Solving the puzzle of an AF patient With renal impairment

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Patient profile

Patient: G.H.A.

Personal Information	
Sex	Male
Age	80
Weight	71 kg
Blood Pressure	145/90 mmHg
Heart Rate	120 bpm, irregular
Renal function	CrCl 42 ml/min

Patient History	
Medical History	• Arterial hypertension. • Diabetes Mellitus.
Medications	• Amlodipine. • Sitagliptin.

Presentation
• Recurrent palpitations.

ECG: electrocardiogram; AF: atrial fibrillation

What is the CHA_2DS_2-VASc score of this patient?

Male patient	Renal function is impaired
Weight: 71 kg	Newly diagnosed NVAF
Blood pressure: 145/90 mmHg	Diabetes mellitus
	80 years of age

A) CHA_2DS_2-VASc = 1

B) CHA_2DS_2-VASc = 2

C) CHA_2DS_2-VASc = 3

D) CHA_2DS_2-VASc = 4

E) CHA_2DS_2-VASc = 5

The CHA_2DS_2-VASc score of this patient

CHA_2DS_2-VASc[1]

	Risk Factors[2]	Points
C	Congestive heart failure/LV dysfunction	1
H	**Hypertension**	**1**
A_2	Age ≥75 years	2
D	Diabetes mellitus	1
S_2	Stroke/TIA/thromboembolism	2
V	Vascular disease[a]	1
A	**Age 65 to 74 years**	**1**
Sc	**Sex category (female)**	**1**
	Maximum score	**9**

LV: left ventricular; TIA: transient ischemic attack; INR: international normalized ratio
[a] Vascular disease includes myocardial infarction, complex aortic plaque, and peripheral artery disease

1. Camm et al. Europace. 2012;14:1385–1413.
2. Lip et al. CHEST. 2010;137:263–272.

Answer

What is the CHA2DS2-VASc score of this patient?

Male patient	Renal function is impaired
Weight: 71 kg	Newly diagnosed NVAF
Blood pressure: 145/90 mmHg	Diabetes mellitus
	80 years of age

1. CHA_2DS_2-VASc = 1
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3. CHA_2DS_2-VASc = 3
4. CHA_2DS_2-VASc = 4
5. CHA_2DS_2-VASc = 5

GERD: gastroesophageal reflux disease; NVAF: non-valvular atrial fibrillation

After rate control, what would be your strategy for stroke prevention in this elderly patient with renal impairment?

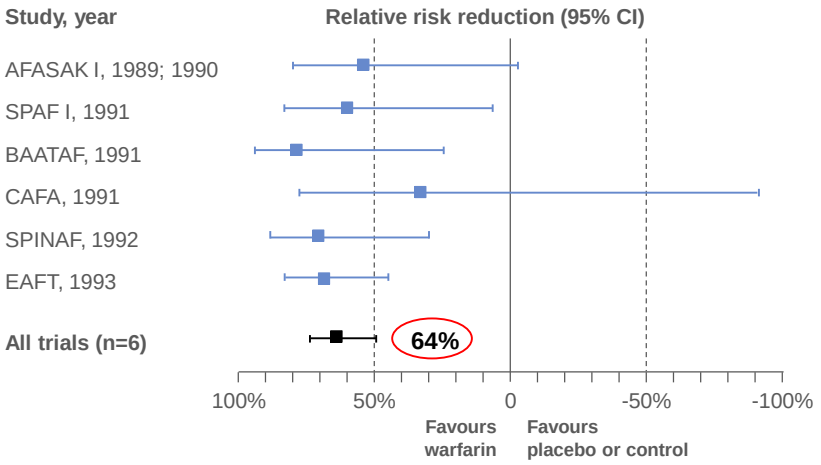
A) Aspirin only as this patient is at high risk for bleeding.

B) Warfarin.

C) A NOAC.

D) Aspirin and an oral anticoagulant as the patient is high risk for thromboembolism.

