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
Kahoot.it
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.

\[ \text{Glomerular filtration rate (GFR)} = \frac{\text{volume of fluid filtered}}{\text{time}} \]

\[ \text{Excretion} = \text{Filtration} - \text{Reabsorption} + \text{Secretion} \]
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 m² 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

American College of Cardiology 2008;51:991-996
Annals of Pharmacotherapy 2006;40:1248-1253
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/1.73m²
  – CKD-EPI= 34ml/min/1.73m²
  – 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
Case Example

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  - MDRD = 33ml/min/1.73m²
  - CKD-EPI = 34ml/min/1.73m²
  - CrCL = 29 ml/min

- Literature suggest to avoid in patient with CrCL < 30ml/min

- How do you dose?
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
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
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 $\alpha_1$-acid glycoprotein.

• MW albumin: 69,000.

• MW $\alpha_1$-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
  \(\text{Cl}_M = \text{Cl}_{\text{renal}} + \text{Cl}_{\text{nonrenal}}\)

• In dialysis patients, \(\text{Cl}_{\text{renal}}\) is largely replaced by dialysis clearance (\(\text{Cl}_{\text{dial}}\)).

• If \(\text{Cl}_{\text{nonrenal}}\) is large compared to \(\text{Cl}_{\text{renal}}\), \(\text{Cl}_{\text{dial}}\) of a drug may be minimal.

• If \(\text{Cl}_{\text{dial}}\) increases \(\text{Cl}_M\) by 30% or more, \(\text{Cl}_{\text{dial}}\) 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

Duloxetine 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

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<tr>
<td>Increasing time</td>
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<tr>
<td>Time and Frequency</td>
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- SDHD
- 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

- Cardiovascular disease
  - CAD
  - Hypertension
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  - Encephalopathy
- Dialysis
  - Hemodialysis
  - Peritoneal Dialysis
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
- CaCO3 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

- Cardiovascular disease
  - CAD
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  - Pericarditis
- Volume overload
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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 sevalemper
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
• Parathyroidectomy 3 years ago
Case 2

Medications
- Ramipril 5mg daily
- Atorvastatin 20mg daily
- Replavite 1 tab daily
- Darbeopoieitin 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
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) Dabigatran
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

Bone Marrow

- Erythropoietin
- Iron

Circulation

- Reticulocytes
- RBCs

Stem Cell  BFU-E  CFU-E  Pro-erythroblast  Reticulocytes  RBCs

Time to Mature Cell Development, days

0  15  19  21  25

Anemia Occurs Early and Its Prevalence Increases as Renal Function Declines

Prevalence of Anemia by GFR

N=5,222

Anemia=Hb ≤12 g/dL

Chronic Kidney Disease and Anemia: Cardiovascular Double Jeopardy
The Pathophysiologic Consequences of Untreated Anemia

- Cardiac function
- Cognitive function
- Exercise and physical performance
- Health-related quality of life
- Increased cardiac output requirement
- LVMI
- Transfusion requirements
- Hospitalization
- Mortality
- Expenditures

6. EPOGEN® (Epoetin alfa) [prescribing information]. Amgen, Inc; 2003.
<table>
<thead>
<tr>
<th>Study</th>
<th>Study Population</th>
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Anemia Management Guidelines and Target Hb

- **KDIGO 2012**: 90-115 g/L
- **CSN 1999**: 110-120 g/L
- **DOQI 1997**: 110-120 g/L
- **EBPG 1999**: >110 g/L (upper limit not defined)
- **K/DOQI 2001**: 110-120 g/L
- **CARI 2000**: 110-120 g/L CVD, 120-140 g/L no CVD
- **UK 2002**: >100 g/L
- **CSN 2007**: 100 – 120g/L
- **K/DOQI 2006 update**: 110-130g/L
- **EBPG 2004**: >110 g/L (upper limit individualized)
- **CARI 2003**: >110 g/L CVD, 120-140 g/L no CVD
- **NICE 2006**: 105 – 125g/L
- **K/DOQI 2007 revised**: 110-120 g/L
- **KDIGO 2012**: 90-115g/L

**CVD=cardiovascular disease**
Anemia of CKD - Treatment

• **Erythropoietin (Eprex®)**
  – initial dose: 50 units/kg 2-3 x /week
  – maintenance dose varies widely
  – sc vs iv dosing
  – 2-3 x/week vs 1x/week

• **Darbepoietin (Aranesp®)**
  – initial dose: 0.45 mcg/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 QoL

• **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:
  – iron deficiency
  – GI blood loss
  – 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

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

Advantages

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

Disadvantages

• Gastrointestinal side effects
• Drug interactions
  – Calcium
  – H₂-blockers/PPIs
• Poor absorption
<table>
<thead>
<tr>
<th>Chemical description</th>
<th>Iron Dextran</th>
<th>Iron Sucrose</th>
<th>Iron Gluconate</th>
<th>Ferrumoxytol</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Ferric oxyhydroxide-dextran complex</td>
<td>Iron (III) hydroxide sucrose complex</td>
<td>Sodium ferric gluconate complex in sucrose</td>
<td>carbohydrate-coated, superparamagnetic iron oxide nanoparticle</td>
</tr>
</tbody>
</table>

| 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  
• Formation 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 its superparamagnetic properties | • Hypersensitivity to product  
• Anemia unrelated to iron deficiency  
• Patients with iron overload |

