COMMON PACE MEDICATIONS THAT REQUIRE RENAL DOSING
OBJECTIVES

- Why Do We Renally Dose Medications?
- The Aging Kidney
- Calculating Renal Clearance
- Renal Dosing for the Elderly
- Common PACE Medications That Require Renal Dosing
Adverse Drug Reactions are 3-10 times higher in those with CKD compared to those without

Many drugs and drug metabolites eliminated by kidney filtration

Few medications well studied in elderly and CKD
THE AGING KIDNEY

- Changes in kidney structure\(^1\)
  - Decrease in size and areas of filtration
  - Decrease in the number of nephrons
  - Nephron sclerosis

- Decreased renal blood flow\(^2\)
CVD, hypertension, diabetes, tobacco use, and high protein diet add to renal stress

- High incidence in the elderly in the United States
- Changes absorption, protein binding, volume of distribution and clearance

Other factors

- Drug interactions
- Nephrotoxic drugs
- Dehydration
MDRD Study Equation

- Used to calculate eGFR when a SCr lab test is ordered
- Used for staging CKD
- Best estimate of renal function in the elderly

Cockcroft-Gault Equation\(^3,4\)

\[
\text{CrCl} = \frac{(140 - \text{age}) \times \text{IBW} \times (0.85 \text{ if F})}{(72 \times \text{SCr})}
\]

- Used to determine dosing for drug labeling
- Developed using “average” men
  - Healthy, middle-aged, approximately 70 kg
- IBW versus actual
  - Using IBW can underestimate CrCl
  - Using ABW in obese (BMI > 30) can overestimate CrCl
- Production/elimination of SCr decreases with age\(^1\)
  - May overestimate CrCl in older adult
RENAL DOSING FOR THE ELDERLY

- Medical History
  - Kidney Disease
    - Acute vs. chronic
    - Etiology
  - Obtain comprehensive medication list
  - Calculate BMI

- Calculate CrCl using Cockcroft-Gault equation

- Loading Dose
  - Most likely NOT adjusted in renal impairment
    - Reduced if $V_D$ is significantly decreased (i.e. dialysis)\(^1\)
RENAL DOSING FOR THE ELDERLY

- Determine Maintenance Dose
  - Dose reduction
  - Extend dosing interval

- Therapeutic Drug Monitoring
  - Peaks/troughs
  - Reserved for agents with serum levels correlated with toxicity or efficacy
    - Aminoglycosides, digoxin, lithium, phenytoin (free unbound), vancomycin

1. vancomycin
Nitrofurantoin

- Contraindicated if est. CrCl <60 ml/min
- Inadequate bladder concentration
- Peripheral neuropathy, pulmonary and hepato-toxicity

Ciprofloxacin and levofloxacin

- Renal dose adjust for CrCl <50 ml/min
- Tendon rupture, QTc prolongation
Sulfamethoxazole/trimethoprim
- For estimated CrCl <30 ml/min, reduce dose by 50%\textsuperscript{5}
- Change in mental status, hyperkalemia

Amoxicillin/clavulanate
- For CrCl <30 ml/min:
  - Avoid 875 mg and XR \textsuperscript{5}
  - Reduce to Q12H \textsuperscript{5}
  - Q24H for dialysis\textsuperscript{5}
- Avoid serious adverse GI effects
**Fluconazole**

- No adjustment needed for single dose vaginal candidiasis\(^5\)
- For CrCl ≤50 mL/minute (no dialysis), reduce maintenance dose by 50%\(^5\)
  - No change to loading dose (maximum 400 mg)
- QTc prolongation risk
- Dose dependent clinical drug interactions due to P450 inhibition
  - Strong 2C19 (clopidogrel substrate)
  - Moderate 3A4 (statins)
ANTIVIRALS

**Acyclovir**
- 800 mg PO 5 times/day herpes zoster outbreak\(^5\)
- Reduce to Q8H for CrCl <25 ml/min. \(^5\)
- Reduced to Q12H in HD or CrCl <10 ml/min. \(^5\)