VKA vs. Placebo/No treatment is Effective at Preventing Stroke in AF Patients

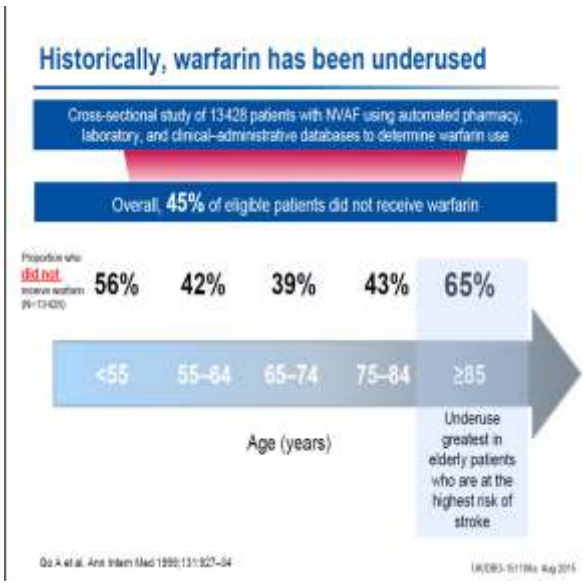


Hart RG et al. Ann Intern Med. 2007;146(12):857-867

Recommendations	Class[a]	Level[b]	Ref[c]
Oral anticoagulation therapy to prevent thromboembolism is recommended for all male AF patients with a CHA_2DS_2-VASc score of 2 or more.	I	A	38, 318–321, 354, 404
Oral anticoagulation therapy to prevent thromboembolism is recommended in all female AF patients with a CHA_2DS_2-VASc score of 3 or more.	I	A	38, 318–321, 354, 404
Oral anticoagulation therapy to prevent thromboembolism should be considered in male AF patients with a CHA_2DS_2-VASc score of 1, considering individual characteristics and patient preferences.	IIa	B	371, 375–377
Oral anticoagulation therapy to prevent thromboembolism should be considered in female AF patients with a CHA_2DS_2-VASc score of 2, considering individual characteristics and patient preferences.	IIa	B	371, 376, 377
Vitamin K antagonist therapy (INR 2.0–3.0 or higher) is recommended for stroke prevention in AF patients with moderate-to-severe mitral stenosis or mechanical heart valves.	I	B	274, 435–440
When oral anticoagulation is initiated in a patient with AF who is eligible for a NOAC (apixaban, dabigatran, edoxaban, or rivaroxaban), a NOAC is recommended in preference to a Vitamin K antagonist.	I	A	39, 318–321, 404
When patients are treated with a vitamin K antagonist, time in therapeutic range (TTR) should be kept as high as possible and closely monitored.	I	A	395, 432, 441–444
AF patients already on treatment with a vitamin K antagonist may be considered for NOAC treatment if TTR is not well controlled despite good adherence, or if patient preference without contra-indications to NOAC (e.g. prosthetic valve).	IIb	A	39, 318, 319, 404, 408
Combinations of oral anticoagulants and platelet inhibitors increase bleeding risk and should be avoided in AF patients without another indication for platelet inhibition.	III (Harm)	B	429, 445
In male or female AF patients without additional stroke risk factors, anticoagulant or antiplatelet therapy is not recommended for stroke prevention.	III (Harm)	B	368, 371, 376, 377
Antiplatelet monotherapy is not recommended for stroke prevention in AF patients, regardless of stroke risk.	III (Harm)	A	38, 429, 430
NOACs (apixaban, dabigatran, edoxaban, and rivaroxaban) are not recommended in patients with mechanical heart valves (Level of evidence B) or moderate-to-severe mitral stenosis (Level of evidence C).	III (Harm)	B C	318–321, 400, 404

ESC guidelines 2016

The old are being denied anticoagulation

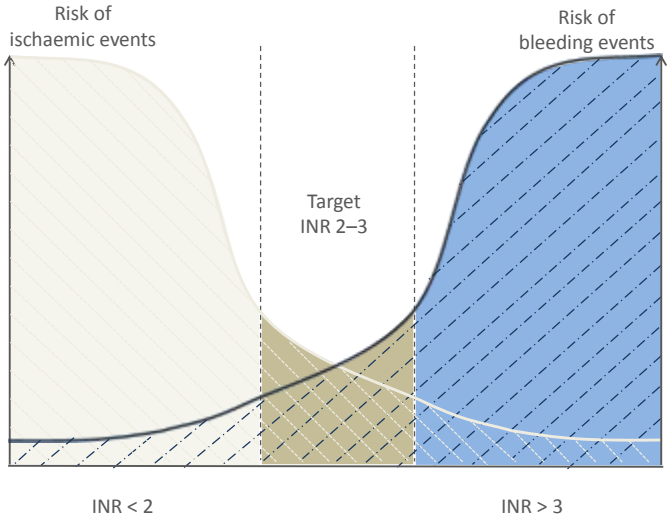


There Are Many Limitations of VKA Therapy

- **Significant inter- and intra-patient variability in dose–response**,[1] due to:
  - Co-morbid conditions
  - Genetic polymorphisms
  - Numerous interactions with food and concomitant drugs
  - Unpredictable pharmacology
- **Narrow therapeutic window**[1]
  - Regular coagulation monitoring and dose adjustments required
  - Failure to stay within the therapeutic range increases the risk of stroke or adverse bleeding events[2]
- **Underuse**[2–4]
  - Fear of haemorrhage; intracranial haemorrhage is the most devastating bleeding event[5]
  - Particularly in elderly patients because of high perceived risk of bleeding versus possible benefits[5]