<p>| 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 |</p>
<table>
<thead>
<tr>
<th></th>
<th>Iron Dextran</th>
<th>Iron Saccharate/Sucrose</th>
<th>Iron Gluconate</th>
<th>Ferumoxytol</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Administration</strong></td>
<td>IM or IV</td>
<td>IV</td>
<td>IV</td>
<td>IV push</td>
</tr>
<tr>
<td><strong>Adverse effects</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Life-threatening anaphylactoid reaction in 0.6-0.7% of patients</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Increased risk of adverse effects with TDI</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Symptoms: arthralgia, backache, chills, dizziness, fever, headache, malaise, myalgia, nausea &amp; vomiting, subsiding in 3-4 days</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other effects seen: chest pain, hypotension, pruritus, abdominal pain</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Post-marketing anaphylactoid reactions 0.006%</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Life-threatening reactions 0.002%</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypotension (36%) may be related to rate and total dose administered</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cramps 23%</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Effects &gt;5%: nausea, vomiting, diarrhea, headache</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Life-threatening reaction 0.1%</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Others: hypotension, flushing, hypertension, syncope, tachycardia, cramps, dizziness, pruritus, nausea, vomiting, myalgia, arthralgia, dyspnea, chest pain, asthenia, headache, abdominal pain, fatigue</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>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%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Drug interactions</strong></td>
<td>Do not mix any medications</td>
<td>No studies</td>
<td>No studies</td>
<td>No studies</td>
</tr>
<tr>
<td><strong>Approximate cost</strong></td>
<td>$</td>
<td>$$</td>
<td>$$</td>
<td>$$</td>
</tr>
</tbody>
</table>
## 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 3-6 months 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
  – GI blood loss
  – infection/inflammation
  – hyperparathyroidism
  – malignancy
  – other anemias
Anemia of CKD

Hyporesponse to EPO

• Consider:
  – iron deficiency
  – GI blood loss
  – infection/inflammation
  – hyperparathyroidism
  – malignancy
  – other anemias
Infection & Inflammation in Anemia Management

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 – 115 g/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

↑ PO4

↑ PTH

↑ Mobilization of Ca & PO4 from bone

↓ calcitriol

↓ Ca
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

<table>
<thead>
<tr>
<th>Guideline</th>
<th>Target Intact PTH</th>
<th>Target Calcium</th>
<th>Target Phosphorous</th>
</tr>
</thead>
<tbody>
<tr>
<td>Europe (2000)</td>
<td>9.35-18.7 pmol/L</td>
<td>2.1-2.7 mmol/L</td>
<td>1.49-1.81 mmol/L</td>
</tr>
<tr>
<td>Australia (2000)</td>
<td>2-3 times upper limit of normal</td>
<td>2.1-2.6 mmol/L</td>
<td>&lt;2.20, preferably &lt;1.81 mmol/L</td>
</tr>
<tr>
<td>K/DOQI (2003)</td>
<td>16.5-33 pmol/L&lt;br&gt;Stage 3: 3.85-7.7&lt;br&gt;Stage 4: 7.7-12.1</td>
<td>2.1-2.4 mmol/L&lt;br&gt;Stage 3&amp;4: 2.2-2.6</td>
<td>1.13-1.78 mmol/L&lt;br&gt;Stage3&amp;4: 0.84-1.49</td>
</tr>
<tr>
<td>KDIGO/CSN</td>
<td>&lt; 50pmol/L</td>
<td>Normal range</td>
<td>Normal Range</td>
</tr>
</tbody>
</table>
Elevated Serum Phosphorus Levels Are Associated with Increased Mortality Risk

<table>
<thead>
<tr>
<th>Serum Phosphorus Quintile (mmol/L)</th>
<th>Relative Mortality Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.35 – 1.5</td>
<td>1</td>
</tr>
<tr>
<td>1.5 – 1.8</td>
<td>1.02</td>
</tr>
<tr>
<td>1.8 – 2.1</td>
<td>1.18*</td>
</tr>
<tr>
<td>2.1 – 2.5</td>
<td>1.39**</td>
</tr>
<tr>
<td>2.5 – 5.4</td>
<td></td>
</tr>
</tbody>
</table>

* *p=0.03
** p<0.0001

Vertical bars indicate 5% to 95% confidence intervals; n=6407
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
- Cbfa-1

Inhibitors
- MGP
- Osteoprotegerin
- Fetuin-A

PO4
Pathogenesis

Elevated Phosphorus
Elevated Calcium

Na \rightarrow P

\uparrow P

SMC phenotype modulation
- Runx2
- alkaline phosphatase
- osteocalcin

\rightarrow \text{Ca/P loading of matrix vesicles}

\rightarrow \text{mineral}

\rightarrow \text{matrix vesicle}

\rightarrow \text{collagen}

\rightarrow \text{Matrix Mineralization}

\uparrow \text{Ca X P}
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

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

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®)
  – $1\alpha$-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

