accumulation
  - Cost: $12/day
  - EAP:
    - Ca > 2.6
    - P > 1.8

Niacin

- Small studies using different forms of Niacin (Nicotinic acid) and niacinamide (Nicotinamide)
- Various doses used: 375-1500mg
- MOA: Inhibits Na-P co transporter in the small intestine
- SEs: flushing, GI Intolerance, thrombocytopenia, hepatitis
- Cost: Niaspan® 500mg tab is $1.16 ($3.48/dose)

Management of 2° Hyperparathyroidism

- Management of Phosphorous & Calcium
- Vitamin D analogues
  - Calcitriol (Rocaltrol® & Calcijex®)
  - 1∝-hydroxyvitamin D2 (One-Alpha®)
- Calcimimetic Agents
  - Cinacalcet (Sensipar®)
- Surgical Management

Vitamin D Analogues - Calcitriol

Actions:

- Increases Ca and PO_4 absorption - Decreases PTH production and secretion

Availability & Dosing

- Iv or oral
- Daily vs pulse therapy
- Covered by ODB

Limitations

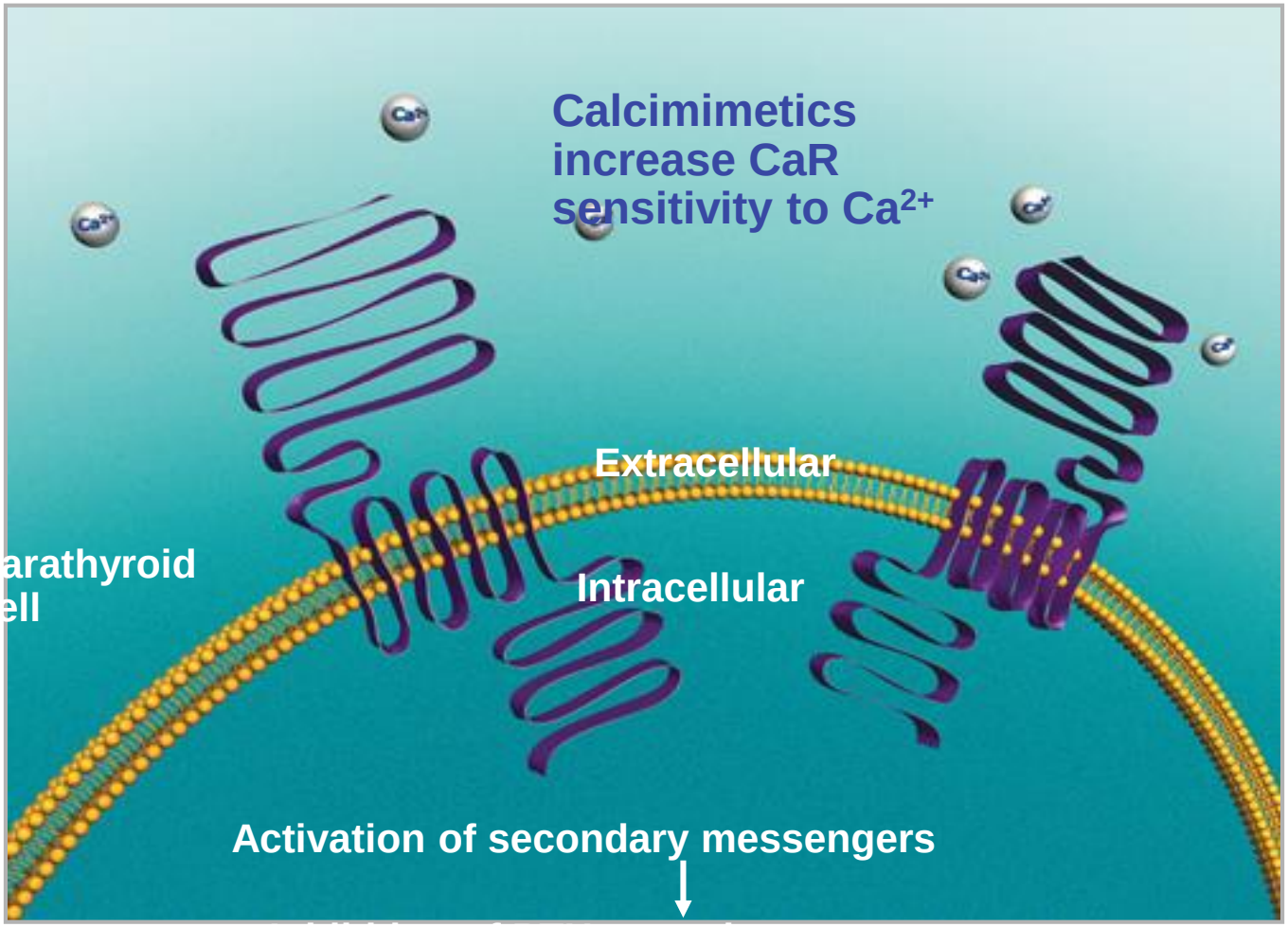
- Hypercalcemia & Hyperphosphatemia

Vitamin D Analogues

One-Alpha

- Prodrug: Needs to be activated in liver
- Covered by ODB; Available as iv and oral
- Hypercalcemia and hyperphosphatemia

Calcimimetic - Cinacalcet



Calcimimetic - Cinacalcet

- **SEs**
  - N & V
  - Hypocalcemia
- **Dosing:**
  - Once daily with or without food (t1/2: 30-40 hours)
- **Drug Interactions:**
  - Strong inhibitor of **CYP2D6** in vitro: TCA antidepressants may require adjustments
- **Limitations**
  - Cost and Coverage ($10.71 for 30mg tabs)
  - Limited long term data available on Bone Disease & Mortality

Surgical Management

- Successful in >95% of cases
- Re-operation in 1% of cases
- Long wait times for surgery
- Immediate Medical Complications:
  - Hypocalcemia
  - Local bleeding

Final Thoughts on CKD Bone Disease

- Mineral metabolism is complex
- Disorders of mineral and hormonal metabolism associated with morbidity & mortality
- Many questions remain unanswered
- Health care team (RNs, dietitians, Pharm, MDs) play important role in helping patients with these disorders

Management of Atrial Fibrillation In CKD and Dialysis Patients

UHN
Toronto General
Toronto Western
Princess Margaret
Toronto Rehab
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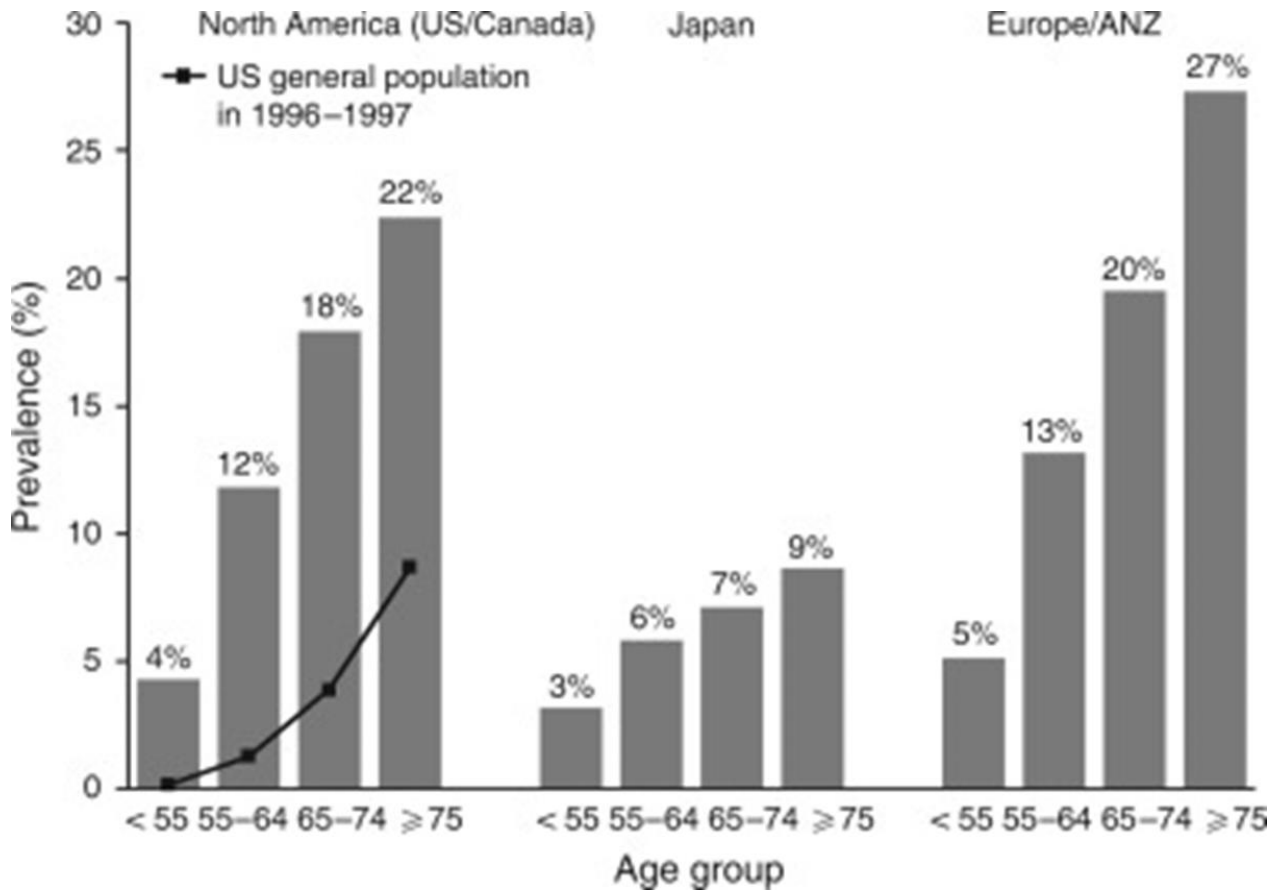
UNIVERSITY OF TORONTO
LESLIE DAN FACULTY OF PHARMACY

Prevalence of AF in HD



Wizemann. KI 2010 (77): 1098-1106

Management of AF in HD patients

2011 Kidney Disease: Improving Global Outcomes

"Routine **anticoagulation** of (dialysis) patients with atrial fibrillation for primary prevention of stroke is **not indicated**"

(Recommendation based on weak evidence or on the opinion of reviewers)

2012 Canadian Cardiovascular Society Guidelines

GFR < 15mL per minute (on dialysis):

"We suggest that such patients **not routinely receive either an oral anticoagulant or aspirin** for stroke prevention in AF"

(Conditional Recommendation, Low-Quality Evidence)

2014 American College of Cardiology/AHA/HRS Guidelines

"for patients with non-valvular AF with a CHA_2DS_2-VASc score of 2 or greater and who have GFR <15 mL/min or are on hemodialysis, it is **reasonable to prescribe warfarin"**

(Level of Evidence: B)

Skanes A, et al. Can J Cardiol. 2012;28:125-136.
Herzog et al. Kid Int. 2011;80:572-586.

