Safety and Efficacy of Direct Oral Anticoagulant Therapy in Chronic Kidney Disease

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Disclosure

• No Conflicts of Interest
Clinical Case

- 65 yo man with stage G3bA2 chronic kidney disease due to hypertension and diabetic kidney disease recently diagnosed with paroxysmal AF is seen in clinic for follow up

- CHA2DS2-VASc Score for Stroke Risk = 3

- He is married, worked as a Public Defender for most of his career and is planned to retire this year

- 10 pack-year history of tobacco, quit >20 years prior, one glass of wine ~2-3 times per week

- Labs: Creatinine 1.8 mg/dL, eGFR 39 ml/min CKD-Epi, 102 mg/g albuminuria

- He asks what can be done to reduce his risk of stroke as he read that he is at an increased risk from “WebMD/Google”
• *Which therapy*, if any, would you recommend?
• Vitamin K antagonist (*VKA* – *Warfarin*) or Direct Oral Anticoagulant Therapy (*DOAC*)?
• Is there evidence for efficacy of DOACs in CKD?
• Is there an increased burden of harm/adverse events in CKD patients with DOACs?
• How would your recommendation *change* if this patient was on chronic renal replacement therapy with *hemodialysis*?
• Define **Chronic Kidney Disease (CKD)** and stages

• Epidemiology of **atrial fibrillation (AF)** in CKD population

• Define **Direct Oral Anticoagulants (DOACs)**

• Evidence for **safety and efficacy** of DOACs in CKD

• A practical approach to using DOACs in CKD patients
Chronic kidney disease (CKD) - pathophysiologic process characterized by progressive loss of nephrons and function due to multiple etiologies and frequently leading to end stage kidney disease.

- Presence of either:
  - Kidney damage or
  - Decreased kidney function for ≥3 months with decreased glomerular filtration rate (GFR) - <60 ml/min

- Prevalence ~ 14.8% adult population
- 726,000 individuals on renal replacement therapy
• Estimated GFR (eGFR) – *Chronic Kidney Disease Epidemiology Collaboration equation* (**CKD-EPI**)

• Developed in order to create a formula *more accurate* than MDRD when actual \( \text{GFR} > 60 \text{ml/min}/1.73\text{m}^2 \)

• Like MDRD estimates GFR based on:
  • Age
  • Gender
  • Ethnicity
  • Creatinine

• *Better accuracy* than MDRD when \( \text{GFR} > 60 \text{ml/min}/1.73\text{m}^2 \)

• May eventually replace MDRD
## Stages of Chronic Kidney Disease with Albuminuria

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

<table>
<thead>
<tr>
<th>GFR stages, description, and range (mL/min per 1.73 m²)</th>
<th>Albuminuria stages, description, and range (mg/g)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>A1 Optimal and high-normal</td>
</tr>
<tr>
<td>G1 High and optimal</td>
<td>&gt; 105</td>
</tr>
<tr>
<td>G2 Mild</td>
<td>75-89</td>
</tr>
<tr>
<td>G3a Mild-moderate</td>
<td>45-59</td>
</tr>
<tr>
<td>G3b Moderate-severe</td>
<td>30-44</td>
</tr>
<tr>
<td>G4 Severe</td>
<td>15-29</td>
</tr>
<tr>
<td>G5 Kidney failure</td>
<td>&lt; 15</td>
</tr>
</tbody>
</table>
Chronic Kidney Disease: A Prothrombotic State

- **Increased risk** - arterial and venous thromboembolism (VTE) in CKD patients
- Stage 3-5 CKD (eGFR <60 ml/min) have **2-3-fold risk** of VTE
- Increased **risk of bleed** and all cause mortality - VTE in End-Stage Kidney Disease (ESKD)
- Increased risk of ACS, stroke, PAD, and dialysis access thrombosis in CKD population
Chronic Kidney Disease: An Independent Risk Factor for Atrial Fibrillation

- **Atrial fibrillation (AF)** – high prevalence in CKD
  - 18% prevalence in CKD-nondialysis (CKD-ND)
  - 12-25% prevalence in CKD-dialysis (CKD-D)
- CKD and AF – share several **risk factors**
  - Advanced age, HTN, DM, pre-existing heart disease
- CKD and AF - Increased risk of stroke, thromboembolism, heart failure, MI, and all cause mortality
Anticoagulant Therapy: **AF and VTE**

- Anticoagulant (AC) therapy – prevention of cardiovascular thrombotic and VTE events
- AC recommended in AF
  - CHA$_2$DS$_2$-VASc score $\geq 2$