- Calcimimetics increase CaR sensitivity to Ca\(^{2+}\)
- Activation of secondary messengers
- Extracellular
- Intracellular
- Parathyroid cell

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
Prevalence of AF in HD

Wizemann. KI 2010 (77): 1098-1106
Management of AF in HD patients
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\textsubscript{2}DS\textsubscript{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)

## Warfarin In HD

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

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

rivaroxaban

dabigatran

edoxaban

apixaban
Mechanism of Action of the DOACs

- **Dabigatran** (Pradaxa)
- **Rivaroxaban** (Xarelto)
- **Apixaban** (Eliquis)
## Phase III Trials of DOACs approved for AF

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dabigatran 150mg, 110mg</th>
<th>Rivaroxaban 20mg, 15mg</th>
<th>Apixaban 5mg, 2.5mg</th>
<th>Edoxaban 60mg, 30mg, 15mg</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Study</strong></td>
<td>RE-LY</td>
<td>ROCKET AF</td>
<td>ARISTOTLE</td>
<td>ENGAGE AF-TIMI 48</td>
</tr>
<tr>
<td><strong>No. of patients</strong></td>
<td>18,113</td>
<td>14,264</td>
<td>18,201</td>
<td>21,105</td>
</tr>
<tr>
<td><strong>Warfarin (INR 2-3)</strong></td>
<td>Open label</td>
<td>Double blind</td>
<td>Double blind</td>
<td>Double blind</td>
</tr>
<tr>
<td><strong>Average CHADS$_2$</strong></td>
<td>2.1</td>
<td>3.5</td>
<td>2.1</td>
<td>2.8</td>
</tr>
<tr>
<td><strong>Median age (yrs)</strong></td>
<td>71</td>
<td>73</td>
<td>70</td>
<td>72</td>
</tr>
<tr>
<td><strong>Median follow-ups</strong></td>
<td>2.0</td>
<td>1.9</td>
<td>1.8</td>
<td>2.8</td>
</tr>
<tr>
<td><strong>Dose adjustment</strong></td>
<td>None; patients were randomized to 150mg or 110mg BID</td>
<td>15mg OD if CrCl 30-49 mL/min</td>
<td>2.5mg BID if CrCl &gt;25 and 2/3 criteria: age ≥80, weight ≤60kg, creatinine ≥133μmol/L</td>
<td>Randomized to 60 or 30mg; dose halved if CrCl 30-50mL/min, weight ≤60kg, concomitant use of verapamil or quinidine</td>
</tr>
<tr>
<td><strong>Warfarin in therapeutic range</strong></td>
<td>67 (54-78)</td>
<td>58 (43-71)</td>
<td>66 (52-77)</td>
<td>68 (55-77)</td>
</tr>
<tr>
<td><strong>Exclusion criteria related to CKD</strong></td>
<td>CrCl &lt;30mL/min</td>
<td>CrCl &lt;30mL/min</td>
<td>CrCl &lt;25mL/min</td>
<td>CrCl &lt;30mL/min</td>
</tr>
</tbody>
</table>
Stroke or Systemic Events

![Graph showing comparison between NOAC and Warfarin for stroke or systemic events.](image)

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

Data are n/N, unless otherwise indicated. Heterogeneity: I² = 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

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, MSca,*, S. Michael Gharacholou, MD, MSca, Thomas M. Munger, MDa,
Paul A. Friedman, MDa, Samuel J. Asirvatham, MDa, Douglas L. Packer, MDa,
and Peter A. Noseworthy, MDa,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 in subjects with renal impairment compared to normal renal function, independent of type.