Warfarin In HD

Study	Design	Risk of Stroke HR (95% CI)		Risk of Major Bleeding HR (95% CI)
		Ischemic	Hemorrhagic	
Chan et al. 2009	Retrospective cohort, n=1671	**1.81 (1.12-2.92)**	**2.22 (1.01-4.91)**	1.04 (0.73-1.46)
Winkelmayer et al. 2011	Prospective cohort, n=2313	0.92 (0.61-1.37)	**2.38 (1.15-4.96)**	0.96 (0.70-1.31) (GI bleed)
Garg et al 2016	Retrospective cohort, n=302	0.93 (0.49-1.82)	Not specified	1.53 (0.94-2.51)
Genovesi et al 2015	Prospective cohort,n=296	0.12 (0.00-3.59)	Not specified	**3.96 (1.15-13.68)**
Wakasugi et al	Prospective cohort, n=60	3.36 (0.67-16.66)	Not specified	0.85 (0.19-3.64)
Shah et al 2014	Retrospective cohort, n=1626	1.17(0.79-1.75)	Not specified	**1.41 (1.09-1.81)**
Yodagawa et al 2016	Retrospective cohort, n=84	1.07 (0.2-5.74)	Not specified	Not specified

Systematic Review Discussion

Conclusion

- Our review suggested a lack of association between warfarin use and reduced risk of stroke
- And an association between warfarin use and increased risk of bleeding in patients with AF on HD

Limitations

- Differences in definitions and reporting of outcomes make direct comparison difficult
- INR not recorded in studies

What about the Direct Oral Anticoagulants (DOACS)?

DOACs

dabigatran

rivaroxaban

apixaban

edoxaban

Indications: DVT/PE, NVAF, post-op thromboprophylaxis **

UHN Toronto General Toronto Western Princess Margaret Toronto Rehab
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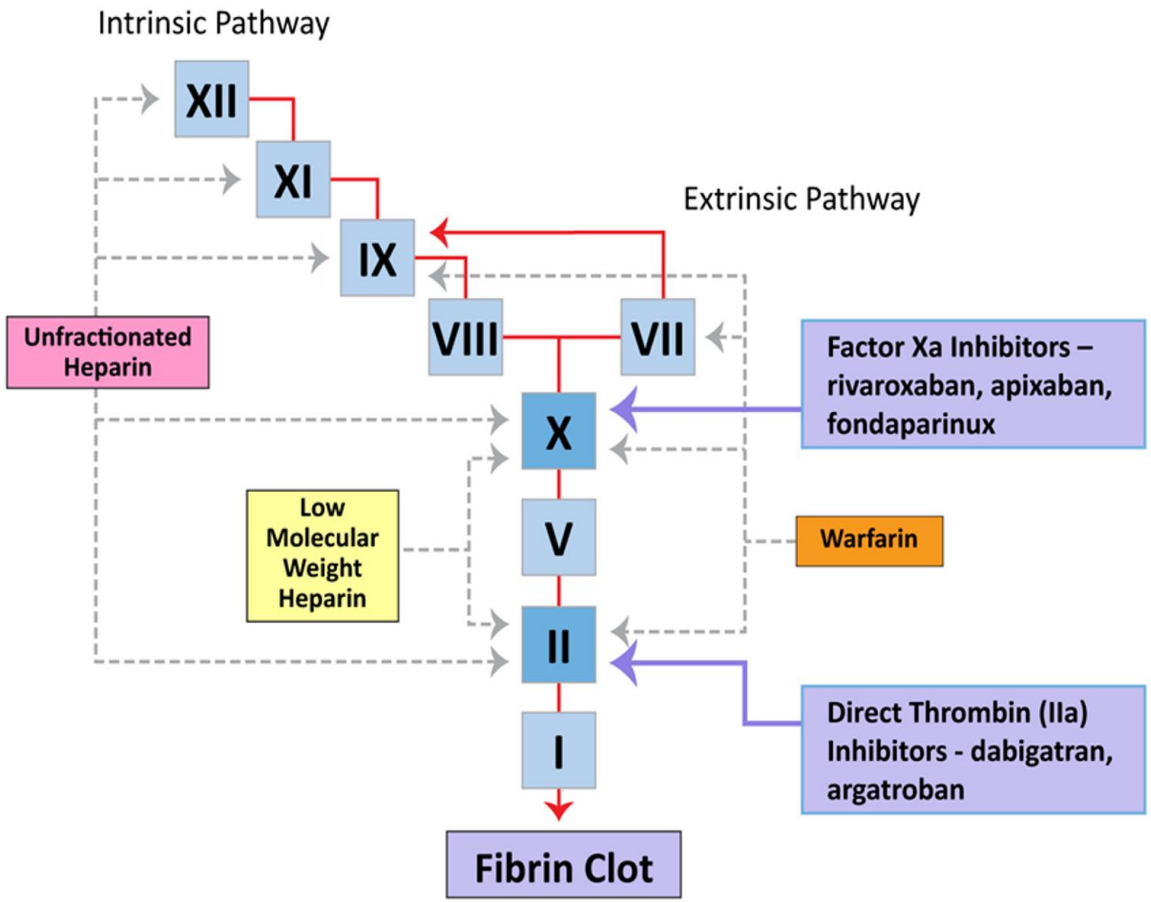
Mechanism of Action of the DOACs



Dabiga**t**ran
(Pradaxa)

Rivaro**xa**ban
(Xarelto)

Api**xa**ban
(Eliquis)

Phase III Trials of DOACs approved for AF

Drug	Dabigatran 150mg, 110mg	Rivaroxaban 20mg, 15mg	Apixaban 5mg, 2.5mg	Edoxaban 60mg, 30mg, 15mg
Study	RE-LY	ROCKET AF	ARISTOTLE	ENGAGE AF-TIMI 48
No. of patients	18,113	14,264	18,201	21,105
Warfarin (INR 2-3)	Open label	Double blind	Double blind	Double blind
Average $CHADS_2$	2.1	3.5	2.1	2.8
Median age (yrs)	71	73	70	72
Median follow-ups	2.0	1.9	1.8	2.8
Dose adjustment	None; patients were randomized to 150mg or 110mg BID	15mg OD if CrCl 30-49 mL/min	2.5mg BID if CrCl >25 and 2/3 criteria: age ≥80, weight ≤60kg, creatinine ≥133μmol/L	Randomized to 60 or 30mg; dose halved if CrCl 30-50mL/min, weight ≤60kg, concomitant use of verapamil or quinidine
Warfarin in therapeutic range	67 (54-78)	58 (43-71)	66 (52-77)	68 (55-77)
Exclusion criteria related to CKD	CrCl <30mL/min	CrCl <30mL/min	CrCl <25mL/min	CrCl <30mL/min

Stroke or Systemic Events

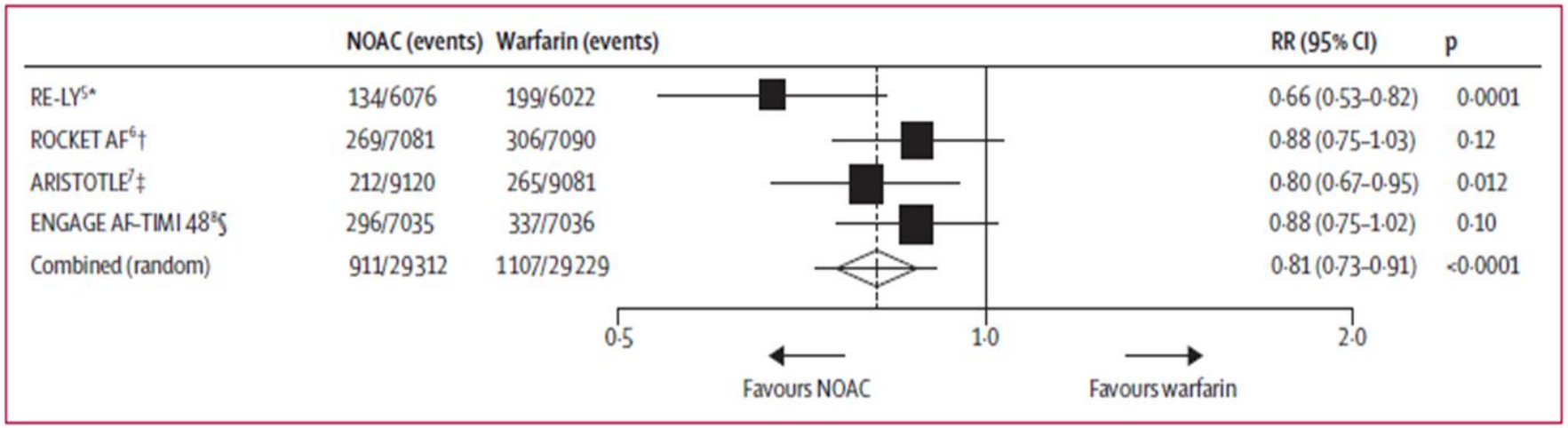


***Figure 1*: Stroke or systemic embolic events**

Data are n/N, unless otherwise indicated. Heterogeneity: I^2=47%; p=0·13. NOAC=new oral anticoagulant. RR=risk ratio. *Dabigatran 150 mg twice daily. †Rivaroxaban 20 mg once daily. ‡Apixaban 5 mg twice daily. §Edoxaban 60 mg once daily.