<table>
<thead>
<tr>
<th>Condition</th>
<th>Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>C Congestive heart failure (or Left ventricular systolic dysfunction)</td>
<td>1</td>
</tr>
<tr>
<td>H Hypertension: blood pressure consistently above 140/90 mmHg (or treated hypertension on medication)</td>
<td>1</td>
</tr>
<tr>
<td>A$_2$ Age $\geq 75$ years</td>
<td>2</td>
</tr>
<tr>
<td>D Diabetes Mellitus</td>
<td>1</td>
</tr>
<tr>
<td>S$_2$ Prior Stroke or TIA or thromboembolism</td>
<td>2</td>
</tr>
<tr>
<td>V Vascular disease (e.g. peripheral artery disease, myocardial infarction, aortic plaque)</td>
<td>1</td>
</tr>
<tr>
<td>A Age 65–74 years</td>
<td>1</td>
</tr>
<tr>
<td>Sc Sex category (i.e. female sex)</td>
<td>1</td>
</tr>
</tbody>
</table>
Anticoagulant Therapy:
DOAC vs. VKA

• Terminology:

• Traditional oral anticoagulants
  • Vitamin K antagonist – coumarins/warfarin

• NOAC
  • Novel oral anticoagulant
  • Non-Vitamin K oral anticoagulants

• DOAC
  • Direct oral anticoagulant
  • Directly binds to specific clotting factors
  • Endorsed by the International Society of Thrombosis and Hemostasis
Oral Anticoagulants: 
**Mechanism of Action**

**DOAC – attractive alternatives to VKA**
- Rapid onset of action
- No need for regular monitoring
- Less interaction with drugs/food
- Lower risk of stroke and bleeding compared to VKA in patients with normal renal function

**Diagram:**
- Intrinsic Pathway
  - XII → XIIa
  - XI → Xla
- Extrinsic Pathway
  - Warfarin
  - Factor VII Deficiency
- Apixaban
- Edoxaban
- Rivaroxaban
- Betrixaban
- Enoxaparin
- Heparin
- Dabigatran
- Common Pathway
  - Fibrinogen → Fibrin
  - Fibrin Clot
  - X → Xa
  - Xa → IXa
  - IX → VIIa
  - VII → VIIa
  - XI → IXa
  - XII → XIIa

**References:**
Paulus et al. Drug Safety-Case Reports. Dec 2016; 3:8
Anticoagulant Therapy: In CKD Patients

- Less anticoagulants—prescribed to advanced CKD patients
- Increased risk of bleeding, questionable benefit
- Vitamin K antagonist/warfarin—warfarin-associated calciphylaxis, warfarin-related nephropathy
- Less known with direct oral anticoagulants (DOAC)
- Exclusion of CKD patients in most clinical trials evaluating safety and efficacy of therapy
Figure 2. Pharmacokinetics of (A) warfarin, (B) apixaban, (C) rivaroxaban, (D) dabigatran, and (E) edoxaban. from the study by Chan et al41 with permission.

DOI: (10.1177/1074248419858116)
# DOACs in CKD Patients: Recommendations by Regulatory Agencies

## Table 1. Recommendation of major regulatory agencies

<table>
<thead>
<tr>
<th></th>
<th>Dabigatran</th>
<th>Apixaban</th>
<th>Rivaroxaban</th>
<th>Edoxaban</th>
</tr>
</thead>
</table>
| **EMA** 2014 | 150 mg twice daily for CKD stage G3 (CrCl 30 to 50 mL/min) | 2.5 mg twice daily in patients with at least two of the following characteristics:  
- age ≥ 80 years  
- body weight ≤ 60 kg  
- SCR > 1.5 mg/dL | 15 mg daily for CKD stage G3 and G4 (CrCl 15 to 50 mL/min) | 30 mg once daily for CKD stage G3 and G4 (CrCl 15 to 50 mL/min) |
| **No recommendation for CKD stage G4** | | | |
| **FDA** 2014 | 150 mg twice daily for CKD stage G3 (CrCl > 30 mL/min) | 2.5 mg twice daily in patients with at least two of the following characteristics:  
- age ≥ 80 years  
- body weight ≤ 60 kg  
- SCR > 1.5 mg/dL | 15 mg daily for CKD stage G3 and G4 (CrCl 15 to 50 mL/min) | 30 mg once daily for CKD stage G3 and G4 (CrCl 15 to 50 mL/min) |
| **75 mg twice daily for CKD stage G4 (CrCl 15 to 30 mL/min)** | | | |
| **Health Canada** 2017 | 110 or 150 mg twice daily for CKD stage G3 (CrCl 30 to 50 mL/min) | 2.5 mg twice daily in patients with at least two of the following characteristics:  
- age ≥ 80 years  
- body weight ≤ 60 kg  
- SCR > 1.5 mg/dL | 15 mg daily for CKD stage G3 (CrCl 30 to 50 mL/min) | 30 mg once daily for CKD stage G3 (CrCl 30 to 50 mL/min) |
| **No recommendation for CKD stage G4** | | | |

DOACs in CKD Patients: Where Is the Evidence?