Stroke Outcomes

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

### Bleeding Outcomes

**Table:**

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>NOACs</th>
<th>Warfarin</th>
<th>Risk Ratio M-H, Fixed, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>2.4.1 Major Bleeding in GFR &lt;50 ml/min</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ARISTOTLE</td>
<td>73</td>
<td>1493</td>
<td>7.9% 0.52 [0.40, 0.68]</td>
</tr>
<tr>
<td>ENGAGE AF-TIMI 48</td>
<td>96</td>
<td>1287</td>
<td>7.1% 0.76 [0.59, 0.97]</td>
</tr>
<tr>
<td>RE-LY</td>
<td>129</td>
<td>1232</td>
<td>6.8% 1.02 [0.80, 1.28]</td>
</tr>
<tr>
<td>ROCKET AF</td>
<td>99</td>
<td>1502</td>
<td>5.7% 0.97 [0.74, 1.27]</td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td>5514</td>
<td>5411</td>
<td>27.5% 0.80 [0.70, 0.91]</td>
</tr>
<tr>
<td><strong>Total events</strong></td>
<td>397</td>
<td>486</td>
<td></td>
</tr>
<tr>
<td><strong>Heterogeneity:</strong></td>
<td>Chi² = 15.66, df = 3 (P = 0.001), 95% CI = 81%</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Test for overall effect:</strong></td>
<td>Z = 3.48 (P = 0.0005)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>2.4.2 Major Bleeding in GFR 50-80 ml/min</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ARISTOTLE</td>
<td>157</td>
<td>3807</td>
<td>11.2% 0.78 [0.63, 0.90]</td>
</tr>
<tr>
<td>ENGAGE AF-TIMI 48</td>
<td>206</td>
<td>2985</td>
<td>15.1% 0.89 [0.74, 1.07]</td>
</tr>
<tr>
<td>RE-LY</td>
<td>188</td>
<td>2652</td>
<td>11.6% 0.91 [0.76, 1.11]</td>
</tr>
<tr>
<td>ROCKET AF</td>
<td>163</td>
<td>3313</td>
<td>10.9% 0.98 [0.79, 1.16]</td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td>12857</td>
<td>13096</td>
<td>46.8% 0.88 [0.80, 0.97]</td>
</tr>
<tr>
<td><strong>Total events</strong></td>
<td>734</td>
<td>840</td>
<td></td>
</tr>
<tr>
<td><strong>Heterogeneity:</strong></td>
<td>Chi² = 2.22, df = 3 (P = 0.53), 95% CI = 0%</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Test for overall effect:</strong></td>
<td>Z = 2.51 (P = 0.01)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>2.4.3 Major Bleeding in GFR &gt;80 ml/min</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ARISTOTLE</td>
<td>98</td>
<td>3750</td>
<td>6.7% 0.81 [0.62, 1.05]</td>
</tr>
<tr>
<td>ENGAGE AF-TIMI 48</td>
<td>108</td>
<td>2612</td>
<td>8.7% 0.70 [0.55, 0.89]</td>
</tr>
<tr>
<td>RE-LY</td>
<td>91</td>
<td>1945</td>
<td>5.3% 0.86 [0.64, 1.14]</td>
</tr>
<tr>
<td>ROCKET AF</td>
<td>112</td>
<td>2266</td>
<td>5.1% 1.22 [0.93, 1.60]</td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td>10603</td>
<td>10512</td>
<td>25.7% 0.86 [0.75, 0.98]</td>
</tr>
<tr>
<td><strong>Total events</strong></td>
<td>297</td>
<td>457</td>
<td></td>
</tr>
<tr>
<td><strong>Heterogeneity:</strong></td>
<td>Chi² = 9.60, df = 3 (P = 0.02), 95% CI = 69%</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Test for overall effect:</strong></td>
<td>Z = 2.24 (P = 0.03)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td>29074</td>
<td>29019</td>
<td>100.0% 0.85 [0.80, 0.91]</td>
</tr>
<tr>
<td><strong>Total events</strong></td>
<td>1528</td>
<td>1783</td>
<td></td>
</tr>
</tbody>
</table>

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


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**UHN**

Toronto General
Toronto Western
Princess Margaret
Toronto Rehab

**COURAGE LIVES HERE**
What about Patients with “Real” Chronic Kidney Disease?
## Drug Properties

<table>
<thead>
<tr>
<th>Property</th>
<th>Warfarin</th>
<th>Apixaban</th>
<th>Rivaroxaban</th>
<th>Dabigatran</th>
<th>Edoxaban</th>
</tr>
</thead>
<tbody>
<tr>
<td>Renal clearance of parent drug</td>
<td>&lt;1%</td>
<td>27%</td>
<td>36%</td>
<td>80%</td>
<td>50%</td>
</tr>
<tr>
<td>Removal with 4h of hemodialysis</td>
<td>&lt;1%</td>
<td>7%</td>
<td>&lt;1%</td>
<td>50-60%</td>
<td>9%</td>
</tr>
<tr>
<td>Volume of distribution</td>
<td>8</td>
<td>21</td>
<td>50</td>
<td>50-70</td>
<td>107</td>
</tr>
<tr>
<td>Protein binding</td>
<td>99%</td>
<td>87%</td>
<td>92-95%</td>
<td>35%</td>
<td>55%</td>
</tr>
<tr>
<td>Metabolism</td>
<td>CYP2C9 Minor: CYP2C8, 2C18, 2C19, 1A2, 3A4</td>
<td>CYP3A4/5</td>
<td>CYP3A4/5, CYP2J2</td>
<td>Activated by esterases</td>
<td>Minimal: hydrolysis, CYP3A4</td>
</tr>
</tbody>
</table>
Is there any evidence with the DOACs in CKD 4 or 5/Dialysis?
## Dosing for atrial fibrillation

