Novel (Non-Vitamin K) Oral Anticoagulants in CKD and ESRD

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Our Plans Today......

1. Pharmacology / Epidemiology of NOACs in advanced CKD/dialysis (GFR<30 cc/min)
2. Summary of evidence for NOACs in CKD
3. AF: Anticoagulate CKD/ESRD patients?
4. Discontinuation and reversal of NOACs in CKD/dialysis
Non-Vitamin K Anticoagulants

- New class of oral anticoagulants (NOACs)
  - First FDA approved October 2010 (Dabigatran)
- Mechanism of action:
  - Direct Xa inhibitor
  - Thrombin inhibitor
- Phase III studies in *general population* show
  - Equivalent or better than Warfarin (stroke prevention and bleeding)
Non-Vitamin K Anticoagulants

- All dependent on kidney for elimination
- All Phase III trials excluded eGFR <25-30
- Originally contraindicated if eGFR <30
  - AHA guidelines recommend warfarin if eGFR<30
But, Use in CKD Increasing

NOAC use among anticoagulated patients on dialysis

Chan et al. Circulation 2015
But, Use in CKD Increasing

NOAC dose among anticoagulated patients on *dialysis*

Chan et al. Circulation 2015
NOAC Use in CKD Increasing

NOAC use among anticoagulated patients on **dialysis**
NOAC Use in CKD Increasing

NOAC use among anticoagulated patients with eGFR < 30 cc/min

NOAC use among anticoagulated patients with **advanced CKD**

Chan et al. JACC 2016
Renal pharmacokinetics of Anticoagulants

• Uremia
  – Affects many organs
  – Alters PK of many drugs
    • Renal excretion – Filtration and/or secretion
    • Disease affects glomerular and/or tubular function
    • Drug clearance decreases
    • $T_{1/2}$ increases
Effect of decreased clearance
Drug Bioaccumulation
Renal Pharmacokinetics of Anticoagulants

- Renal dose adjustment
  - Decrease dose or……
  - Decrease frequency
- eGFR and NOAC dosing data*
  - Pivotal Phase III trials used Cockcroft-Gault
  - MDRD or CKD-Epi more accurate

Diversion Down History Lane

• Warfarin
  – Rat poison 1948
  – Anticoagulant 1954
  – Studies suggest lower doses in CKD
    • eGFR > 60: 4.8 mg/day
    • eGFR 30-59: 4.3 mg/day
    • eGFR < 30: 3.9 mg/day
  – Generally more difficult to manage in CKD*

If Difficult, Why Not ASA?

- In “Normals”

<table>
<thead>
<tr>
<th>Outcomes of Warfarin vs Aspirin</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>HR for stroke (vs aspirin)</strong></td>
</tr>
<tr>
<td>meta-analysis</td>
</tr>
<tr>
<td>eGFR=30-50 cc/min</td>
</tr>
</tbody>
</table>

- Warfarin: Less strokes and probably not more dangerous compared to ASA
PK of Warfarin

warfarin → parent drug (99% bound)

CYP2C9 metabolized

Inactive metabolite

renal elimination
Dabigatran ("Pradaxa")

• First NOAC
  – Approved for Atrial Fibrillation 2010
  – Direct Thrombin Inhibitor

• Outcomes: Dabigatran vs Warfarin (n=18,113)

<table>
<thead>
<tr>
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<th>HR for stroke (vs warfarin)</th>
<th>HR for bleed (vs warfarin)</th>
</tr>
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<tbody>
<tr>
<td>Full study</td>
<td>0.66 (superior)</td>
<td>0.93 (NS)</td>
</tr>
<tr>
<td>eGFR=30-50 cc/min</td>
<td>0.56 (superior)</td>
<td>1.01 (NS)</td>
</tr>
</tbody>
</table>

– Dose: 150 mg BID (75 mg BID if eGFR 15-30 ml/min)
PK of Dabigatran

dabigatran etexilate

→
dabigatran active
(35% bound)

→
50-60% cleared with dialysis

→
80% renal elimination
Rivaroxiban ("Xarelto")

• Approved by FDA 2011
  – Factor Xa inhibitor
• Outcomes Rivaroxiban vs Warfarin (n=14,264)

<table>
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<th>HR for stroke (vs warfarin)</th>
<th>HR for bleed (vs warfarin)</th>
</tr>
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<tbody>
<tr>
<td>Full study</td>
<td>0.88 (non-inferior)</td>
<td>1.03 (NS)</td>
</tr>
<tr>
<td>eGFR=30-50 cc/min</td>
<td>0.88 (NS)</td>
<td>0.98 (NS)</td>
</tr>
</tbody>
</table>

• Dose 20 mg QD (15 mg if eGFR 15 – 50 ml/min)
PK of Rivaroxiban

- Rivaroxaban
  - Parent drug (95% bound)
  - Metabolized by CYP3A4/5 and CYP2J2
  - 51% inactive metabolite
  - 7% feces
  - 36% renal elimination
Abixaban ("Eliquis")