Cochrane Library

[Intervention Review]

Direct oral anticoagulants versus warfarin for preventing stroke and systemic embolic events among atrial fibrillation patients with chronic kidney disease

Miho Kimachi¹, Toshi A Furukawa², Kimihiko Kimachi¹, Yoshihito Goto³, Shingo Fukuma¹, Shunichi Fukuhara¹,⁴

¹Department of Healthcare Epidemiology, School of Public Health in the Graduate School of Medicine, Kyoto University, Kyoto, Japan. ²Department of Health Promotion and Human Behavior, Kyoto University Graduate School of Medicine/School of Public Health, Kyoto, Japan. ³Department of Health Informatics, Kyoto University School of Public Health, Kyoto, Japan. ⁴Center for Innovative Research for Communities and Clinical Excellence, Fukushima Medical University, Fukushima, Japan
DOACs in CKD Patients: Where Is the Evidence?

- Cochrane Systematic Review
  - Assess the efficacy and safety of DOAC vs VKA
    - Apixaban
    - Dabigatran
    - Edoxaban
    - Rivaroxaban
  - All RCTs comparing efficacy and safety of DOACs with warfarin through August 2017
  - Preventing stroke and systemic embolic events - non-valvular AF patients with CKD
  - Defined as CrCl or eGFR between 15 and 60 mL/min - CKD stage G3 and G4

Kimachi et al. Cochrane Database of Systematic Reviews 2017, 11. Art. No.: CD011373. DOI: http://dx.doi.org.ezproxy3.library.arizona.edu/10.1002/14651858.CD011373.pub2
## DOACs vs Warfarin for Preventing Stroke and Systemic Embolic Events Among AF Patient with CKD:

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Illustrative comparative risks* (95% CI)</th>
<th>Relative effect (95% CI)</th>
<th>No. of participants (studies)</th>
<th>Quality of the evidence (GRADE)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Assumed risk</td>
<td>Corresponding risk</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Warfarin</td>
<td>DOAC</td>
<td></td>
<td></td>
</tr>
<tr>
<td>All strokes and systemic embolic events</td>
<td>29 per 1,000 (19 to 29)</td>
<td>23 per 1,000</td>
<td>12,545 (5)</td>
<td>⊗⊗⊗⊗ ⊗ MODERATE</td>
</tr>
<tr>
<td>Follow up: 1.8 years to 2.8 years</td>
<td></td>
<td>RR 0.81 (0.65 to 1.00)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Major bleeding</td>
<td>55 per 1,000 (32 to 57)</td>
<td>43 per 1,000</td>
<td>12,521 (5)</td>
<td>⊗⊗⊗⊗ ⊗ LOW</td>
</tr>
<tr>
<td>Follow up: 1.8 years to 2.8 years</td>
<td></td>
<td>RR 0.79 (0.59 to 1.04)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>11 per 1,000 (5 to 21)</td>
<td>10 per 1,000</td>
<td>2,740 (1)</td>
<td>⊗⊗⊗ ⊗ -</td>
</tr>
<tr>
<td>Follow up: 2.8 years</td>
<td></td>
<td>RR 0.92 (0.45 to 1.90)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Minor bleeding</td>
<td>74 per 1,000 (43 to 119)</td>
<td>72 per 1,000</td>
<td>3,012 (2)</td>
<td>⊗⊗⊗⊗ ⊗ LOW</td>
</tr>
<tr>
<td>Follow up: 2.5 years to 2.8 years</td>
<td></td>
<td>RR 0.97 (0.58 to 1.61)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gastrointestinal bleeding</td>
<td>17 per 1,000 (17 to 35)</td>
<td>24 per 1,000</td>
<td>5,678 (2)</td>
<td>⊗⊗⊗⊗ ⊗ MODERATE</td>
</tr>
<tr>
<td>Follow up: 1.9 years to 2.8 years</td>
<td></td>
<td>RR 1.40 (0.97 to 2.01)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intracranial haemorrhage</td>
<td>14 per 1,000 (4 to 9)</td>
<td>6 per 1,000</td>
<td>12,521 (5)</td>
<td>⊗⊗⊗⊗ ⊗ MODERATE</td>
</tr>
<tr>
<td>Follow up: 1.8 years to 2.8 years</td>
<td></td>
<td>RR 0.43 (0.27 to 0.69)</td>
<td></td>
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</tr>
<tr>
<td>All-cause mortality</td>
<td>78 per 1,000 (61 to 82)</td>
<td>71 per 1,000</td>
<td>9,595 (4)</td>
<td>⊗⊗⊗⊗ ⊗ MODERATE</td>
</tr>
<tr>
<td>Follow up: 1.8 years to 2.8 years</td>
<td></td>
<td>RR 0.91 (0.78 to 1.05)</td>
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</tbody>
</table>