<table>
<thead>
<tr>
<th>Drug</th>
<th>Canada</th>
<th>US</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dabigatran (Pradaxa)</td>
<td>&gt;30 ml/min: 150mg BID or 110mg BID(^3)</td>
<td>&gt;50 ml/min: 150mg BID</td>
</tr>
<tr>
<td></td>
<td>&lt;30 ml/min: Avoid</td>
<td>30-50 ml/min: 150mg BID(^1)</td>
</tr>
<tr>
<td></td>
<td>HD: Avoid</td>
<td>15-30 ml/min: 75mg BID(^2)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>&lt;15 ml/min: Avoid</td>
</tr>
<tr>
<td></td>
<td></td>
<td>HD: Avoid</td>
</tr>
<tr>
<td>Rivaroxaban (Xarelto)</td>
<td>&gt;50 ml/min: 20mg daily</td>
<td>&gt;50 ml/min: 20mg daily</td>
</tr>
<tr>
<td></td>
<td>30-50 ml/min: 15mg daily</td>
<td>15-50 ml/min: 15mg daily</td>
</tr>
<tr>
<td></td>
<td>&lt;30 ml/min: Avoid</td>
<td>&lt;15 ml/min: Avoid</td>
</tr>
<tr>
<td></td>
<td>HD: Avoid</td>
<td>HD: Avoid</td>
</tr>
</tbody>
</table>

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

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

<table>
<thead>
<tr>
<th></th>
<th>Warfarin</th>
<th>Aspirin</th>
<th>P Value</th>
<th>Dabigatran</th>
<th>P Value</th>
<th>Rivaroxaban</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>8064</td>
<td>6018</td>
<td></td>
<td>281</td>
<td>0.002</td>
<td>244</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Age, y</td>
<td>70.6 (11)</td>
<td>71.7 (11)</td>
<td>0.006</td>
<td>68.4 (12)</td>
<td>0.02</td>
<td>66.9 (12)</td>
<td>0.69</td>
</tr>
<tr>
<td>Male sex</td>
<td>61.2% (4935)</td>
<td>57.3% (3448)</td>
<td>0.46</td>
<td>59.2% (166)</td>
<td>0.29</td>
<td>60.5% (148)</td>
<td>0.69</td>
</tr>
<tr>
<td>White race</td>
<td>75.9% (6120)</td>
<td>73.3% (4411)</td>
<td>0.27</td>
<td>73.3% (206)</td>
<td>0.18</td>
<td>67.7% (165)</td>
<td>0.0009</td>
</tr>
<tr>
<td>Diabetic</td>
<td>67.9% (5475)</td>
<td>66.8% (4020)</td>
<td>0.16</td>
<td>70.4% (198)</td>
<td>0.39</td>
<td>67.3% (165)</td>
<td>0.96</td>
</tr>
<tr>
<td>Years on HD</td>
<td>2.2 (3.5)</td>
<td>2.1 (3.3)</td>
<td>0.02</td>
<td>2.6 (3.6)</td>
<td>0.06</td>
<td>2.5 (3.1)</td>
<td>0.16</td>
</tr>
<tr>
<td>Catheter</td>
<td>29.4% (2371)</td>
<td>29.4% (1769)</td>
<td>0.96</td>
<td>31.4% (88)</td>
<td>0.47</td>
<td>19.3% (47)</td>
<td>0.0008</td>
</tr>
<tr>
<td>Systolic BP, mmHg</td>
<td>131 (24)</td>
<td>133 (25)</td>
<td>&lt;0.0001</td>
<td>128 (25)</td>
<td>0.07</td>
<td>136 (26)</td>
<td>0.003</td>
</tr>
<tr>
<td>Diastolic BP, mmHg</td>
<td>68 (14)</td>
<td>68 (15)</td>
<td>0.006</td>
<td>67 (14)</td>
<td>0.07</td>
<td>70 (14)</td>
<td>0.30</td>
</tr>
<tr>
<td>Albumin, g/dL</td>
<td>3.6 (0.5)</td>
<td>3.6 (0.5)</td>
<td>&lt;0.0001</td>
<td>3.6 (0.5)</td>
<td>0.06</td>
<td>3.6 (0.5)</td>
<td>0.67</td>
</tr>
<tr>
<td>Hemoglobin, g/dL</td>
<td>10.6 (1.3)</td>
<td>10.5 (1.3)</td>
<td>&lt;0.0001</td>
<td>10.8 (1.3)</td>
<td>0.04</td>
<td>10.5 (1.3)</td>
<td>0.06</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>0.2% (16)</td>
<td>0.2% (12)</td>
<td>0.98</td>
<td>0.3% (1)</td>
<td>0.37</td>
<td>0.0% (0)</td>
<td>N/A</td>
</tr>
<tr>
<td>EpoGen-units per HD</td>
<td>4078 (6059)</td>
<td>5122 (6248)</td>
<td>0.17</td>
<td>6266 (7051)</td>
<td>0.0007</td>
<td>4947 (5348)</td>
<td>0.96</td>
</tr>
<tr>
<td>Heparin-units per HD</td>
<td>2799 (3135)</td>
<td>2651 (3186)</td>
<td>0.33</td>
<td>3671 (4126)</td>
<td>&lt;0.0001</td>
<td>3342 (3335)</td>
<td>0.01</td>
</tr>
<tr>
<td>Anti-platelet (%)</td>
<td>3.1% (250)</td>
<td>100% (6013)</td>
<td>N/A</td>
<td>5.6% (16)</td>
<td>0.18</td>
<td>3.4% (8)</td>
<td>0.76</td>
</tr>
<tr>
<td>Charlson score</td>
<td>5.5 (1.9)</td>
<td>5.5 (2.0)</td>
<td>0.10</td>
<td>5.4 (1.7)</td>
<td>0.32</td>
<td>5.5 (2.0)</td>
<td>0.72</td>
</tr>
<tr>
<td>CHADS₃ score</td>
<td>2.4 (1.0)</td>
<td>2.4 (1.1)</td>
<td>0.003</td>
<td>2.3 (1.0)</td>
<td>0.07</td>
<td>2.2 (1.0)</td>
<td>0.01</td>
</tr>
<tr>
<td>CHF</td>
<td>20.8% (1677)</td>
<td>21.3% (1282)</td>
<td>0.55</td>
<td>14.6% (41)</td>
<td>0.01</td>
<td>14.1% (34)</td>
<td>0.01</td>
</tr>
<tr>
<td>HTN</td>
<td>88.5% (7137)</td>
<td>88.9% (5350)</td>
<td>0.44</td>
<td>86.9% (244)</td>
<td>0.41</td>
<td>84.9% (207)</td>
<td>0.09</td>
</tr>
<tr>
<td>Embolic CVA</td>
<td>12.0% (963)</td>
<td>12.8% (770)</td>
<td>0.12</td>
<td>11.2% (31)</td>
<td>0.94</td>
<td>14.6% (36)</td>
<td>0.13</td>
</tr>
<tr>
<td>Bleeding index score</td>
<td>1.9 (0.8)</td>
<td>1.9 (0.8)</td>
<td>&lt;0.0001</td>
<td>1.9 (0.6)</td>
<td>0.24</td>
<td>1.8 (0.5)</td>
<td>0.03</td>
</tr>
<tr>
<td>GI bleed</td>
<td>5.3% (427)</td>
<td>7.5% (451)</td>
<td>&lt;0.0001</td>
<td>7.5% (21)</td>
<td>0.13</td>
<td>6.0% (15)</td>
<td>0.66</td>
</tr>
<tr>
<td>Stroke</td>
<td>12.7% (1024)</td>
<td>14.3% (861)</td>
<td>0.01</td>
<td>12.5% (35)</td>
<td>0.93</td>
<td>16.0% (39)</td>
<td>0.20</td>
</tr>
<tr>
<td>Minor bleed*</td>
<td>2.0% (161)</td>
<td>1.7% (102)</td>
<td>0.13</td>
<td>2.8% (8)</td>
<td>0.0004</td>
<td>4.3% (10)</td>
<td>0.02</td>
</tr>
<tr>
<td>Major bleed*</td>
<td>3.3% (266)</td>
<td>0.7% (42)</td>
<td>&lt;0.0001</td>
<td>4.1% (12)</td>
<td>0.48</td>
<td>4.2% (10)</td>
<td>0.41</td>
</tr>
</tbody>
</table>