**Valacyclovir**
- Renal dose adjustments for CrCl <50 ml/min\(^5\)
  - Extending dosing interval
Injectable
- **Lovenox** (enoxaparin)
  - Dose adjust when CrCl <30 ml/min

Oral
- **Pradaxa** (dabigatran)
- **Xarelto** (rivaroxaban)
- **Eliquis** (apixaban)

Not adjusting the dose for reduced renal function increases the risk of bleeding!
## LOVENOX (ENOXAPARIN)\(^6\)

<table>
<thead>
<tr>
<th>Indication</th>
<th>Recommended Dose</th>
<th>Dose Adjusted for CrCl &lt; 30 mL/min</th>
</tr>
</thead>
<tbody>
<tr>
<td>DVT prophylaxis in abdominal surgery</td>
<td>40 mg SC once daily</td>
<td>30 mg SC once daily</td>
</tr>
<tr>
<td>DVT prophylaxis in knee replacement surgery</td>
<td>30 mg SC every 12 hours</td>
<td>30 mg SC once daily</td>
</tr>
<tr>
<td>DVT prophylaxis in hip replacement surgery</td>
<td>30 mg SC every 12 hours or 40 mg SC once daily</td>
<td>30 mg SC once daily</td>
</tr>
<tr>
<td>DVT prophylaxis in medical patients</td>
<td>40 mg SC once daily</td>
<td>30 mg SC once daily</td>
</tr>
<tr>
<td>Inpatient treatment of acute DVT with or without pulmonary embolism</td>
<td>1 mg/kg SC every 12 hours or 1.5 mg/kg SC once daily</td>
<td>1 mg/kg SC once daily</td>
</tr>
<tr>
<td>Outpatient treatment of acute DVT without pulmonary embolism</td>
<td>1 mg/kg SC every 12 hours</td>
<td>1 mg/kg SC once daily</td>
</tr>
</tbody>
</table>
## ORAL ANTICOAGULANTS

<table>
<thead>
<tr>
<th>Medication</th>
<th>Indication</th>
<th>Recommended Dosing</th>
<th>Renal Dose Adjustments</th>
<th>HD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pradaxa (Dabigatran etexilate)⁵</td>
<td>1. Atrial fibrillation</td>
<td>1. 150 mg BID</td>
<td>1. CrCl 15 to 30ml/min: 75mg BID CrCl &lt;15 ml/min: Not studied</td>
<td>Not studied</td>
</tr>
<tr>
<td></td>
<td>2. DVT and PE</td>
<td>2. 150 mg BID</td>
<td>2. CrCl &lt;30 ml/min: Not studied</td>
<td></td>
</tr>
<tr>
<td></td>
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<td></td>
</tr>
<tr>
<td>Xarelto (Rivaroxaban)⁵</td>
<td>1. DVT/PE treatment</td>
<td>1. 15 mg BID x 21 days then 20 mg daily</td>
<td>1. CrCl &lt;30 ml/min: Avoid use</td>
<td>Avoid Use</td>
</tr>
<tr>
<td></td>
<td>2. DVT prophylaxis</td>
<td>2. 10 mg once daily</td>
<td>2. CrCl &lt;30 ml/min: Avoid use</td>
<td></td>
</tr>
<tr>
<td></td>
<td>3. Atrial fibrillation</td>
<td>3. 20 mg QPM</td>
<td>3. CrCl 15 to 50 ml/min: 15mg QPM CrCl &lt;15 ml/min: Avoid use</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Eliquis (Apixaban)⁵</td>
<td>1. DVT or PE treatment and prevention</td>
<td>1. 10 mg BID x 7 days, then 5 mg BID for at</td>
<td>1. Scr &gt;2.5 mg/dL or CrCl &lt;25 ml/min: Not studied</td>
<td>Avoid Use</td>
</tr>
<tr>
<td></td>
<td>2. Prophylaxis</td>
<td>least 6 months, then 2.5 mg BID</td>
<td>2. CrCl &lt;30 ml/min: Not studied</td>
<td></td>
</tr>
<tr>
<td></td>
<td>3. Atrial fibrillation</td>
<td>2. 2.5 mg BID</td>
<td>3. Any 2 of the following: Age ≥80 years, weight ≤60 kg, or</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>3. 5 mg BID</td>
<td>Scr ≥1.5 mg/dL: 2.5 mg BID</td>
<td></td>
</tr>
</tbody>
</table>

