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 **G3bA_2** chronic kidney disease due to hypertension and diabetic kidney disease recently diagnosed with paroxysmal AF is seen in clinic for follow up
- **CHA_2DS_2-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"

Clinical Case

- *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*?

Outline

- 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
Defined

- **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
CKD-EPI formula

- *Estimated GFR* (eGFR) – ***Chronic Kidney Disease Epidemiology Collaboration equation*** *(CKD-EPI)*
- Developed in order to create a formula ***more accurate*** than MDRD when actual ***GFR >60ml/min/1.73m^2***
- Like MDRD estimates GFR based on:
  - **Age**
  - **Gender**
  - **Ethnicity**
  - **Creatinine**
- *Better accuracy* than MDRD when *GFR >60ml/min/1.73m^2*
- May eventually replace MDRD

Stages of Chronic Kidney Disease with Albuminuria

Composite ranking for relative risks by GFR and albuminuria (KDIGO 2009)				Albuminuria stages, description, and range (mg/g)				
				A1		A2	A3	
				Optimal and high-normal		High	Very high and nephrotic	
				< 10	10-29	30-299	300-1999	≥ 2000
GFR stages, description, and range (mL/min per 1.73 m^2)	G1	High and optimal	> 105					
			90-104					
	G2	Mild	75-89					
			60-74					
	G3a	Mild-moderate	45-59					
	G3b	Moderate-severe	30-44					
	G4	Severe	15-29					
	G5	Kidney failure	< 15					