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.

Prevalence of Dabigatran and Rivaroxaban in HD patients with AF

## Results

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

<table>
<thead>
<tr>
<th>Event Rate (per 100 Patient-Years)</th>
<th>Unadjusted Rate Ratios</th>
</tr>
</thead>
<tbody>
<tr>
<td>Warf</td>
<td>ASA</td>
</tr>
<tr>
<td>47.1</td>
<td>35.9</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Total</th>
<th>ASA</th>
<th>Dabi</th>
<th>Riva</th>
<th>ASA Versus Warf</th>
<th>Dabi Versus Warf</th>
<th>Riva Versus Warf</th>
</tr>
</thead>
<tbody>
<tr>
<td>110.0</td>
<td>58.8</td>
<td>149.4</td>
<td>120.6</td>
<td>0.53 (0.51–0.56)</td>
<td>1.10 (0.93–1.29)</td>
<td>1.36 (1.12–1.64)</td>
</tr>
</tbody>
</table>
## Efficacy Outcome

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

<table>
<thead>
<tr>
<th>Event Rate (per 100 Patient-Years)</th>
<th>Unadjusted Rate Ratios</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>ASA Versus Warf</td>
</tr>
<tr>
<td>Warf</td>
<td>ASA</td>
</tr>
<tr>
<td>Embolic stroke</td>
<td>5.8</td>
</tr>
<tr>
<td>Arterial embolism</td>
<td>0.7</td>
</tr>
<tr>
<td>Total embolic events</td>
<td>6.2</td>
</tr>
</tbody>
</table>
Mortality

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

<table>
<thead>
<tr>
<th>Group</th>
<th>Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dabigatran</td>
<td>19.2</td>
</tr>
<tr>
<td>Rivaroxaban</td>
<td>16.2</td>
</tr>
<tr>
<td>Warfarin</td>
<td>10.2</td>
</tr>
<tr>
<td>Aspirin</td>
<td>7.7</td>
</tr>
</tbody>
</table>
Sensitivity Analysis

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

<table>
<thead>
<tr>
<th>Group</th>
<th>Rate ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Major bleeding</strong></td>
<td></td>
</tr>
<tr>
<td>Dabigatran</td>
<td>1.64 (1.27-2.12)</td>
</tr>
<tr>
<td>Rivaroxaban</td>
<td>1.39 (1.00-1.94)</td>
</tr>
</tbody>
</table>
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 rivaroxaban in HD patients
• No difference in ischemic events
Removal of Dabigatran by Dialysis

