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Slides for Presentation

ANTI-THROMBOTIC THERAPY FOR NON-VALVULAR ATRIAL FIBRILLATION IN PATIENTS WITH CHRONIC KIDNEY DISEASE: CURRENT VIEWS

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Use of anti-coagulants to decrease thrombo-embolic risk in most patients with atrial fibrillation



Stages of Chronic Kidney Disease

Stage	Description	GFR (mL/min/1.73m ²)
1	Kidney damage with normal or ↑ GFR	≥ 90
2	Kidney damage with mild ↓ GFR	60 - 89
3	Moderate ↓ GFR	30-59
4	Severe ↓ GFR	15-29
5	Kidney failure	< 15 (or dialysis)

Chronic kidney disease is defined as either kidney damage or GFR of < 60mL/min/1.73m² for ≥ 3 months. Kidney damage is defined as pathologic abnormalities or markers of damage, including abnormalities in the blood or urine tests or imaging studies.

NKF, KDOQI Clinical Practice Guidelines for Chronic Kidney Disease: Evaluation, Classification, and Stratification. *Am J Kidney Dis.* 2002;39(Suppl 1):S1-S266. www.lipid.org

FREQUENCY OF CKD IN PATIENTS WITH ATRIAL FIBRILLATION

Frequency of CKD in Atrial Fibrillation Patients

Category	Percentage
Stage III	34%
eGFR < 60ml/m	67%
Stage IV	2%
Stage V	1%

Hart et al, *Can J Cardiol* 29:S71, 2013

FACTORS CONTRIBUTING TO THROMBO-EMBOLIC RISK IN CKD/ESRD

- Acute changes in intravascular volume in hemodialysis patients which predisposes to hyperviscosity
- Increased atherosclerosis and endothelial damage
- RAAS activation
- Prothrombotic state due to alterations in protein C metabolism, glycoprotein Ib expression, increased PAI-1:t-PA ratio, and plasmin inhibition by Lp(a)

FACTORS CONTRIBUTING TO INCREASED BLEEDING RISK IN CKD/ESRD

- CKD is associated with increased bleeding risk, particularly from the GI tract.
- Contributing factors:
 - Impaired platelet function from uremic toxins
 - Abnormal platelet arachidonic acid metabolism
 - Altered vWF
 - Reduced intracellular ADP and serotonin
 - Defective COX activity
 - Increased formation of vascular prostaglandin I2
 - Increased requirement of invasive procedures

WARFARIN

WARFARIN AND STROKE OR BLEEDING RISK IN CKD PATIENTS WITH NON-VALVULAR ATRIAL FIBRILLATION

- Chan et al reported that warfarin ± antiplatelet drug use was associated with higher ischemic and hemorrhagic stroke risk in hemodialysis patients with pre-existing atrial fibrillation compared to those not receiving warfarin or an antiplatelet drug; related to INR increase and lack of INR monitoring; no effect on mortality (2009).
- Winkelmayr et al reported increased hemorrhagic stroke risk, but no significant difference in ischemic stroke risk in hemodialysis patients with new onset atrial fibrillation treated with warfarin compared to those not treated with warfarin (2011).

WARFARIN AND STROKE OR BLEEDING RISK IN CKD PATIENTS WITH NON-VALVULAR ATRIAL FIBRILLATION

- Wizemann et al reported significantly greater stroke risk in hemodialysis patients > 75 years old with atrial fibrillation treated with warfarin than in those not treated with warfarin (2010).
- Lai et al reported decreased ischemic stroke rate in stages 3-5 CKD patients with atrial fibrillation treated with warfarin compared to those not treated with warfarin (9% vs. 26%, p<0.001); no significant difference in bleeding rates (2009).
- Knoll et al reported no stroke or fatal bleeding events in dialysis patients with atrial fibrillation on sufficient warfarin anticoagulation compared to 12 strokes (10 ischemic and 2 hemorrhagic) in those not treated with warfarin (2012).