- Approved by FDA December 2012
  - Factor Xa inhibitor
- Outcomes Abixaban vs. Warfarin (n=18,201)

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<tr>
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<th>HR for stroke (vs warfarin)</th>
<th>HR for bleed (vs warfarin)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Full study</td>
<td>0.79 (superior)</td>
<td>0.69 (superior)</td>
</tr>
<tr>
<td>eGFR=30-50 cc/min</td>
<td>0.79 (NS)</td>
<td>0.50 (superior)</td>
</tr>
</tbody>
</table>

- Dosing – Very complicated
PK of Abixaban

Apixaban

- Parent drug (87% bound)
- CYP3A4/5 and P-glycoprotein
- Inactive metabolite
- ~50% in feces
- 6% cleared with dialysis
- 27% renal elimination
Abixaban Dosing

• Dose 5mg BID but.........
• Dose 2.5 mg if ≥ 2 of the following:
  – Age ≥ 80 years
  – Body weight ≤ 60 kg
  – Serum creatinine ≥ 1.5 mg/dl
• Dialysis: 5 mg BID unless:
  – Age ≥ 80 years
  – Body weight ≤ 60 kg
Abixaban Dosing

- Pharmacologic data
  - eGFR = 15 ml/min
    - 44% higher Abixaban levels
  - Dialysis patient
    - 36% higher Abixaban levels
  - Studies needed to establish dosing if eGFR < 15 ml/min
Patients with End-Stage Renal Disease on Dialysis

Clinical efficacy and safety studies with ELIQUIIS did not enroll patients with end-stage renal disease (ESRD) on dialysis. In patients with ESRD maintained on intermittent hemodialysis, administration of ELIQUIIS at the usually recommended dose [see Dosage and Administration (2.1)] will result in concentrations of apixaban and pharmacodynamic activity similar to those observed in the ARISTOTLE study [see Clinical Pharmacology (12.3)]. It is not known whether these concentrations will lead to similar stroke reduction and bleeding risk in patients with ESRD on dialysis as was seen in ARISTOTLE.
Edoxaban ("Savaysa")

- FDA approved January 2015
  - Factor Xa inhibitor
- Outcomes Edoxaban vs. Warfarin (n=21,105)

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<th>HR for bleed (vs warfarin)</th>
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<tr>
<td>Full study</td>
<td>0.79 (non-inferior)</td>
<td>0.80 (superior)</td>
</tr>
<tr>
<td>eGFR=30-50 cc/min</td>
<td>0.89 (NS)</td>
<td>0.77 (superior)</td>
</tr>
</tbody>
</table>

- Dose 60 mg QD (30 mg if eGFR 15 – 50 ml / min; Do not use if eGFR > 95!)

AKDHC

27
PK of Edoxaban

10% metabolite

CYP3A4

parent drug (55% bound)

9% cleared with dialysis

40% bile elimination

50% renal elimination

edoxaban
Conclusions:

• NOACs
  – Are equal or better (vs. warfarin) at preventing stroke and bleeding in general AF population
  – All NOACs depend on kidney for elimination
  – No good data for use if eGFR < 30 ml/min

• But, FDA label gives recommendations for dosing down to eGFR of 15 ml/min (and for Abiixaban for eGFR < 15 ml/min)
SHOULD WE ANTI-COAGULATE ADVANCED CKD AND DIALYSIS PATIENTS WITH ATRIAL FIBRILLATION?
Anticoagulation / Decreased eGFR

- Anticoagulation when eGFR < 30?*
  - Warfarin increases risk of major bleeding by 20% or more
  - Efficacy of stroke prevention likely reduced in patients with eGFR < 30
  - Uremic platelet dysfunction
  - Heparin during dialysis
  - “Competing risks” – shortened life expectancy

Anticoagulation / Decreased eGFR

- Anticoagulation when eGFR < 30
  - No trials
- Only data is observational
- Studies show “confounding by indication” meaning those in treatment arm with reason to take the medication are compared to those not on the drug
Anticoagulation / Decreased eGFR

• Clinical Guideline Paradox
  – 2014 AHA /ACC/HRS Guidelines: Warfarin reasonable when CHA$_2$DS$_2$VAS$_C$ > 2*,**, 
  – KDIGO: Routine anticoagulation for primary stroke prevention is not indicated***

**Meta Analysis Stroke vs Warfarin**

Anticoagulation vs Stroke in CKD

• Anticoagulation when eGFR<30?*
  – “Until we have RCT data physicians should individually balance the risk of stroke in each patient against their perceived magnitude of stroke prevention anticoagulants may provide”

SO IF YOU ARE GOING TO ANTICOAGULATE, SHOULD WE USE NOACS OR WARFARIN IN CKD?
CKD Patient – NOACs vs Warfarin

• High risk population*
  – Increased incidence of stroke
  – Increased incidence of bleeding
  – Increased prevalence of atrial fibrillation

• NOACs vs Warfarin
  – Less bleeding / improved safety profile (?)
  – Better stroke reduction