* The risk in the intervention group (and its 95% CI) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

AF: atrial fibrillation; CI: confidence interval; DOAC: direct oral anticoagulants; RR: risk ratio
DOACs in CKD Patients: Implications for Practice

- DOAC – *as likely* as warfarin to *prevent* all strokes and systemic embolic events among AF patients with CKD
- DOAC – *do not increase* the risk of major bleeding events in CKD patients compared to warfarin
- These findings should *encourage physicians to prescribe DOAC* to AF patients with CKD
Efficacy and safety of DOAC among patients with advanced CKD were not assessed (particularly ESKD patients)

Secondary outcomes could not be assessed – MI, minor bleeding, and vascular death due to lack of available data

Follow up maximum was 2.8 years - further studies should assess long term effectiveness and safety of DOAC use

Future studies should compare subtypes of dosages of DOAC
DOACs in CKD Patients: More Evidence

**Benefits and Harms of Oral Anticoagulant Therapy in Chronic Kidney Disease: A Systematic Review and Meta-analysis**

Jeffrey T. Ha, MBBS; Brendon L. Neuen, MBBS(Hons); Lap P. Cheng, MBBS; Min Jun, PhD; Tadashi Toyama, PhD; Martin P. Gallagher, PhD; Meg J. Jardine, PhD; Manish M. Sood, MD; Amit X. Garg, PhD; Suetonia C. Palmer, PhD; Patrick B. Mark, PhD; David C. Wheeler, MD; Vivekanand Jha, MD; Ben Freedman, PhD; David W. Johnson, PhD; Vlado Perkovic, PhD; Sunil V. Badve, PhD

• DOAC and VKA in adults with CKD stage 3-5 including ESKD reporting efficacy or bleeding outcomes
  
  • 45 trials
  • 34,082 patients
  • AF (11 trials), VTE (11 trials), thromboprophylaxis (6 trials)
  • Dialysis access thrombosis (8 trials), CV disease other than AF (9 trials)
  • All but dialysis access thrombosis excluded ESKD patients or GFR <20 ml/min
DOACs had a benefit-risk profile superior to VKA in CKD – GFR >25 ml/min including reduction in stroke, systemic embolism, hemorrhagic stroke in AF

No significant reduction in risk of bleeding with DOAC compared to VKA

Effect of DOAC – uncertain compared to VKA in preventing recurrent VTE/VTE related death

Advanced CKD (GFR <25 ml/min) and ESKD – no RCT data available to evaluate the effects of VKAs or DOACs on the prevention of stroke or systemic embolism in AF or on VTE and VTE-related death
DOACs in CKD Patients: Future Trials

- **The RENAL – AF trial**
  - RENal Hemodialysis Patients ALlocated Apixaban Versus Warfarin in Atrial Fibrillation
  - ClinicalTrials.gov: NCT02942407
  - Compares *apixaban* with *VKA* in participants with *hemodialysis-dependent ESKD and AF*

- **AVKDIAL**
  - Study of the Benefit/Risk Ratio of Oral Anticoagulation in Hemodialysis Patients with Atrial Fibrillation
  - ClinicalTrials.gov: NCT02886962
  - Compares *hemorrhagic and thrombotic risks* from oral anticoagulation with *VKA* in comparison with *no anticoagulation* in hemodialysis patients with AF
DOACs in CKD Patients: Take Home Points for Clinical Practice

- **DOACs** should be prescribed for *nonvalvular AF* in CKD patients with *early stage 4 CKD (eGFR >25 ml/min)* and earlier to prevent stroke and embolic events
  - Data to date does **NOT** show an increase in *risk in bleeding* using DOACs compared to VKA in stage 4 CKD and earlier
- Effect of DOACs are **uncertain** compared to VKA in *preventing VTE/VTE related death* in CKD patients
• **Dosing studies** need to be performed in CKD population
  • Reasonable to *use FDA recommended dosing* based on available pharmacokinetic studies

• **No RCT** data available to evaluate effects of VKAs or DOACs on prevention of stroke, systemic embolism in AF or on VTE/VTE-related death in *advanced CKD (eGFR <25 ml/min)* or ESKD
  • Retrospective cohort study of Medicare beneficiaries with ESKD and AF on dialysis – apixaban may be associated with lower risk of major bleeding compared with warfarin
  • 3 pivotal trials are in the pipeline to answer the following:
    • VKA vs. no anticoagulation in hemodialysis patients with AF
    • Apixaban vs. VKA in hemodialysis patients with AF
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Questions?