WARFARIN AND STROKE OR BLEEDING RISK IN HEMODIALYSIS PATIENTS WITH NON-VALVULAR ATRIAL FIBRILLATION

- Shen et al retrospectively studied 12,284 HD patients with newly-diagnosed atrial fibrillation; warfarin initiated within 30 days in 1836 patients; in 70%, warfarin was discontinued within 1 year. In warfarin users ischemic stroke risk was reduced at 1 year (HR: 0.68; 95% CI: 0.47-0.99) and mortality risk was also reduced (HR: 0.84; 95% CI: 0.73-0.97) (2015).
- Wakasugi et al prospectively studied 60 Japanese HD patients with permanent atrial fibrillation (propensity analysis). During 110 person-years of follow-up, 13 ischemic strokes occurred. After adjusting for CHADS₂ score, warfarin use was not associated with a significant reduction in ischemic stroke risk (HR: 3.36; 95% CI: 0.67-16.66) compared to non-use of warfarin. Warfarin was not associated with increased bleeding or mortality risk (2014).

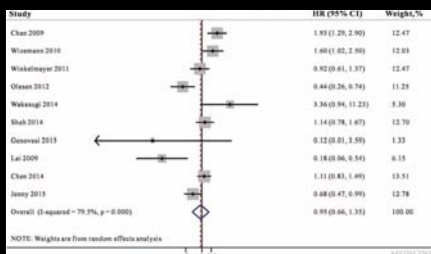
WARFARIN AND STROKE OR BLEEDING RISK IN DIALYSIS PATIENTS WITH NON-VALVULAR ATRIAL FIBRILLATION

- Shah et al studied 1626 HD and PD patients with non-valvular atrial fibrillation followed for 9 years. There was no significant difference in the risk of ischemic stroke between warfarin users and non-users (HR: 1.14; 95% CI: 0.78-1.67) (2014).

WARFARIN AND STROKE OR BLEEDING RISK IN PATIENTS WITH NON-VALVULAR ATRIAL FIBRILLATION AND CKD

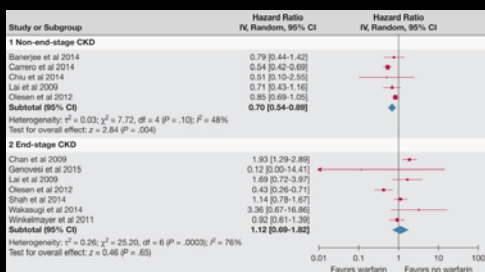
- Olesen et al reported a non-significant decrease in ischemic stroke/systemic embolism risk and a significant increase in bleeding risk in non-end stage CKD patients with atrial fibrillation treated with warfarin compared to those not treated with warfarin. In ESRD patients, warfarin therapy significantly decreased ischemic stroke/systemic embolism risk, but significantly increased bleeding risk compared to those not treated with warfarin (2012).
- Hart et al reported that adjusted dose warfarin significantly reduced stroke/embolism risk compared to fixed low-dose warfarin + ASA in patients with non-valvular atrial fibrillation and stage 3 CKD (2011).

META-ANALYSIS OF ISCHEMIC STROKE RISK IN WARFARIN USERS AND NON-USERS IN DIALYSIS PATIENTS WITH ATRIAL FIBRILLATION



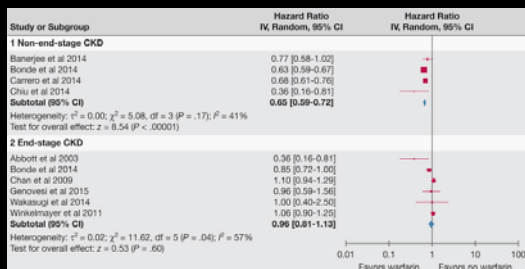
Liu et al, Medicine 94:e2333, 2015

META-ANALYSIS OF STUDIES OF ISCHEMIC STROKE AND EMBOLISM IN WARFARIN USERS AND NON-USERS IN PATIENTS WITH NON-VALVULAR ATRIAL FIBRILLATION AND CKD