CKD Patient – NOACs vs Warfarin

- Phase III trials
  - No Warfarin efficacy proven if eGFR < 30
- But FDA labels provide dosing recommendations to eGFR = 15 and lower
  - Based mostly on pharmacokinetic data
  - PK studies poor predictor of outcomes
CKD Patient – NOACs vs Warfarin

<table>
<thead>
<tr>
<th></th>
<th>Major bleeding</th>
<th>Death from bleeding</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dabigatran</td>
<td>1.48 (1.21-1.81)</td>
<td>1.78 (1.18-2.68)</td>
</tr>
<tr>
<td>Rivaroxaban</td>
<td>1.38 (1.03-1.83)</td>
<td>1.71 (0.93-3.12)</td>
</tr>
<tr>
<td>Warfarin</td>
<td>1.00 (ref)</td>
<td>1.00 (ref)</td>
</tr>
</tbody>
</table>

Differences in bleeding risks exist

CKD Patient – NOACs vs Warfarin

• Guidelines
  – AHA 2014: Warfarin if eGFR < 30 ml/min
  – 2016 European Heart Rhythm: Refrain from NOACs when eGFR < 30 ml/min
CKD Patient – NOACs vs Warfarin

• NOACs as “first line” therapy:
  – Calciphylaxis
  – Warfarin skin necrosis
  – Protein C or S deficiency

• Which NOAC?
  – Apixaban 2.5 mg BID per label
  – Check renal function frequently (every 2 to 4 months) if eGFR > 30
CKD Patient – NOACs vs Warfarin

• CKD – 5 year risk for eGFR < 30 ml/min:
  – 18% if baseline GFR 45 – 60
  – 25% if baseline GFR is 30 – 45

• 5 year risk of AKI:
  – 1% if baseline GFR 45 – 60
  – 2.5% if baseline GFR 30 – 45
CKD Patient – NOACs vs Warfarin

• Recommendation close monitoring of renal function in CKD patient on NOACs:
  – Assess on a GFR/10 = months between lab testing as a guideline
    • If eGFR = 40 test every 4 months
    • If eGFR = 30 test every 3 months
    • Etc.
DISCONTINUATION AND REVERSAL OF NOACS
Non-Urgent Pre-op Hold NOACs

• Generally wait 3 – 4 half-lives for drug to be cleared:

* Table 1: half live of NOAC by CrCl

<table>
<thead>
<tr>
<th>CrCl (cc/min)</th>
<th>dabigatran</th>
<th>rivaroxaban</th>
<th>apixaban</th>
<th>edoxaban</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;60</td>
<td>14h</td>
<td>8.5h</td>
<td>7.5h</td>
<td>8.6h</td>
</tr>
<tr>
<td>30-60</td>
<td>18h</td>
<td>9h</td>
<td>17.5h</td>
<td>9.4h</td>
</tr>
<tr>
<td>15-30</td>
<td>28h</td>
<td>9.5h</td>
<td>&gt;17.5h</td>
<td>17h</td>
</tr>
<tr>
<td>&lt;15</td>
<td>Unknown</td>
<td>Unknown</td>
<td>&gt;17.5h</td>
<td>&gt;17h</td>
</tr>
</tbody>
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Non-Urgent Pre-op Hold NOACs

- Cessation time of NOACs pre-procedure

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<th>apixaban</th>
<th>edoxaban</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;60</td>
<td>2 days</td>
<td>2 days</td>
<td>2 days</td>
<td>2 days</td>
</tr>
<tr>
<td>30-60</td>
<td>4 days</td>
<td>2 days</td>
<td>2 days</td>
<td>2 days</td>
</tr>
<tr>
<td>15-30</td>
<td>4 days</td>
<td>2 days</td>
<td>2 days</td>
<td>2 days</td>
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<tr>
<td>&lt;15</td>
<td>5 days</td>
<td>4 days</td>
<td>4 days</td>
<td>unknown</td>
</tr>
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Urgent Reversal of Dabigatran

- 4 hour HD removes ~ 50% Dabigatran
- DDAVP
- Idarucizumab
  - Monoclonal antibody binds Dabigatran
  - Normalizes Thrombin Time in 30 minutes
  - 6% risk of thrombotic event
Urgent Reversal Xa Inhibitors

- 4 Factor Prothrombin Complex Concentrate (4F-PCC)
  - Concentrated Factor II, VII, IX and X
- Mechanism and issues:
  - “Floods” system with factors quickly
  - Overwhelms Xa inhibition
  - Much less volume than FFP
  - Normalizes coag labs but no outcome data
Urgent Reversal Xa Inhibitors

• 1.4% risk of thrombotic complication
NOACs in AKI

- GFR formulas not accurate in AKI
- Severe AKI associated with decreased clearance of NOAC and potential bioaccumulation / bleeding
- Consider holding NOACs in patient with severe AKI
- Consider reversal agents if patient is bleeding
Conclusions: Advanced CKD and NOACs

- NOAC use is substantial and increasing
- No trial data supporting this in CKD
- AHA and European Hearth Rhythm Association guidelines recommend warfarin
- NOAC RCTs are needed for this vulnerable population