Ruff et al. Lancet 2014; 383

Major Bleeding

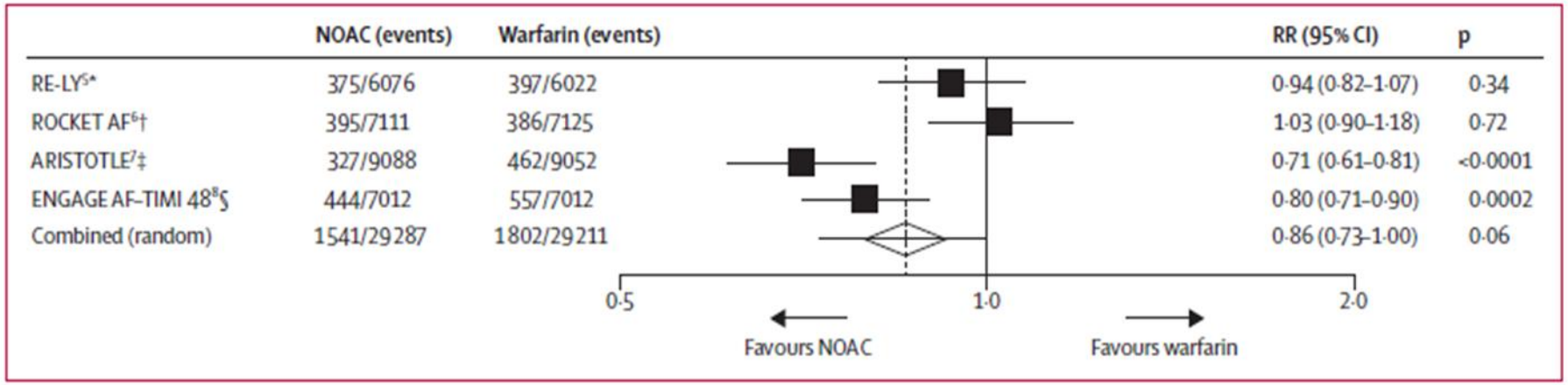


***Figure 3*: Major bleeding**

Data are n/N, unless otherwise indicated. Heterogeneity: I^2=83%; p=0·001. NOAC=new oral anticoagulant. RR=risk ratio. *Dabigatran 150 mg twice daily. †Rivaroxaban 20 mg once daily. ‡Apixaban 5 mg twice daily. §Edoxaban 60 mg once daily.

Ruff et al. Lancet 2014; 383

What about Patients with CKD?

Meta-Analysis of Renal Function on the Safety and Efficacy of Novel Oral Anticoagulants for Atrial Fibrillation

Freddy Del-Carpio Munoz, MD, MSc[a,*], S. Michael Gharacholou, MD, MSc[a], Thomas M. Munger, MD[a], Paul A. Friedman, MD[a], Samuel J. Asirvatham, MD[a], Douglas L. Packer, MD[a], and Peter A. Noseworthy, MD[a,b]

Novel oral anticoagulants (NOACs) are safe and effective for the prevention of stroke or systemic embolism (S/SE) in atrial fibrillation. The efficacy and safety of NOACs compared with warfarin has not been systematically assessed in subjects with mild or moderate renal dysfunction. We performed a meta-analysis of the randomized clinical trials that compared efficacy and safety (major bleeding) outcomes of NOACs compared to warfarin for the treatment of nonvalvular atrial fibrillation and had available data on renal function. We estimated the pooled relative risk (RR) of S/SE and major bleeding in relation to renal function (assessed by baseline estimated glomerular filtration rate divided in 3 groups: normal [estimated glomerular filtration rate >80 ml/min], mildly impaired [50 to 80 ml/min], and moderate impairment [<50 ml/min]). We included 4 randomized clinical trials enrolling a total of 58,338 subjects. The RRs of S/SE and major bleeding were higher

Del-Carpio Munoz, F., *et al. Am J Cardiol.* 2016; 117: 69-75

Stroke Outcomes

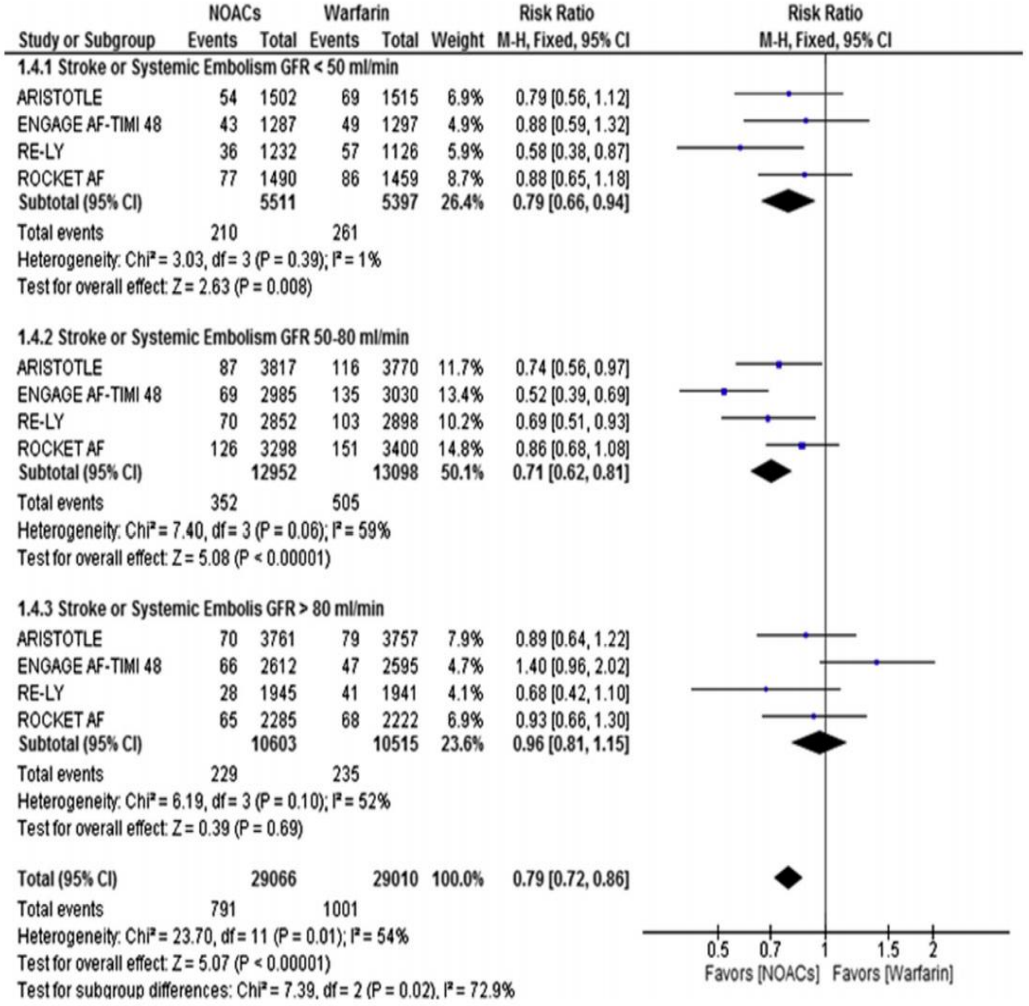


Figure 2. Risk of stroke or systemic embolism and use of NOACs versus warfarin in atrial fibrillation in relation to renal function.