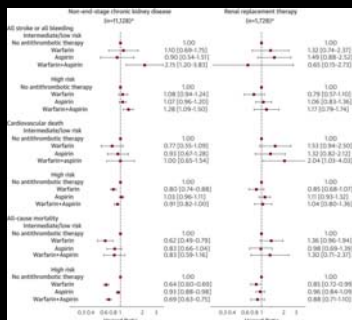
Dahal et al, Chest 149:951-959, 2016

META-ANALYSIS OF STUDIES OF MORTALITY IN WARFARIN USERS AND NON-USERS IN PATIENTS WITH NON-VALVULAR ATRIAL FIBRILLATION AND CKD



Dahal et al, Chest 149:951-959, 2016

CV OUTCOMES AND ALL-CAUSE MORTALITY IN PATIENTS WITH ATRIAL FIBRILLATION AND CKD: EFFECT OF ANTI-THROMBOTIC THERAPY



Bonde et al, JACC 24:2471, 2014

NOVEL ORAL ANTICOAGULANTS (NOACs)

ARISTOTLE: APIXABAN VS. WARFARIN EFFICACY AND SAFETY IN THE ELDERLY (≥75 YEARS ACCORDING TO eGFR)

Primary Outcomes In The Elderly (≥75 years) In Relation To Renal Function (Cockcroft–Gault eGFR, mL/min)					
	No. of patients ≥75 years	Number of events (N/year)		Hazard ratio (95% CI)	Interaction P-value
		Apixaban	Warfarin		
Stroke/systemic embolism					0.4954
>80	597	8 (1.41)	11 (2.16)	0.65 (0.26, 1.62)	
>50–80	2922	39 (1.45)	45 (1.70)	0.86 (0.56, 1.32)	
>30–50	1906	28 (1.74)	44 (2.69)	0.65 (0.40, 1.04)	
≤30	222	3 (1.70)	9 (5.57)	0.29 (0.08, 1.07)	
Major bleeding					0.1635
>80	596	11 (2.10)	15 (3.39)	0.60 (0.28, 1.32)	
>50–80	2912	85 (3.33)	104 (4.45)	0.79 (0.60, 1.06)	
>30–50	1898	47 (3.32)	87 (6.27)	0.53 (0.37, 0.76)	
≤30	221	7 (4.64)	17 (13.4)	0.35 (0.14, 0.86)	

Halvorsen S et al, Eur Heart J 2014;eurheartj.046

NOAC DOSING IN PATIENTS WITH CKD

Agent	Standard AF Dose (Prescribing info)	Renal Dosing	Trial and Other Experience
Dabigatran	150mg Twice Daily (CrCl > 30ml/min)	75mg Twice Daily (CrCl 15-30ml/min)	<ul style="list-style-type: none"> RE-LY trial: 150mg or 110mg BID if CrCl > 30ml/min No trial experience in pts w/ CrCl < 30ml/min 75mg dose not studied in RCTs European dosage: <ul style="list-style-type: none"> 150mg BID if CrCl > 50ml/min 110mg BID if CrCl 30-50ml/min Contraindicated if CrCl < 30ml/min
Rivaroxaban	20mg Once Daily (CrCl > 50ml/min)	15mg Once Daily (CrCl 15-50ml/min)	<ul style="list-style-type: none"> ROCKET-AF trial: <ul style="list-style-type: none"> 20mg Daily if CrCl > 50ml/min 15mg Daily if CrCl 30-50ml/min No trial experience in pts w/ CrCl < 30ml/min
Apixaban	5mg Twice Daily	2.5mg Twice daily if at least 2 of the following: ≥ 80 y/o, Weight ≤ 60kg, SCr ≥ 1.5ml/dl Dosing guidance for ESRD (with or without hemodialysis)	<ul style="list-style-type: none"> ARISTOTLE trial: Renal dose studied as per prescribing information. No trial experience in pts w/ CrCl < 25ml/min No trial experience with ESRD patients
Edoxaban	60mg Once Daily (CrCl 50-95ml/min) BLACK BOX WARNING: Avoid use if CrCl > 95ml/min	30mg Once Daily (CrCl 15-50ml/min)	<ul style="list-style-type: none"> TIMI-ENGAGE: Randomized to 60mg or 30mg Daily <ul style="list-style-type: none"> Dose halved if <ul style="list-style-type: none"> CrCl 30-50ml/min, Weight ≤ 60kg, or Concomitant verapamil, quinidine, or dronedarone (strong P-gp inhibitors) No trial experience in pts w/ CrCl < 30ml/min Worse outcomes in patients with CrCl > 95ml/min