Medscape

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_2DS_2-VASc score ≥ 2

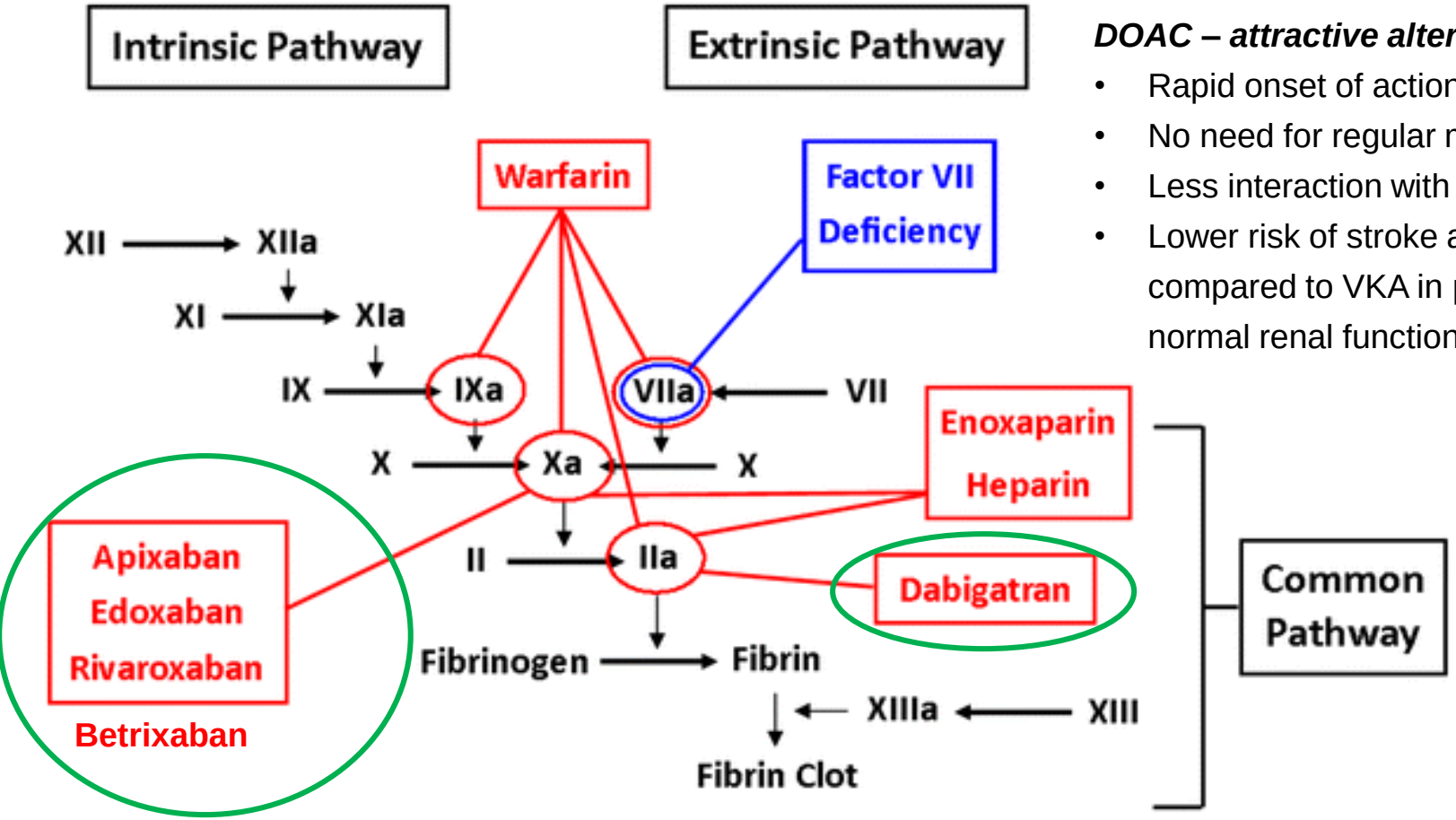
CHA_2DS_2-VASc

	Condition	Points
C	Congestive heart failure (or Left ventricular systolic dysfunction)	1
H	Hypertension: blood pressure consistently above 140/90 mmHg (or treated hypertension on medication)	1
A_2	Age ≥75 years	2
D	Diabetes Mellitus	1
S_2	Prior Stroke or TIA or thromboembolism	2
V	Vascular disease (e.g. peripheral artery disease, myocardial infarction, aortic plaque)	1
A	Age 65–74 years	1
Sc	Sex category (i.e. female sex)	1