Del-Carpio Munoz, F., *et al. Am J Cardiol.* 2016; 117: 69-75

Bleeding Outcomes

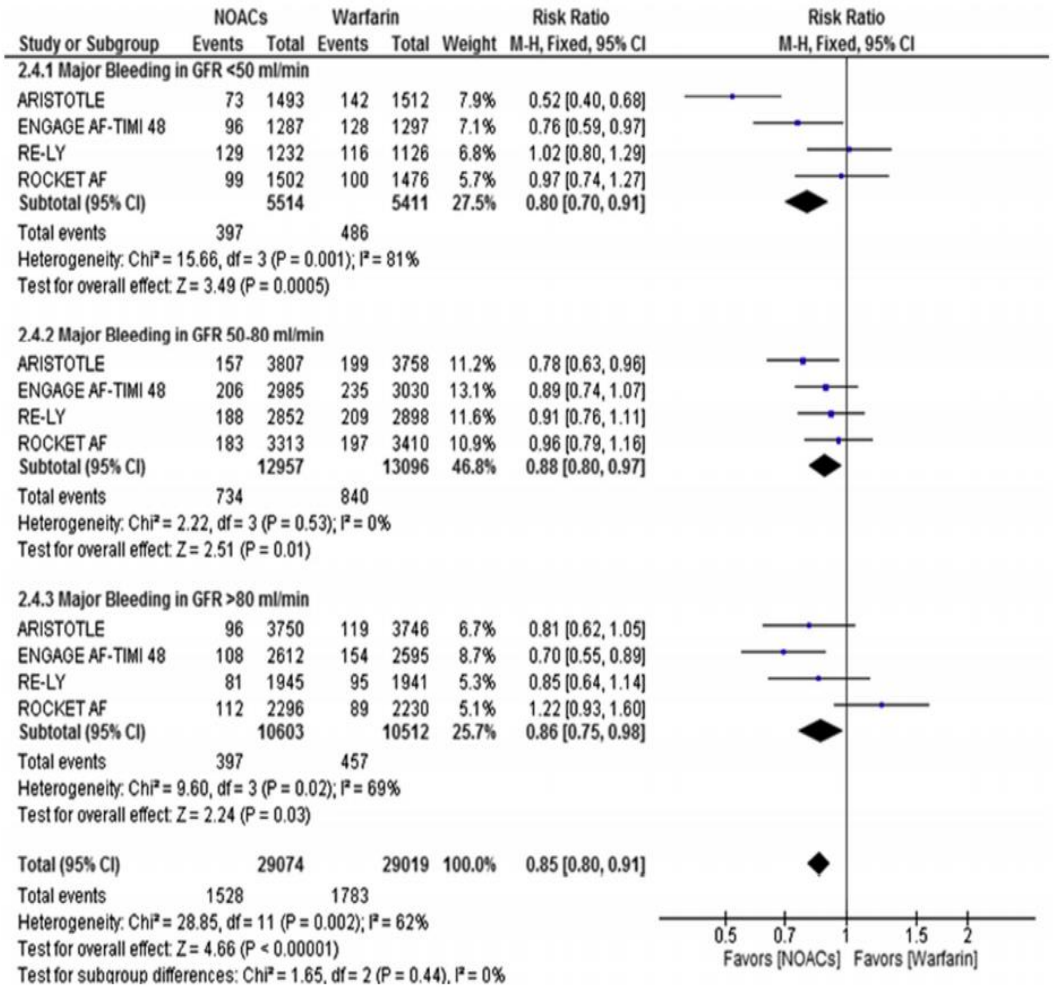


Figure 3. Risk of major bleeding and use of NOACs versus warfarin in relation to renal function.

Del-Carpio Munoz, F., *et al. Am J Cardiol.* 2016; 117: 69-75

What about Patients with “Real” Chronic Kidney Disease?

Drug Properties

	Warfarin	Apixaban	Rivaroxaban	Dabigatran	Edoxaban
Renal clearance of parent drug	<1%	27%	36%	80%	50%
Removal with 4h of hemodialysis	<1%	7%	<1%	50-60%	9%
Volume of distribution	8	21	50	50-70	107
Protein binding	99%	87%	92-95%	35%	55%
Metabolism	CYP2C9 Minor: CYP2C8, 2C18, 2C19, 1A2, 3A4	CYP3A4/5	CYP3A4/5, CYP2J2	Activated by esterases	Minimal: hydrolysis, CYP3A4

Is there any evidence with the DOACs in CKD 4 or 5/Dialysis?

Dosing for atrial fibrillation

Drug	Canada	US
Dabigatran (Pradaxa)	>30 ml/min: 150mg BID or 110mg BID[3] <30 ml/min: Avoid HD: Avoid	>50 ml/min: 150mg BID 30-50 ml/min: 150mg BID[1] 15-30 ml/min: 75mg BID[2] <15 ml/min: Avoid HD: Avoid
Rivaroxaban (Xarelto)	>50 ml/min: 20mg daily 30-50 ml/min: 15mg daily <30 ml/min: Avoid HD: Avoid	>50 ml/min: 20mg daily 15-50 ml/min: 15mg daily <15 ml/min: Avoid HD: Avoid

1. 75mg BID if concomitant dronedarone or ketoconazole
2. Avoid if concomitant P-gp inhibitor
3. Patients with high risk of bleeding including patients >75 years with 1 or more risk factors for bleeding

Dabigatran and Rivaroxaban Use in Atrial Fibrillation: Patients on Hemodialysis

- Retrospective cohort study (Fresenius database)
- Patient population
  - HD patients only
- Outcomes
  - Primary Outcome: use of the medications between Oct 2010 –Oct 2014
  - Secondary Outcomes:
    - Embolic stroke and arterial embolism within 2 yrs of medication initiation
    - Major bleeding and minor bleeding within 2 yrs of medication initiation

Chan et al. Circulation. 2015;131:972-979.

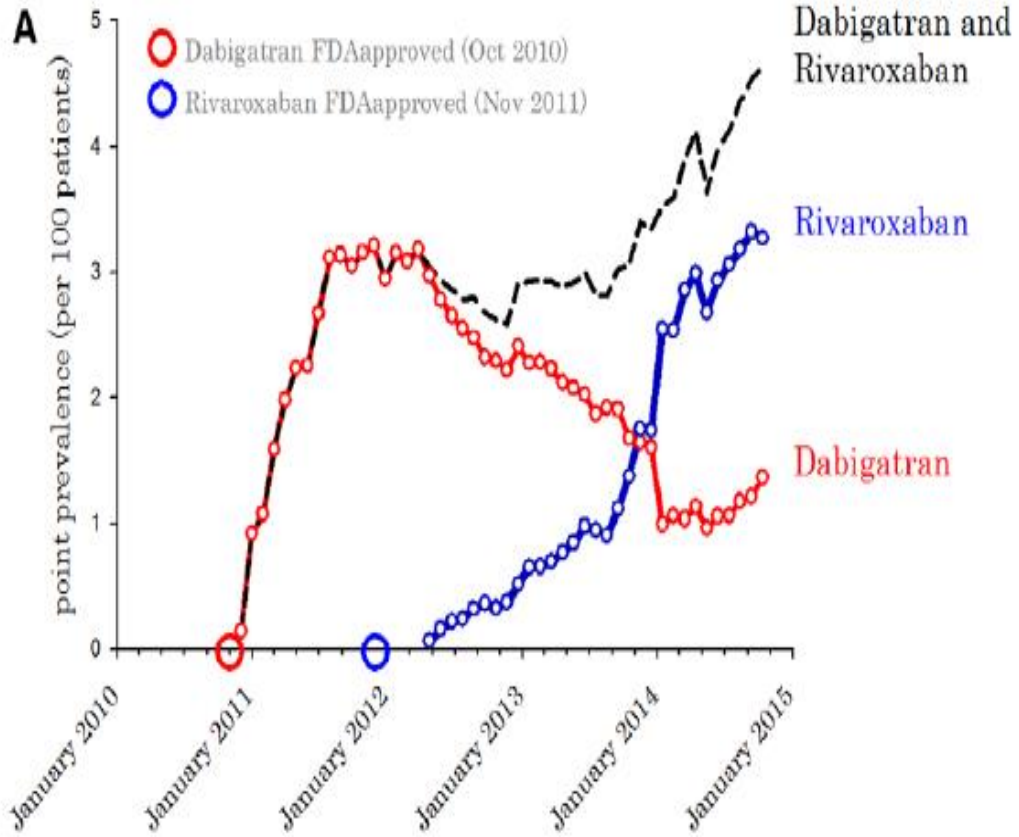
Table 1. Baseline Characteristics of Patients Initiated on Warfarin, Aspirin, Dabigatran, or Rivaroxaban

		Aspirin		Dabigatran		Rivaroxaban	
	Warfarin	Aspirin	*P* Value	Dabigatran	*P* Value	Rivaroxaban	*P* Value
n	8064	6018		281		244	
Age, y	70.6 (11)	71.7 (11)	0.006	68.4 (12)	0.002	66.9 (12)	<0.0001
Male sex	61.2% (4935)	57.3% (3448)	0.46	59.2% (166)	0.29	60.5% (148)	0.69
White race	75.9% (6120)	73.3% (4411)	0.27	73.3% (206)	0.18	67.7% (165)	0.0009
Diabetic	67.9% (5475)	66.8% (4020)	0.16	70.4% (198)	0.39	67.8% (165)	0.96
Years on HD	2.2 (3.5)	2.1 (3.3)	0.02	2.6 (3.6)	0.06	2.5 (3.1)	0.16
Catheter	29.4% (2371)	29.4% (1769)	0.96	31.4% (88)	0.47	19.3% (47)	0.0008
Systolic BP, mm Hg	131 (24)	133 (25)	<0.0001	128 (25)	0.07	136 (26)	0.003
Diastolic BP, mm Hg	68 (14)	68 (15)	0.006	67 (14)	0.07	70 (14)	0.30
Albumin, g/dL	3.6 (0.5)	3.6 (0.5)	<0.0001	3.6 (0.5)	0.08	3.6 (0.5)	0.67
Hemoglobin, g/dL	10.6 (1.3)	10.5 (1.3)	<0.0001	10.8 (1.3)	0.04	10.5 (1.3)	0.06
Thrombocytopenia	0.2% (16)	0.2% (12)	0.98	0.3% (1)	0.37	0.0% (0)	N/A
Epogen-units per HD	4978 (6059)	5122 (6248)	0.17	6266 (7051)	0.0007	4947 (5348)	0.96
Heparin-units per HD	2799 (3135)	2851 (3186)	0.33	3671 (4126)	<0.0001	3342 (3336)	0.01
Anti-platelet (%)	3.1% (250)	100% (6018)	N/A	5.6% (16)	0.18	3.4% (8)	0.76
Charlson score	5.5 (1.9)	5.5 (2.0)	0.10	5.4 (1.7)	0.32	5.5 (2.0)	0.72
$CHADS_2$ score	2.4 (1.0)	2.4 (1.1)	0.003	2.3 (1.0)	0.07	2.2 (1.0)	0.01
CHF	20.8% (1677)	21.3% (1282)	0.55	14.6% (41)	0.01	14.1% (34)	0.01
HTN	88.5% (7137)	88.9% (5350)	0.44	86.9% (244)	0.41	84.9% (207)	0.09
Embolic CVA	12.0% (968)	12.8% (770)	0.12	11.2% (31)	0.94	14.6% (36)	0.13
Bleeding index score	1.9 (0.6)	1.9 (0.6)	<0.0001	1.9 (0.6)	0.24	1.8 (0.6)	0.03
GI bleed	5.3% (427)	7.5% (451)	<0.0001	7.5% (21)	0.13	6.0% (15)	0.66
Stroke	12.7% (1024)	14.3% (861)	0.01	12.5% (35)	0.93	16.0% (39)	0.20
Minor bleed*	2.0% (161)	1.7% (102)	0.13	2.8% (8)	0.0004	4.3% (10)	0.02
Major bleed*	3.3% (266)	0.7% (42)	<0.0001	4.1% (12)	0.48	4.2% (10)	0.41