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Bottom Line:
None have been evaluated in randomized trials for CrCl < 25-30 or dialysis

CHADS₂ -> CHA₂DS₂VASc

CHADS ₂ Risk	Score	CHA ₂ DS ₂ -VASc Risk	Score
CHF	1	CHF or LVEF ≤ 40%	1
Hypertension	1	Hypertension	1
Age > 75	1	Age ≥ 75	2
Diabetes	1	Diabetes	1
Stroke or TIA	2	Stroke/TIA/Thromboembolism	2
		Vascular Disease	1
		Age 65 - 74	1
		Female	1

From ESC AF Guidelines
<http://www.escardio.org/guidelines-surveys/esc-guidelines/Guidelines/Documents/guideline-af-FT.pdf>

RISK-BASED ANTI-THROMBOTIC THERAPY IN CKD PATIENTS WITH ATRIAL FIBRILLATION

ACC Recommendations

	COR	LOE
For patients with non-valvular AF and a CHA ₂ DS ₂ VASc score of 0, it is reasonable to omit anti-thrombotic therapy.	IIa	B
For patients with non-valvular AF with a CHA ₂ DS ₂ VASc score of 2 or greater and who have end-stage CKD (CrCl <15 mL/min) or are on hemodialysis (stage 5), it is reasonable to prescribe warfarin (INR 2.0 to 3.0) for oral anticoagulation.	IIa	B
For patients with non-valvular AF and a CHA ₂ DS ₂ VASc score of 1, no anti-thrombotic therapy or treatment with an oral anticoagulant or aspirin may be considered.	IIb	C
For patients with non-valvular AF and severe CKD (stage 4) with CHA ₂ DS ₂ VASc scores of 2 or greater, treatment with reduced doses of direct thrombin or factor Xa inhibitors may be considered (e.g., dabigatran, rivaroxaban, or apixaban), but safety and efficacy have not been established.	IIb	C

CKD STAGE-BASED RECOMMENDATIONS

Stage 3:

CHADS₂ 0: Anticoagulation or ASA preferred; no anti-thrombotic therapy reasonable (personal choice)

CHADS₂ ≥1: Anticoagulation preferred over no anticoagulation; direct thrombin or factor Xa inhibitor

Stage 4:

CHADS₂ 0: Opinion divided between anticoagulation with warfarin and no anticoagulation

CHADS₂ ≥1: Anticoagulation recommended; warfarin favored over NOACS

CKD STAGED-BASED RECOMMENDATIONS

Stage 5 (non-dialysis):

CHADS₂ 0: Rare; recommendations same as for Stage 4

CHADS₂ ≥1: Recommendations same as for Stage 4

Stage 5 (dialysis):

CHADS₂ 0: Rare; no anticoagulation recommended

CHADS₂ ≥1: Opinion divided; no anticoagulation recommended in most; warfarin in high-risk patients (atrial thrombus, stroke or TIA); AHA/ACC/HRS: weak recommendation for warfarin anti-coagulation