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

![Graph showing decrease in dabigatran levels during hemodialysis](image)
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

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

<table>
<thead>
<tr>
<th>Drug</th>
<th>Canada</th>
<th>US</th>
</tr>
</thead>
</table>
| Apixaban (Eliquis) | >30 ml/min: 5mg BID<sup>1</sup>  
15-29 ml/min: Use with caution  
<15 ml/min: Not recommended  
HD: Not recommended | 5 mg BID<sup>1</sup>  
HD: 5 mg BID<sup>1</sup> |

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
  - 2\textsuperscript{nd} 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
<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Apikaban Group (n=73)</th>
<th>Warfarin Group (n=73)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yrs)</td>
<td>79 ± 11.8</td>
<td>79 ± 13.5</td>
<td>0.994</td>
</tr>
<tr>
<td>LOS (days)</td>
<td>6.3 ± 5.5</td>
<td>5.7 ± 5.3</td>
<td>0.515</td>
</tr>
<tr>
<td>Race-ethnicity</td>
<td></td>
<td></td>
<td>0.124</td>
</tr>
<tr>
<td>Caucasian</td>
<td>54 (74)</td>
<td>62 (84.9)</td>
<td></td>
</tr>
<tr>
<td>Black</td>
<td>16 (21.9)</td>
<td>6 (8.2)</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>3 (4.1)</td>
<td>5 (6.9)</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>44 (60.3)</td>
<td>43 (58.9)</td>
<td>0.866</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>82 ± 24.5</td>
<td>81.5 ± 23.7</td>
<td>0.893</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>166.1 ± 11.1</td>
<td>166.7 ± 11.0</td>
<td>0.718</td>
</tr>
<tr>
<td>SCR (mg/dL)</td>
<td>2.9 ± 1.8</td>
<td>3.2 ± 2.3</td>
<td>0.341</td>
</tr>
<tr>
<td>Renal function</td>
<td></td>
<td></td>
<td>&gt;0.99</td>
</tr>
<tr>
<td>Severe renal impairment</td>
<td>46 (63)</td>
<td>45 (63)</td>
<td></td>
</tr>
<tr>
<td>ESRD</td>
<td>7 (9.5)</td>
<td>7 (9.6)</td>
<td></td>
</tr>
<tr>
<td>ESRD on dialysis</td>
<td>20 (27.4)</td>
<td>20 (27.4)</td>
<td></td>
</tr>
<tr>
<td>Dialysis type</td>
<td></td>
<td></td>
<td>&gt;0.99</td>
</tr>
<tr>
<td>Hemodialysis</td>
<td>19 (26.1)</td>
<td>19 (26.1)</td>
<td></td>
</tr>
<tr>
<td>Peritoneal dialysis</td>
<td>2 (2.7)</td>
<td>2 (2.7)</td>
<td></td>
</tr>
<tr>
<td>INVAF</td>
<td>53 (72.6)</td>
<td>53 (72.6)</td>
<td></td>
</tr>
<tr>
<td>VTE</td>
<td>19 (26)</td>
<td>19 (26)</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>1 (1.4)</td>
<td>1 (1.4)</td>
<td></td>
</tr>
<tr>
<td>CHA₂DS₂-VASc score</td>
<td>6.1 ± 1.3</td>
<td>5.6 ± 1.5</td>
<td>0.100</td>
</tr>
<tr>
<td>HAS-BLED score</td>
<td>3.4 ± 0.9</td>
<td>3 ± 0.9</td>
<td>0.062</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>38 (52.1)</td>
<td>28 (38.4)</td>
<td>0.096</td>
</tr>
<tr>
<td>Previous stroke, TIA, or VTE</td>
<td>42 (57.5)</td>
<td>33 (45.2)</td>
<td>0.136</td>
</tr>
<tr>
<td>Prior MI/CAD</td>
<td>36 (49.3)</td>
<td>41 (56.2)</td>
<td>0.407</td>
</tr>
<tr>
<td>Cirrhosis</td>
<td>5 (6.8)</td>
<td>7 (9.6)</td>
<td>0.547</td>
</tr>
<tr>
<td>Concomitant antithrombotic</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>agents</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aspirin</td>
<td>44 (50.3)</td>
<td>36 (49.3)</td>
<td>0.183</td>
</tr>
<tr>
<td>Clopidogrel</td>
<td>7 (9.6)</td>
<td>2 (2.7)</td>
<td>0.166</td>
</tr>
<tr>
<td>Aspirin and/or clopidogrel</td>
<td>47 (54.4)</td>
<td>36 (49.3)</td>
<td>0.66</td>
</tr>
</tbody>
</table>
Results

- No significant difference in any outcomes
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
Discussion

Conclusion

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

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Apixaban Pharmacokinetics at Steady State in Hemodialysis Patients

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*Division of Nephrology, Jewish General Hospital, McGill University, Montreal, Quebec, Canada; and †Division of General Internal Medicine and ‡Department of Clinical Pharmacology and Toxicology, Geneva University Hospitals, Geneva, Switzerland