BP indicates blood pressure; CHF, congestive heart failure; CVA, stroke; GI, gastrointestinal; HD, hemodialysis; and HTN, hypertension.
*Bleeding event occurred in the past 30 days before initiation of drug.

Chan et al. Circulation. 2015;131:972-979.

Prevalence of Dabigatran and Rivaroxaban in HD patients with AF



Chan et al. Circulation. 2015;131:972-979.

Results

Table 2. Major Bleeding in Patients Initiated on Warfarin, Aspirin, Dabigatran, or Rivaroxaban

	Event Rate (per 100 Patient-Years)				Unadjusted Rate Ratios		
	Warf	ASA	Dabi	Riva	ASA Versus Warf	Dabi Versus Warf	Riva Versus Warf
Total	47.1	35.9	83.1	68.4	0.76 (0.71–0.82)	1.76 (1.44–2.15)	1.45 (1.09–1.93)

Table 3. Minor Bleeding in Patients Initiated on Warfarin, Aspirin, Dabigatran, or Rivaroxaban

Total	110.0	58.8	120.6	149.4	0.53 (0.51–0.56)	1.10 (0.93–1.29)	1.36 (1.12–1.64)

Efficacy Outcome

Table 4. Ischemic Stroke and Arterial Embolism in Patients Initiated on Warfarin, Aspirin, Dabigatran, or Rivaroxaban

	Event Rate (per 100 Patient-Years)				Unadjusted Rate Ratios		
	Warf	ASA	Dabi	Riva	ASA Versus Warf	Dabi Versus Warf	Riva Versus Warf
Embolic stroke	5.8	4.9	9.0	11.2			
Arterial embolism	0.7	0.3	1.6	0.0			
Total embolic events	6.2	5.0	10.6	11.2	0.81 (0.66–0.99)	1.71 (0.97–2.99)	1.80 (0.89–3.64)

Mortality

Mortality rate from bleeding (deaths per 100 patient-years)

Group	Rate
Dabigatran	19.2
Rivaroxaban	16.2
Warfarin	10.2
Aspirin	7.7

Sensitivity Analysis

Matched each dabigatran and rivaroxaban subject to 2 warfarin subjects on 20 data parameters

Group	Rate ratio
Major bleeding	
Dabigatran	1.64 (1.27-2.12)
Rivaroxaban	1.39 (1.00-1.94)

Discussion

Limitations

- Underpowered
- Mean follow-up time (years)
  - Warfarin: 0.48
  - Dabigatran: 0.44
  - Rivaroxaban: 0.30

Conclusion

- Increased risk of bleeding with dabigatran and rivaroxabn in HD patients
- No difference in ischemic events

Removal of Dabigatran by Dialysis

- PK Studies show 50% removal by HD
- Used in overdoses

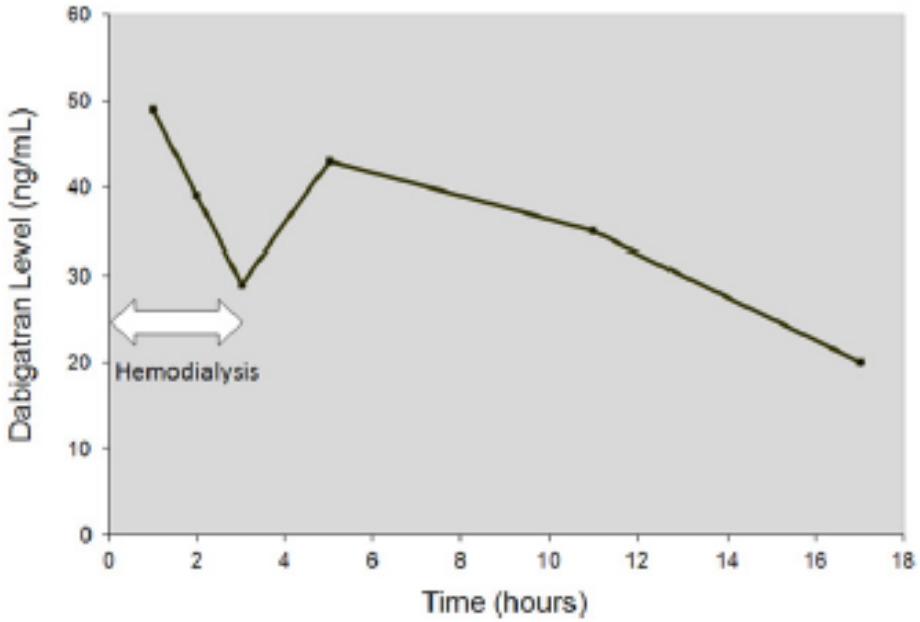


Figure 1. Decrease in dabigatran levels during hemodialysis and rebound after treatment.

Dose-Finding Study of Rivaroxaban in Hemodialysis Patients

- PK study
- Groups
  - 10mg rivaroxaban at end of 3 consecutive dialysis sessions (n=12)
  - 10mg single dose 6-8hrs before dialysis (n=12)
  - 10mg once daily before dialysis for 7 days (n=6)
- Results
  - ↑AUC 1.7 fold compared to healthy volunteers receiving 10mg and similar to healthy volunteers receiving 20mg
  - No accumulation after multiple daily dosing
  - No effect of HD on plasma concentrations and anticoagulation effect

Am J Kidney Dis. 2015;66(1):91-98

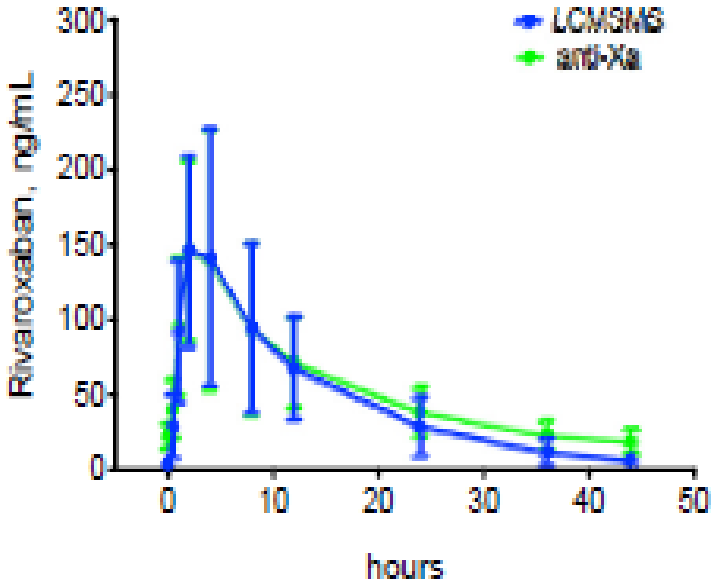


Figure 2. Rivaroxaban concentrations and response following single-dose administration. Mean (± standard deviation) values for (left panel) plasma rivaroxaban measured by liquid chromatography–tandem mass spectrometry (LC-MS/MS) and anti–factor Xa

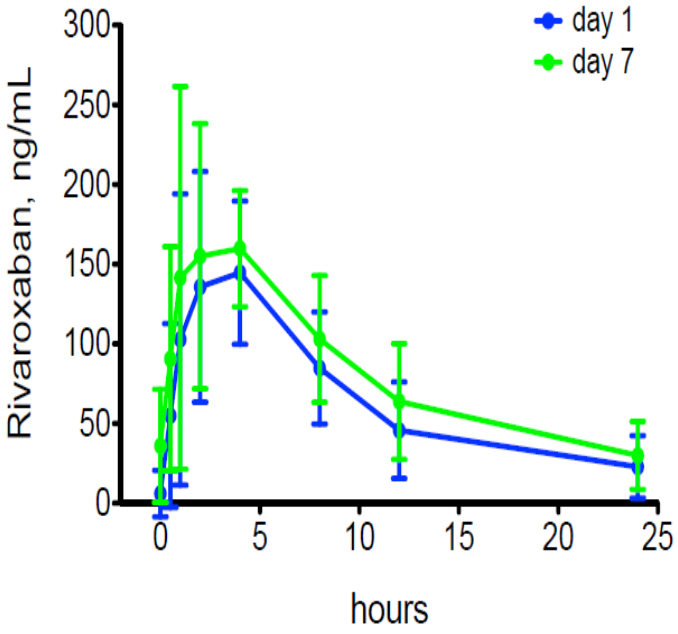


Figure 4. Rivaroxaban concentrations based on multiple-dose administration. Mean (± standard deviation) plasma rivaroxaban concentrations measured by liquid chromatography–tandem mass spectrometry on days 1 and 7 after administration of 10 mg of rivaroxaban in 6 patients.