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

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

Pharmacokinetics of DOACs

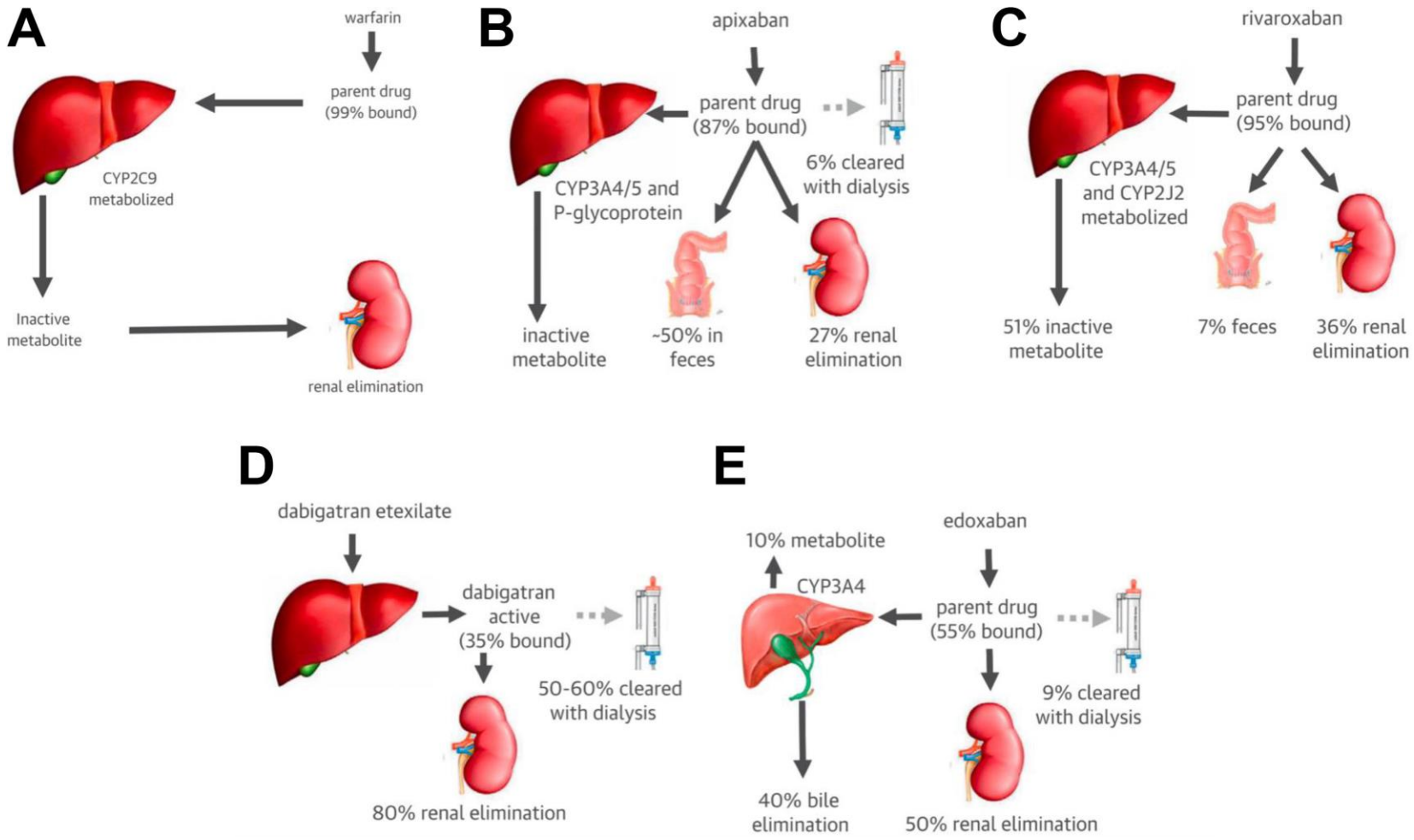


Figure 2. Pharmacokinetics of (A) warfarin, (B) apixaban, (C) rivaroxaban, (D) dabigatran, and (E) edoxaban. from the study by Chan et al41 with permission.

DOI: (10.1177/1074248419858116)

DOACs in CKD Patients:
Recommendations by Regulatory Agencies

Table 1. Recommendation of major regulatory agencies

	Dabigatran	Apixaban	Rivaroxaban	Edoxaban
EMA 2014	150 mg twice daily for CKD stage G3 (CrCl 30 to 50 mL/min) No recommendation for CKD stage G4	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)
FDA 2014	150 mg twice daily for CKD stage G3 (CrCl > 30 mL/min) 75 mg twice daily for CKD stage G4 (CrCl 15 to 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)
Health Canada 2017	110 or 150 mg twice daily for CKD stage G3 (CrCl 30 to 50 mL/min) No recommendation for CKD stage G4	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) No recommendation for CKD stage G4	30 mg once daily for CKD stage G3 (CrCl 30 to 50 mL/min)

Kimachi M et al. Direct oral anticoagulants versus warfarin for preventing stroke and systemic embolic events among atrial fibrillation patients with chronic kidney disease. Cochrane Database of Systematic Reviews 2017, 11. Art. No.: CD011373.

DOACs in CKD Patients:
Where Is the Evidence?

Cochrane Library
Trusted evidence.
Informed decisions.
Better health.

Cochrane Database of Systematic Reviews

[Intervention Review]

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

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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:

Patient or population: atrial fibrillation patients with CKD

Setting: Hospital-based setting

Intervention: DOAC

Comparison: Dose-adjusted warfarin

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

***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

ARISTOTLE Study 2010

ENGAGE AF-TIMI Study 2013

J-ROCKET AF Study 2012

RELY Study 2009

ROCKET AF Study 2010

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

DOACs in CKD Patients:
Future Research Needed

- 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

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REVIEWS | 6 AUGUST 2019

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

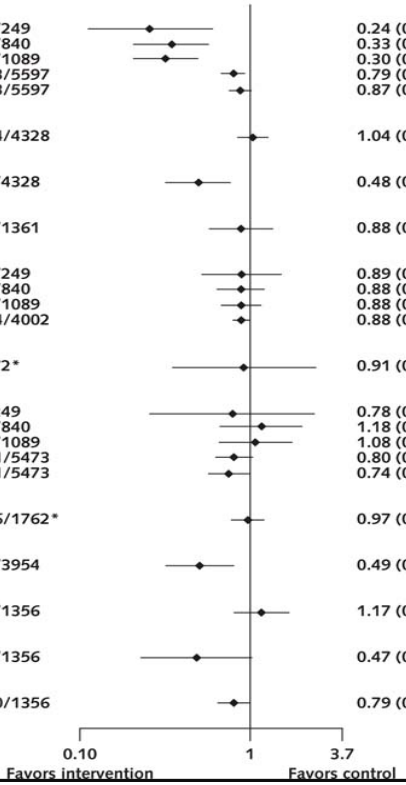
Jeffrey T. Ha, MBBS; Brendon L. Neuen, MBBS(Hons); Lap P. Cheng, MBBS; Min Jun, PhD; Tadashi Toyama, PhD; Martin P. Gallagher, PhD; Meg J. Jardine, PhD; Manish M. Sood, MD; Amit X. Garg, PhD; Suetonia C. Palmer, PhD; Patrick B. Mark, PhD; David C. Wheeler, MD; Vivekanand Jha, MD; Ben Freedman, PhD; David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