CJASN 2017; 28
Study Methods

![Study Method Diagram]

**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
### 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

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Apixaban 2.5 mg Twice Daily</th>
<th>Day 1</th>
<th>Day 8</th>
<th>P Value</th>
<th>Reference Levels (for the 2.5 mg twice daily dose)</th>
</tr>
</thead>
<tbody>
<tr>
<td>AUC_{0-14}, ng·h/ml</td>
<td>298.6 (38.0%)</td>
<td>1009.8 (30.7%)</td>
<td>&lt;0.001</td>
<td>—</td>
<td></td>
</tr>
<tr>
<td>AUC_{0-24}, ng·h/ml</td>
<td>597.3 (38.0%)</td>
<td>2019.7 (30.7%)</td>
<td>&lt;0.001</td>
<td>1661 (1120–2620) ^19</td>
<td></td>
</tr>
<tr>
<td>C_{max}, ng/ml</td>
<td>45.2 (49.9%)</td>
<td>131.5 (31.1%)</td>
<td>&lt;0.001</td>
<td>123 (69–221) ^20</td>
<td></td>
</tr>
<tr>
<td>t_{max}, h</td>
<td>4.4 (62%)</td>
<td>3.6 (48%)</td>
<td>0.32</td>
<td>—</td>
<td></td>
</tr>
<tr>
<td>C_{min}, ng/ml</td>
<td>22.3 (41.2%)</td>
<td>58.0 (31.2%)</td>
<td>&lt;0.001</td>
<td>56 (24–103) ^19</td>
<td></td>
</tr>
<tr>
<td>t_{1/2}, h</td>
<td>5.9 (15.8%)</td>
<td>7.5 (64.3%)</td>
<td>0.94</td>
<td>—</td>
<td></td>
</tr>
<tr>
<td>A1</td>
<td>N/A</td>
<td>3.6 (33.9%) [3.4]</td>
<td>N/A</td>
<td>[1.3–1.7] ^14,22</td>
<td></td>
</tr>
</tbody>
</table>

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 A1. t_{max}, Time to peak apixaban concentration; A1, accumulation index; N/A, not applicable.

*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.
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

<table>
<thead>
<tr>
<th>Apixaban 5 mg Twice Daily</th>
<th>Day 22</th>
<th>P Value</th>
<th>Reference Levels (for the 5 mg twice daily dose)</th>
</tr>
</thead>
<tbody>
<tr>
<td>(AUC_{0-12}), ng h/ml</td>
<td>3026.6±46.6% [2770.4]</td>
<td>0.03</td>
<td>[1474–1717]¹⁸</td>
</tr>
<tr>
<td>(AUC_{0-24}), ng h/ml</td>
<td>6053.2±46.6% (3505.5–9469.7)</td>
<td>0.03</td>
<td>3370 (2070–5250)¹⁹</td>
</tr>
<tr>
<td>C_{max}, ng/ml</td>
<td>307.0±39.4% (189.0–455.0)</td>
<td>0.02</td>
<td>171 (91–321)²⁰</td>
</tr>
<tr>
<td>t_{max}, h</td>
<td>3.8±35.6% (2.5–6.0)</td>
<td>0.89</td>
<td>—</td>
</tr>
<tr>
<td>C_{min}, ng/ml</td>
<td>217.5±51.9% (91.0–337.4)</td>
<td>0.03</td>
<td>107 (56–203)⁹</td>
</tr>
<tr>
<td>t_{1/2}, h</td>
<td>17.4±51.3% (7.1–29.8)</td>
<td>0.13</td>
<td>—</td>
</tr>
</tbody>
</table>

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.

*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

<table>
<thead>
<tr>
<th>Drug</th>
<th>Canada</th>
<th>US</th>
</tr>
</thead>
</table>
| Edoxaban (Lixiana) | 50-80 ml/min: 60mg daily¹  
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
<table>
<thead>
<tr>
<th>DOAC</th>
<th>Stroke/ Systemic Embolism</th>
<th>Major Bleeding</th>
</tr>
</thead>
<tbody>
<tr>
<td>Apixaban^{21}</td>
<td>↓</td>
<td>↓</td>
</tr>
<tr>
<td>Dabigatran 110mg^{25,27,28}</td>
<td>↔</td>
<td>↔</td>
</tr>
<tr>
<td>Dabigatran 150mg^{25}</td>
<td>↓</td>
<td>↔</td>
</tr>
<tr>
<td>Rivaroxaban^{26-29}</td>
<td>↔</td>
<td>↔</td>
</tr>
<tr>
<td>Edoxaban^{24}</td>
<td>↔</td>
<td>↓</td>
</tr>
</tbody>
</table>
DOAC versus warfarin in HD patients with AF

<table>
<thead>
<tr>
<th>DOAC</th>
<th>Stroke/Systemic Embolism</th>
<th>Major Bleeding</th>
</tr>
</thead>
<tbody>
<tr>
<td>Apixaban</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dabigatran</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rivaroxaban</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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)