- Conclusion: "reduced dose of rivaroxaban in hemodialysis patients without residual kidney function results in anticoagulation with similar variability and exposure as the standard dose in patients with normal kidney function."

Apixaban dosing for atrial fibrillation

Drug	Canada	US
Apixaban (Eliquis)	>30 ml/min: 5mg BID[1] 15-29 ml/min: Use with caution <15 ml/min: Not recommended HD: Not recommended	5 mg BID[1] HD: 5 mg BID[1]

1. 2.5mg BID if any 2 of following: ≥80 years, weight≤60kg or SrCr≥1.5mg/dL (133 umol/L)

Comparison of the Safety and Effectiveness of Apixaban vs Warfarin in Patients with Severe Renal Impairment

- Single centre- retrospective, matched cohort study
- Apixaban (n=73) vs Warfarin (n=73)
- Patient population
  - Patients with CrCl < 25 ml/min or on PD/HD
  - NVAF: 72%
  - VTE: 26%
  - Thromboprophylaxis: 1 patient
- Outcomes
  - 1 Outcome: Major bleeding
  - 2nd Outcome:
    - Composite of major bleeding, clinically relevant non-major bleeding and minor bleeding
    - Ischemic stroke for NVAF or recurrent VTE for DVT/PE
- Mean followup
  - Warfarin: 1.54 years
  - Apixaban: 1.01 years

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Table 2. Baseline Demographic and Clinical Characteristics of the Study Patients

Characteristic	Apixaban Group (n=73)	Warfarin Group (n=73)	P value
Age (yrs)[a]	79 ± 11.8	79 ± 13.5	0.994
LOS (days)	6.3 ± 6.5	5.7 ± 5.3	0.515
Race-ethnicity			0.124
Caucasian	54 (74)	62 (84.9)	
Black	16 (21.9)	6 (8.2)	
Other	3 (4.1)	5 (6.9)	
Female	44 (60.3)	43 (58.9)	0.866
Weight (kg)[a]	82 ± 24.5	81.5 ± 23.7	0.893
Height (cm)	166.1 ± 11.1	166.7 ± 11	0.718
SCr (mg/dL)	2.9 ± 1.8	3.2 ± 2.3	0.341
Renal function[a]			>0.99
Severe renal impairment	46 (63)	46 (63)	
ESRD	7 (9.6)	7 (9.6)	
ESRD on dialysis	20 (27.4)	20 (27.4)	
Dialysis type			>0.99
Hemodialysis	19 (26.1)	19 (26.1)	
Peritoneal dialysis	2 (2.7)	2 (2.7)	
NVAF	53 (72.6)	53 (72.6)	
VTE	19 (26)	19 (26)	
Other[b]	1 (1.4)	1 (1.4)	
CHA_2DS_2-VASc score[c]	6.1 ± 1.3	5.6 ± 1.5	0.100
HAS-BLED score[a,c]	3.4 ± 0.9	3 ± 0.9	0.062
Diabetes mellitus[a]	38 (52.1)	28 (38.4)	0.096
Previous stroke, TIA, or VTE[a]	42 (57.5)	33 (45.2)	0.136
Prior MI/CAD[a]	36 (49.3)	41 (56.2)	0.407
Cirrhosis[a]	5 (6.8)	7 (9.6)	0.547
Concomitant antiplatelet agents[a,d]			
Aspirin	44 (60.3)	36 (49.3)	0.183
Clopidogrel	7 (9.6)	2 (2.7)	0.166
Aspirin and/or clopidogrel	47 (64.4)	36 (49.3)	0.66

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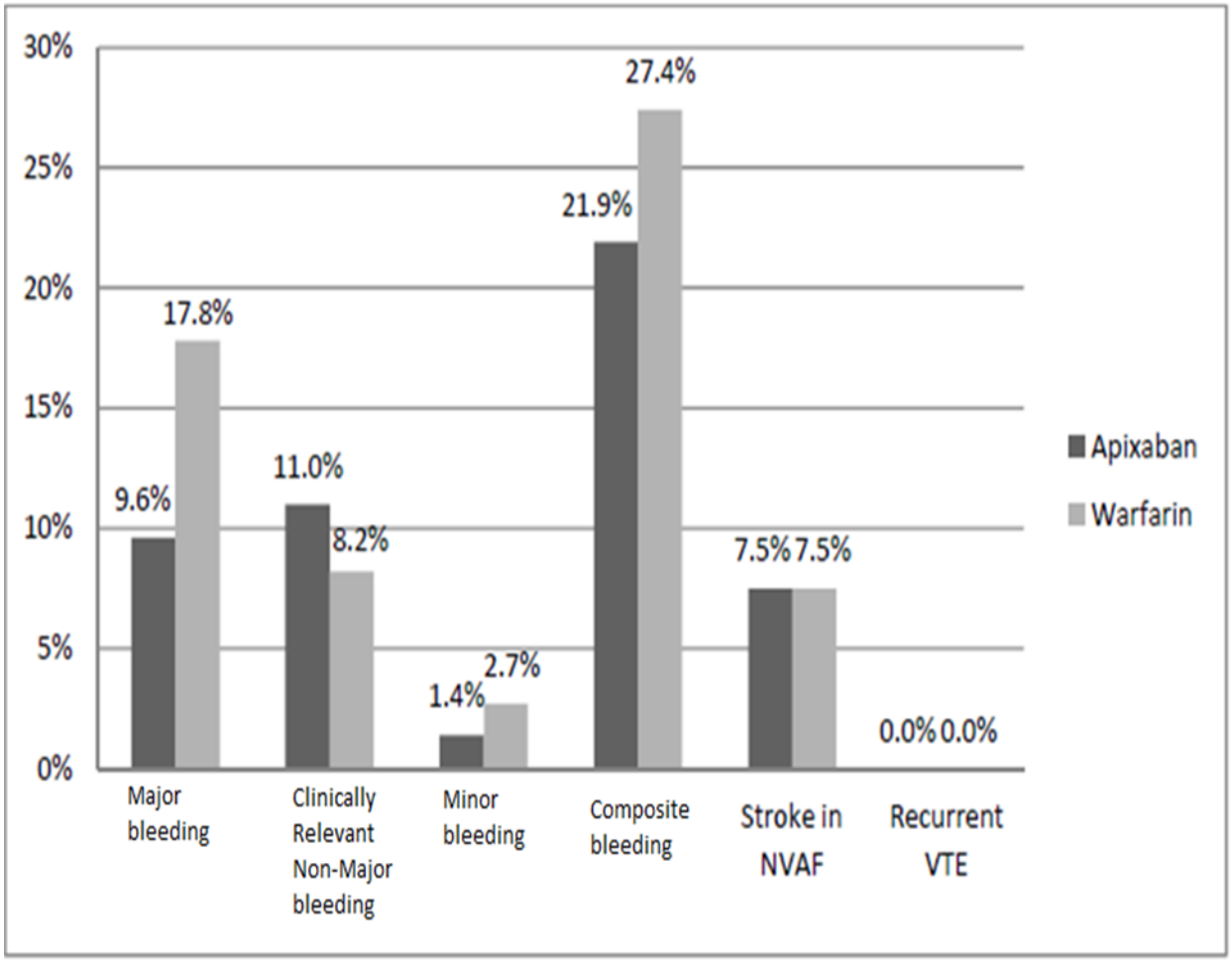
Results



- No significant difference in any outcomes

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Discussion

Limitations

- Underpowered
- Follow-up time: Not clear (min of 5 months post discharge)
  - 26,944 patient-days of follow-up for patients receiving apixaban compared to 41,010 for warfarin

Pharmacotherapy2017

Discussion

Conclusion

- Adjusted major bleeding outcome (events per 100 patient-days)
  - Apixaban: 0.26
  - Warfarin: 0.317
- No difference in stoke outcome

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Pharmacokinetics and Safety of Apixaban in Subjects on Hemodialysis

- Open-label, single dose study
- Groups: HD (n=8) vs CrCl >80 ml/min(n=8)
  - Matched according to age (±5 years), weight (±20% post dialysis weight) and sex
- Results
  - ↑AUC by 36% higher in ESRD
  - Similar protein binding
  - 4-hr dialysis session: ↓exposure by 14%
  - No difference in INR, PT and aPTT