Ann Intern Med. 2019;171(3):181-189. doi:10.7326/M19-0087

DOACs in CKD Patients: *More Evidence*

Comparison, by Outcome	Trials, *n*	Events/Participants, *n/N* Intervention	Control	RR (95%CI)	I^2, %	GRADE Certainty of Evidence
Stroke or systemic embolism						
VKA vs. ASA	1	6/267	23/249	0.24 (0.10–0.59)	NA	Very low
NOAC vs. ASA	1	17/857	51/840	0.33 (0.19–0.56)	NA	Very low
Any OAC vs. ASA	2	23/1124	74/1089	0.30 (0.19–0.48)	0	Moderate
High-dose NOAC vs. VKA	5	227/5735	283/5597	0.79 (0.66–0.93)	0	High
High- and low-dose NOAC vs. VKA	5	389/8265	283/5597	0.87 (0.74–1.02)	8	High
Nonhemorrhagic stroke						
High-dose NOAC vs. VKA	3	151/4362	144/4328	1.04 (0.83–1.30)	0	Moderate
Hemorrhagic stroke						
High-dose NOAC vs. VKA	3	27/4362	57/4328	0.48 (0.30–0.76)	0	Moderate
Myocardial infarction						
High-dose NOAC vs. VKA	1	34/1379	38/1361	0.88 (0.56–1.39)	NA	Very low
All-cause death						
VKA vs. ASA	1	21/267	22/249	0.89 (0.50–1.58)	NA	Very low
NOAC vs. ASA	1	59/857	66/840	0.88 (0.62–1.23)	NA	Very low
Any OAC vs. ASA	2	80/1124	88/1089	0.88 (0.66–1.18)	0	Low
High-dose NOAC vs. VKA	3	598/4113	664/4002	0.88 (0.78–0.99)	22	Moderate
Death or ischemic event after PCI/ACS						
High-dose NOAC vs. VKA	2	13/73*	8/72*	0.91 (0.33–2.56)	75	Very low
Major bleeding						
VKA vs. ASA	1	5/267	6/249	0.78 (0.24–2.51)	NA	Very low
NOAC vs. ASA	1	24/857	20/840	1.18 (0.65–2.11)	NA	Very low
Any OAC vs. ASA	2	29/1124	26/1089	1.08 (0.64–1.83)	0	Low
High-dose NOAC vs. VKA	5	402/5600	491/5473	0.80 (0.61–1.04)	75	Low
High- and low-dose NOAC vs. VKA	5	574/8121	491/5473	0.74 (0.55–1.00)	83	Low
Major or nonmajor clinically relevant bleeding						
High-dose NOAC vs. VKA	5	401/1792*	396/1762*	0.97 (0.76–1.23)	28	Low
Intracranial hemorrhage						
High-dose NOAC vs. VKA	3	41/4102	81/3954	0.49 (0.30–0.80)	36	Moderate
Gastrointestinal bleeding						
High-dose NOAC vs. VKA	1	51/1372	43/1356	1.17 (0.79–1.75)	NA	Very low
Fatal bleeding						
High-dose NOAC vs. VKA	1	9/1372	19/1356	0.47 (0.21–1.03)	NA	Very low
Minor bleeding						
High-dose NOAC vs. VKA	1	120/1372	150/1356	0.79 (0.63–0.99)	NA	Very low



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Treatment effects in trials involving participants with atrial fibrillation on stroke or systemic embolism, nonhemorrhagic stroke, hemorrhagic stroke, myocardial infarction, all-cause death, and bleeding outcomes

- 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

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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

DOACs in CKD Patients:
Take Home Points for Clinical Practice

- ***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

Clinical Case

- 65 yo man with stage **G3bA_2** chronic kidney disease due to hypertension and diabetic kidney disease recently diagnosed with paroxysmal AF is seen in clinic for follow up
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Questions?