

# Oral Anticoagulation in Patients with Atrial Fibrillation and Chronic Kidney Disease

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## Disclosure

- Dr. Mandy Liu has no relevant financial relationships with ineligible companies to disclose.

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## Objectives

- 1 Review current practice guideline recommendations for oral anticoagulant use in patients with atrial fibrillation (AF) and chronic kidney disease (CKD)
- 2 Review primary literature of direct-acting oral anticoagulant use in patients with AF and CKD
- 3 Discuss appropriate oral anticoagulant management of patients with AF and CKD

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### Background

- Atrial fibrillation (AF) patients with chronic kidney disease (CKD) are at greater risk of stroke, systemic embolism, and bleeding than AF patients without CKD
- Historically, warfarin was the drug of choice as it undergoes extensive hepatic metabolism rather than renal excretion
- Patients with kidney impairment were excluded from landmark clinical trials of factor Xa and direct thrombin inhibitors
  - CrCl <30 mL/min: rivaroxaban (ROCKET-AF), edoxaban (ENGAGE-AF TIMI 48), dabigatran (RE-LY)
  - CrCl <25 mL/min: apixaban (ARISTOTLE)

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### 2019 AHA/ACC/HRS Focused Update on Atrial Fibrillation<sup>1</sup>

**Recommendations**

For patients with AF (except with moderate-to-severe mitral stenosis or a mechanical heart valve), and moderate-to-severe CKD, treatment with reduced doses of DOACs may be considered:

- Apixaban (Scr ≥ 1.5 mg/dL)
- Edoxaban (CrCl 15 to 50 mL/min)
- Rivaroxaban (CrCl ≤50 mL/min)
- Dabigatran (CrCl 15 to 30 mL/min)

For patients with AF with a CHA<sub>2</sub>DS<sub>2</sub>-VASc score of ≥2 in men or ≥3 in women and have end-stage CKD (CrCl <15mL/min) or are on dialysis, anticoagulation may be reasonable:

- Warfarin (INR 2.0 to 3.0)
- Apixaban

Not recommended in patients with AF and end-stage CKD or on dialysis:

- Dabigatran
- Edoxaban
- Rivaroxaban

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### 2020 European Guidelines<sup>2</sup>

**Recommendation**

For patients with severe CKD (CrCl 15 to 30 mL/min), reduced doses of DOACs are feasible options:

- Apixaban
- Edoxaban
- Rivaroxaban

No recommendation for or against anticoagulation in end-stage CKD or dialysis

- DOACs have not been approved for use in CrCl < 15mL/min or dialysis in the UK

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## 2020 Canadian Guidelines<sup>3</sup>

### Recommendations

For AF patients with stage 1 to 4 CKD, DOAC is preferred over warfarin

Anticoagulation is not recommended in stage 5 CKD (eGFR < 15mL/min) or dialysis

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## Comparison of Guideline Recommendations

	2019 AHA/ACC/HRS Guideline	2020 European Guideline	2020 Canadian Guideline
Moderate-to-severe CKD SCr ≥ 1.5 mg/dL CrCl > 15 mL/min	DOACs preferred over warfarin		
End-stage CKD or dialysis	Warfarin or apixaban	No recommendation	Anticoagulation not recommended

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## Renal Dosing of DOACs

CrCl	FDA-Approved Dosages			
	Apixaban	Edoxaban	Rivaroxaban	Dabigatran
>95 mL/min	5mg twice daily	Not FDA-approved	20mg once daily	150mg twice daily
50-95 mL/min	Reduce to 2.5mg twice daily if 2 of the following: - Age ≥ 80 years - SCr ≥ 1.5 mg/dL - Weight ≤ 60 kg	60mg once daily	15mg once daily	75mg twice daily
30-50 mL/min		30 mg once daily		
15-30 mL/min				
<15 mL/min or dialysis		Not FDA-approved	Not FDA-approved	Not FDA-approved

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### Pharmacokinetic Profile of DOACs<sup>4</sup>