The Journal of Clinical Pharmacology 2016. 56(5) 628-636

Apixaban Pharmacokinetics at Steady State in Hemodialysis Patients

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CJASN 2017; 28

Study Methods

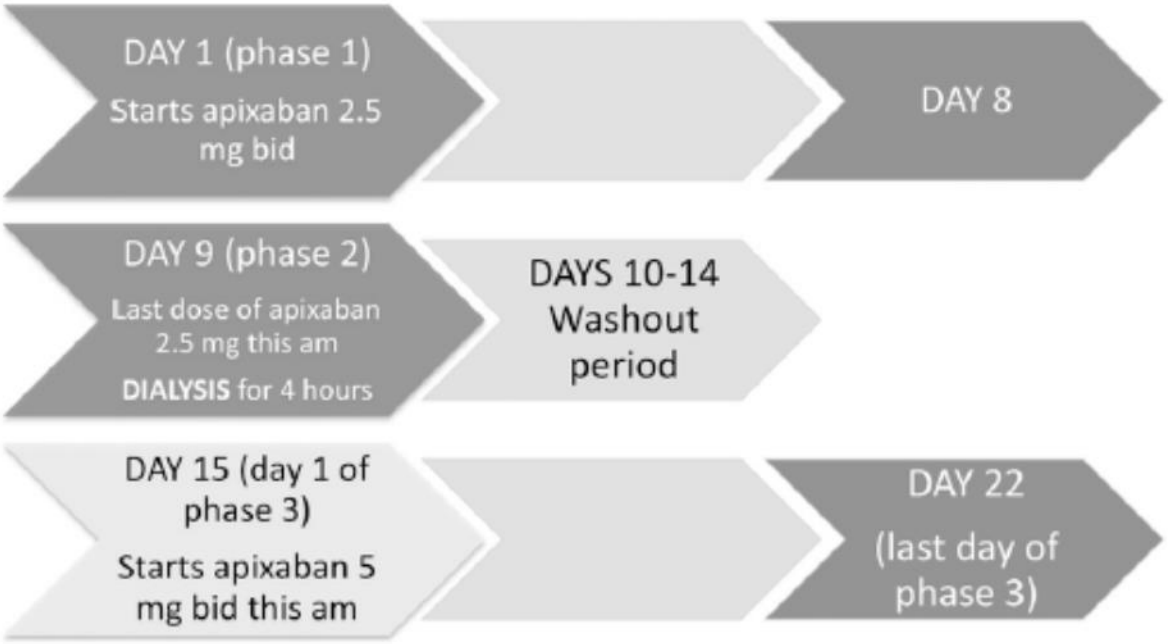
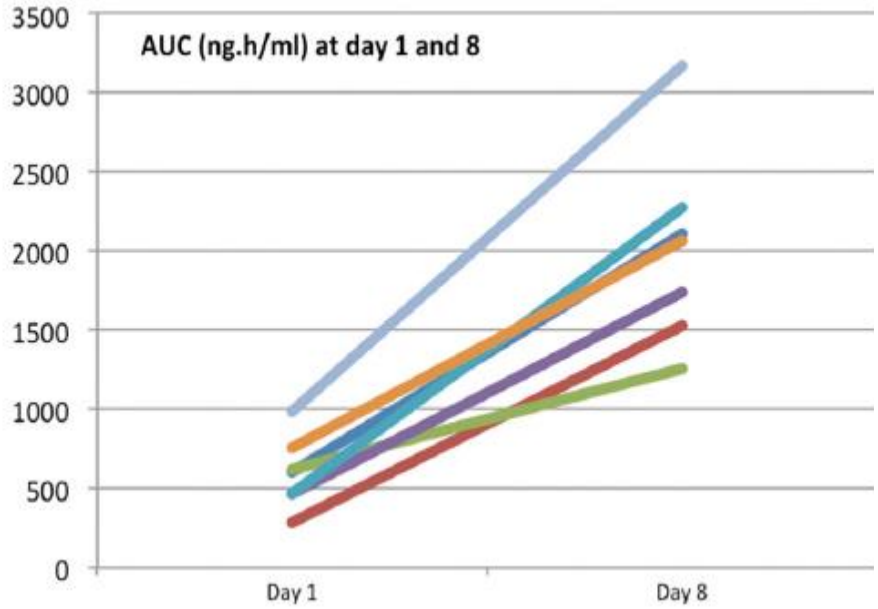


Figure 4. Schematic presentation of study interventions (phases 1–3). Phase 1: apixaban exposure after a 2.5 mg single dose and at steady state (day 8). Phase 2: effect of hemodialysis on apixaban concentration at steady state. Phase 3: apixaban exposure at steady state with a 5 mg bid dose. Bid, twice daily.

CJASN 2017; 28

CJASN 2017; 28

Results



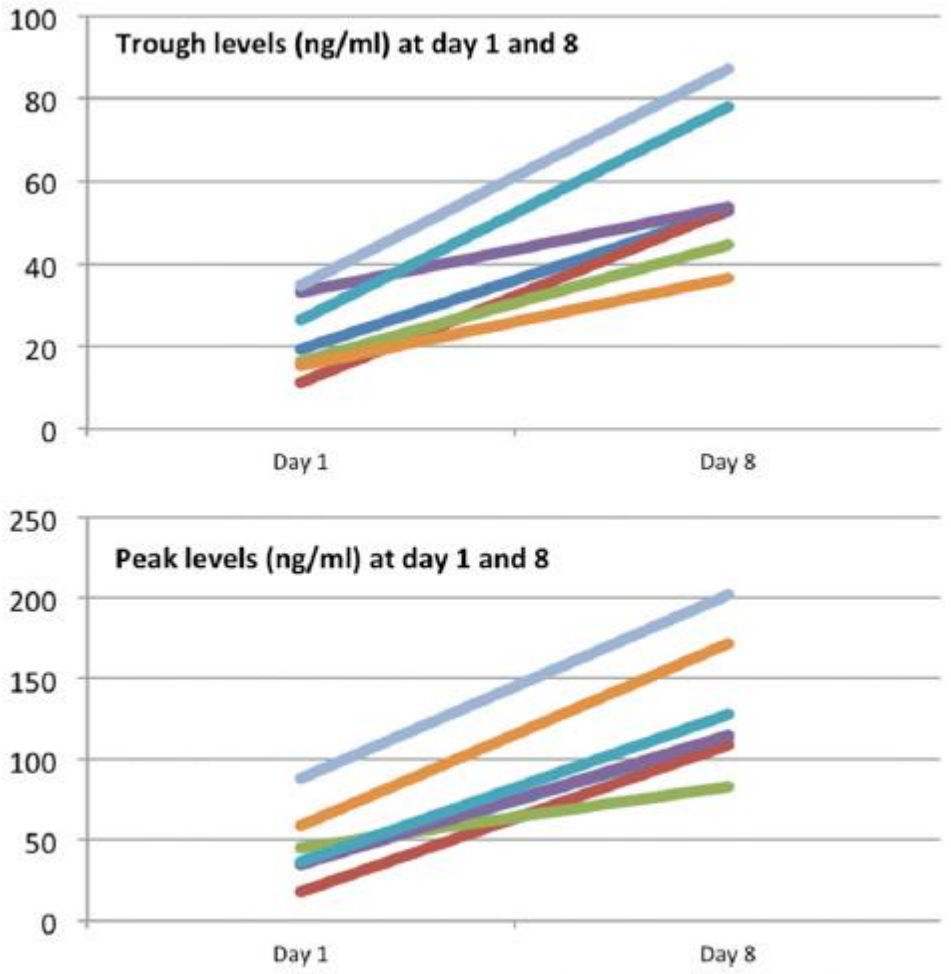


Figure 1. Apixaban PK parameters with the 2.5-mg twice daily dose on days 1 and 8, showing significant accumulation of the drug.

Table 1. PK parameters during phase 1

Apixaban 2.5 mg Twice Daily	Day 1	Day 8	*P* Value	Reference Levels (for the 2.5 mg twice daily dose)
AUC_{0-12}, ng h/ml	298.6 (38.0%)	1009.8 (30.7%)	<0.001	—
AUC_{0-24}, ng h/ml	597.3 (38.0%)	2019.7 (30.7%)	<0.001	1661 (1120–2620)[19]
C_{max}, ng/ml	45.2 (49.9%)	131.5 (31.1%)	<0.001	123 (69–221)[a][20]
t_{max}, h	4.4 (62%)	3.6 (48%)	0.32	—
C_{min}, ng/ml	22.3 (41.2%)	58.0 (31.2%)	<0.001	56 (24–103)[19]
$t_{1/2}$, h	5.9 (15.8%)	7.5 (64.3%)	0.94	—
AI	N/A	3.6 (33.9%) [3.4]	N/A	[1.3–1.7][14,22]

Results are presented as mean (coefficient of variation), median (10th–90th percentile), or median (5th–95th percentile). The geometric mean (in brackets) is also provided for the AI. t_{max}, Time to peak apixaban concentration; AI, accumulation index; N/A, not applicable.
[a]Median (5th–95th percentile).

Results

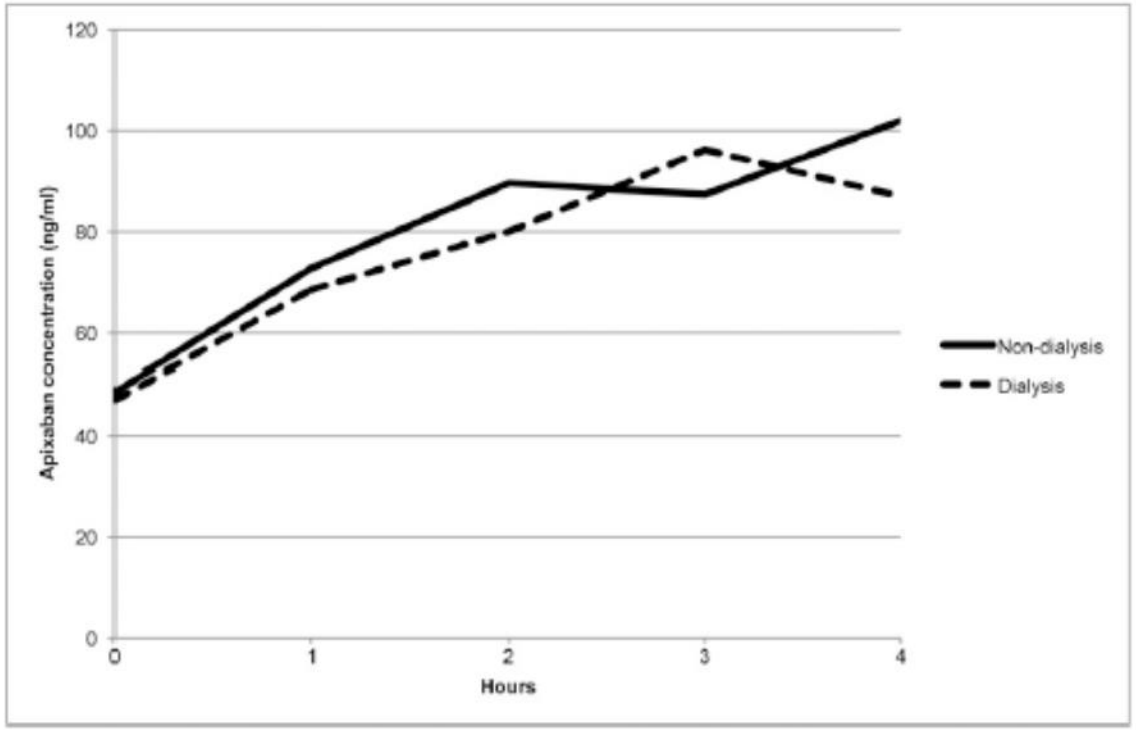


Figure 2. Effect of hemodialysis on apixaban levels. The solid line shows apixaban levels during the first 4 hours after drug administration (2.5 mg) on day 8 (nondialysis day). The dotted line shows apixaban levels during hemodialysis on day 9. The dialysis session started immediately after the drug administration (2.5 mg) and lasted for 4 hours.