**Notes:**
- BID: Twice a day
- QPM: Three times a day
- HD: Hemodialysis
- CrCl: Creatinine clearance
- DVT: Deep vein thrombosis
- PE: Pulmonary embolism
- Scr: Serum creatinine
Ranitidine
- If CrCl <50 ml/min, recommend 150 mg daily\textsuperscript{5}
- Titrating upward cautiously as needed
- Adverse CNS effects
  - Vertigo, mental confusion, somnolence
  - Falls Risk

Famotidine
- For CrCl <50 ml/min, give 50\% of normal dose
  OR
- Extend interval to every 36-48 hours\textsuperscript{5}
ANTICONVULSANTS

- **Levetiracetam**
  - Dose adjust when CrCl < 80 ml/min\(^7\)
- **Gabapentin**
  - Dose adjust when CrCl < 60 ml/min\(^5\)
- **Lyrica (pregabalin)**
  - Dose adjust when CrCl < 60 ml/min\(^5\)

**CAUTION!**

Not adjusting the dose for renal impairment increases level of sedation, increasing falls risk!
Metformin

- Use Contraindicated: SCr ≥1.5 mg/dL (males) or ≥1.4 mg/dL (females)\(^8\)
  - Due to the risk of lactic acidosis
- However...
  - Experts suggest use should be allowed in mild to moderate renal impairment with *stable* renal function and close monitoring\(^8\)
  - Incidence of lactic acidosis very rare
  - ADA and other organizations agree that avoiding use with above SCr thresholds may be overly restrictive

### Approach for Prescribing Metformin in Renal Dysfunction\(^8\)

<table>
<thead>
<tr>
<th>CrCl (ml/min)</th>
<th>Maximum Daily Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;60</td>
<td>2,550 mg</td>
</tr>
<tr>
<td>45-59</td>
<td>2,000 mg</td>
</tr>
<tr>
<td>30-44</td>
<td>1,000 mg</td>
</tr>
<tr>
<td>&lt;30</td>
<td>Do not use</td>
</tr>
</tbody>
</table>
ANTIDIABETICS

- **Januvia (sitagliptan)**
  - 100 mg if CrCl ≥50 ml/min
  - 50 mg if CrCl 30-49 ml/min
  - 25 mg if CrCl <30 ml/min
  - Hypoglycemic events

- **Glyburide**
  - High Alert Drug (BEERS)
    - Extremely long half life in geriatrics
    - Hypoglycemic events
**ANTIHYPERTENSIVES**

- **Atenolol**
  - Maximum 50 mg daily if CrCl between 15-35 ml/min\textsuperscript{5}
  - Maximum 25 mg daily if CrCl <15 ml/min\textsuperscript{5}

- **Bisoprolol**
  - Initiate 2.5 mg daily if CrCl <40 ml/min, titrate cautiously\textsuperscript{5}

- **Lisinopril**
  - Start 2.5 mg daily if CrCl <30 ml/min\textsuperscript{5}

- **Quinapril**
  - CrCl 10-30 ml/min, give 2.5 mg daily\textsuperscript{5}
  - Recommendations differ per indication CHF vs. HTN
Namenda (memantine) 5

- Dose adjust for severe impairment CrCl 5-29 ml/min
  - 5 mg daily for 1 week, if tolerated increase to 5 mg twice daily
  - Namenda XR maximum 14 mg daily
- Adverse GI effects, dizziness, drowsiness, confusion, etc.


7. Keppra Package Insert (http://www.accessdata.fda.gov/drugsatfda_docs/label/2009/021035s078s080_021505s021s024lbl.pdf)


QUESTIONS AND COMMENTS?