Drug	Metabolism and Clearance	Dialyzable?
Apixaban	27% renal clearance	Partial
Edoxaban	50% renal clearance	No
Rivaroxaban	66% renal clearance (36% as unchanged drug)	No
Dabigatran	80% renal clearance, metabolized by esterases for activation	Yes

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### Safety and Efficacy of Apixaban in CKD<sup>5</sup>

- Outcomes Associated With Apixaban Use in Patients With End-Stage Kidney Disease and Atrial Fibrillation in the United States
  - Meta-analysis of 25,523 patients with AF and ESRD on dialysis
- Apixaban 2.5mg twice daily or 5mg twice daily compared to warfarin
- No difference in risk of stroke/systemic embolism
- Apixaban was associated with significantly lower risks of major bleeding
- Apixaban 5mg twice daily was associated with lower risks of stroke/systemic embolism and death compared to either apixaban 2.5mg twice daily and warfarin
- Limitation: observational studies

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### Safety and Efficacy of Rivaroxaban in CKD<sup>7</sup>

- Rivaroxaban versus warfarin in patients with nonvalvular atrial fibrillation and stage IV-V chronic kidney disease
  - Retrospective cohort study of 2317 patients
- Rivaroxaban compared to warfarin in patients with AF and CKD (CrCl <30 mL/min) with or without dialysis
- The risk of ischemic stroke/systemic embolism and major bleeding in rivaroxaban patients was similar to the risk observed in warfarin patients
- Limitations
  - Observational study, small sample size, underpowered to compare rivaroxaban and warfarin in patients with stage V CKD

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**Safety and Efficacy of Edoxaban in CKD<sup>6</sup>**

- Safety of Edoxaban 30 mg in Elderly Patients with Severe Renal Impairment
  - Retrospective cohort study of 46 patients with AF and CKD (CrCl 15-29 mL/min)
- Edoxaban 30mg daily
- No major bleeding events, strokes, systemic embolisms, or cardiovascular deaths reported
- Limitations
  - Observational study, small sample size, no comparator, excluded patients with CrCl <15 mL/min

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**Safety and Efficacy of Dabigatran in CKD<sup>8</sup>**

- Pharmacokinetics and Pharmacodynamics of Dabigatran 75 mg B.I.D. in Patients With Severe Chronic Kidney Disease
  - Open label, pharmacokinetic study of 16 patients with CrCl 15-30 mL/min
- Dabigatran resulted in mean steady-state drug exposure in patients with severe CKD comparable to predicted exposure, confirming outcomes of PK models
- Dabigatran 75mg twice daily did not result in drug accumulation after 5 days of treatment
- Limitations
  - Not randomized, not designed to study efficacy and safety, no comparator
- Dabigatran 75mg twice daily has not been studied in clinical trials and use not recommended

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**Summary and Key Take Away Points**

- DOACs may be a safer and more effective alternative to warfarin in patients with AF and CKD
- Most evidence with apixaban use in AF and CKD
  - Apixaban is FDA-approved and guideline recommended for use in CKD/ESRD
  - Dose reduction is based on meeting criteria
- Rivaroxaban, edoxaban, and dabigatran have renal dosing recommendations
  - Less evidence and lower quality of evidence
- Anticoagulation management should be patient-specific

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Landmark trials (RE-LY, ROCKET-AF, and ENGAGE-AF TIMI 48) excluded patients with:

- A. CrCl <60 mL/min
- B. CrCl <50 mL/min
- C. CrCl <30 mL/min**
- D. CrCl <15 mL/min

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According to the 2019 AHA/ACC/HRS guideline for atrial fibrillation (AF) management, which of the following options could be considered in a patient with AF, a CHA<sub>2</sub>DS<sub>2</sub>-VASc score of 3, without mechanical heart valve, and has chronic kidney disease (CrCl 40 mL/min) without dialysis?

- A. Warfarin (INR 2.0 to 3.0)
- B. Rivaroxaban
- C. No anticoagulation
- D. A and B**

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