CJASN 2017; 28

Results

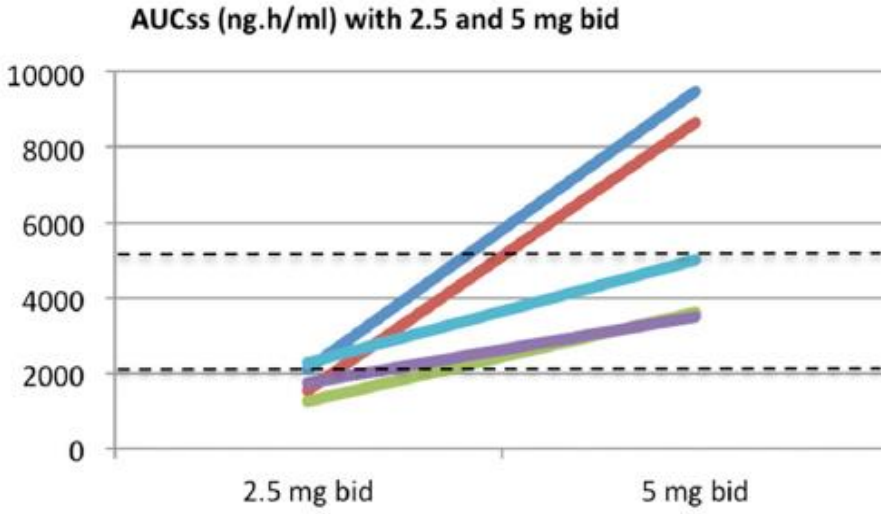


Table 2. PK parameters of apixaban after administration of 5 mg twice daily for a week and comparison with expected levels in the general population

Apixaban 5 mg Twice Daily	Day 22	*P* Value	Reference Levels (for the 5 mg twice daily dose)
AUC_{0-12}, ng h/ml	3026.6±46.6% [2770.4]	0.03	[1474–1717][18]
AUC_{0-24}, ng h/ml	6053.2±46.6% (3505.5–9469.7)	0.03	3370 (2070–5250)[19]
C_{max}, ng/ml	307.0±39.4% (189.0–455.0)	0.02	171 (91–321)[a][20]
t_{max}, h	3.8±35.6% (2.5–6.0)	0.89	—
C_{min}, ng/ml	217.5±51.9% (91.0–337.4)	0.03	107 (56–203)[19]
$t_{1/2}$, h	17.4±51.3% (7.1–29.8)	0.13	—

This table shows the PK parameters of apixaban 5 mg twice daily at steady state (day 8). Results are presented as mean ± coefficient of variation (range), median (10th–90th percentile), or median (5th–95th percentile). For AUC_{0-12}, the geometric mean (in brackets) is also depicted. *P* values are comparing apixaban 5 mg twice daily (day 22) with apixaban 2.5 mg twice daily at steady state (day 8; data depicted in Table 1, column 3). t_{max}, Time to peak apixaban concentration.
[a]Median (5th–95th percentile).

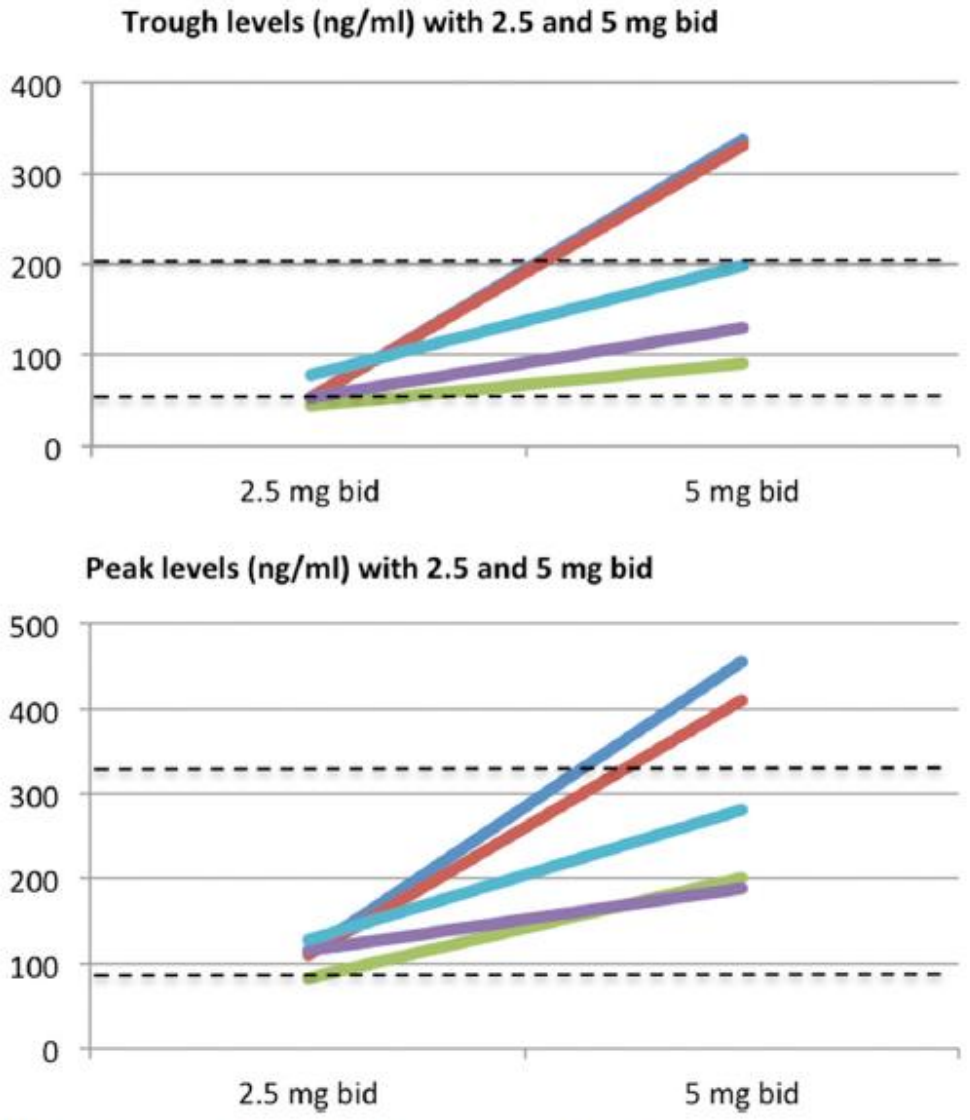


Figure 3. Comparison of the PK parameters at steady state (*i.e.*, after 8 days of apixaban administration) achieved with the reduced dose (2.5 mg twice daily) and with the standard dose (5 mg twice daily) of apixaban. The dotted lines represent the 10th and 90th percentiles of the predicted levels for the 5-mg twice daily dose in patients with preserved renal function (5th and 95th percentiles for C_{max}). AUCss, area under the concentration-time curve at steady state; bid, twice daily.

Edoxaban dosing for atrial fibrillation

Drug	Canada	US
Edoxaban (Lixiana)	50-80 ml/min: 60mg daily[1] 30-50 ml/min: 30mg daily <30 ml/min: Not recommended HD: Not recommended	≥95 ml/min: Not recommended 51-95 ml/min: 60mg daily 15-50 ml/min: 30mg daily <15 ml/min: Not recommended HD: Not recommended

1. If ≤60kg or P-gp inhibitors except amiodarone and verapamil

DOAC versus warfarin in CKD patients with AF

DOAC	Stroke/ Systemic Embolism	Major Bleeding
Apixaban[21]	↓	↓
Dabigatran 110mg[25,27,28]	↔	↔
Dabigatran 150mg[25]	↓	↔
Rivaroxaban[26-29]	↔	↔
Edoxaban[24]	↔	↓

NDT 2018

DOAC versus warfarin in HD patients with AF

DOAC	Stroke/Systemic Embolism	Major Bleeding
Apixaban[20]	↔	↔
Dabigatran[19] 110mg +150mg	↔	↑
Rivaroxaban[19]	↔	↑

NDT 2018

What do we do with this data?

Clinicaltrials.gov

- Trial to Evaluate Anticoagulation Therapy in Hemodialysis Patients With Atrial Fibrillation (RENAL-AF)

- Compare Apixaban and Vitamin-K Antagonists in Patients With Atrial Fibrillation (AF) and End-Stage Kidney Disease (ESKD) (AXADIA)