1. Ansell J et al. Chest 2008;133(6 Suppl):160S-198S; 2. Nieuwlaat R et al. Am Heart J. 2007;153(6):1006-1012;
3. Ogilvie IM et al. Am J Med. 2010;123(7):638-645; 4. Nieuwlaat R et al. Eur Heart J. 2005;26(22):2422-2434;
5. Waldo A et al. J Am Coll Cardiol 2005;46(9):1729-1736

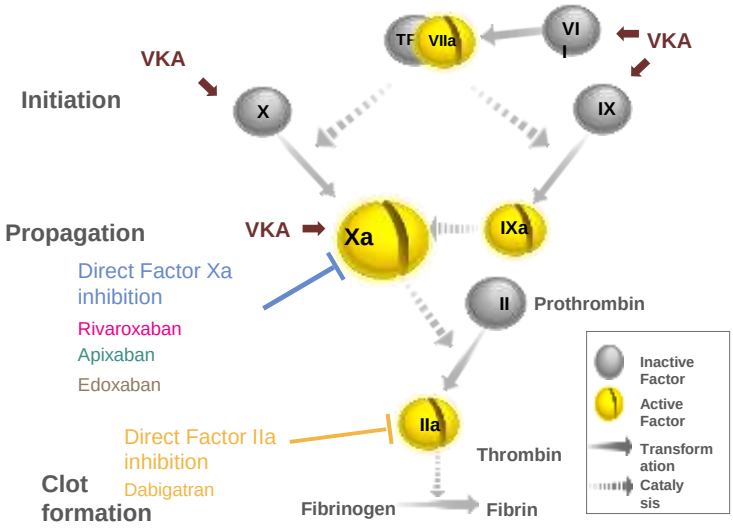
VKAs Have a Narrow Therapeutic Window



Ferreiro JL et al. Thromb Haemost. 2010;103(6):1128-1135

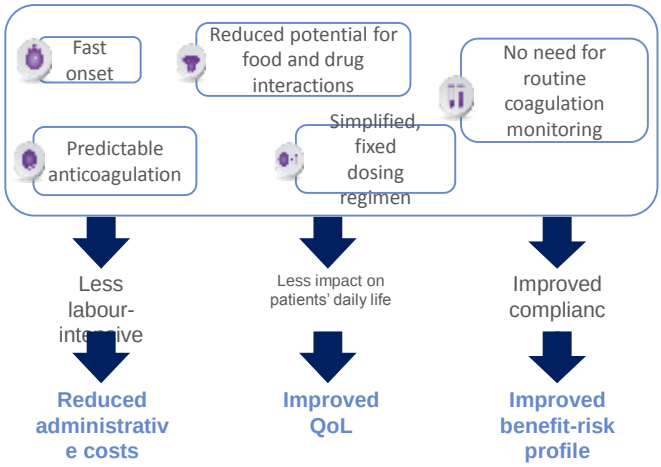
What about NOACs?

Targets for Anticoagulants[1,2]



1. Piccini JP et al. Curr Opin Cardiol. 2010;25(4):312-320; 2. Spyropoulos AC et al. Expert Opin Investig Drugs 2007;16(4):431-440

Important Benefits of NOACs Over VKAs[1–7]



1. Ansell J et al. Chest 2004;126(3):204S-233S; 2. Mueck W et al. Int J Clin Pharmacol Ther. 2007;45(6):335-344; 3. Mueck W et al. Clin Pharmacokinet. 2008;47(3):203-216; 4. Mueck W et al. Thromb Haemost. 2008;100(3):453-461; 5. Raghavan N et al. Drug Metab Dispos. 2009;37(1):74-81; 6. Shantsila E, Lip GY. Curr Opin Investig Drugs 2008;9(9):1020-1033; 7. Ageno W et al. Chest 2012;141(2):e44S-e88S

NOACs are the New Standard of Care for Stroke Prevention in Eligible Patients with AF*

Recommendations	Class	Level
When oral anticoagulation is initiated in a patient with AF who is eligible for a NOAC (apixaban, dabigatran, edoxaban, or rivaroxaban), a **NOAC is recommended in preference to a Vitamin K antagonist**.	I	A
AF patients already on treatment with a vitamin K antagonist may be considered for **NOAC treatment if TTR is not well controlled** despite good adherence, **or if patient preference** without contra-indications to NOAC (e.g. prosthetic valve).	IIb	A
Antiplatelet monotherapy is not recommended for stroke prevention in AF patients, regardless of stroke risk.	III (harm)	A

*Those without mechanical heart valves or moderate or severe mitral stenosis

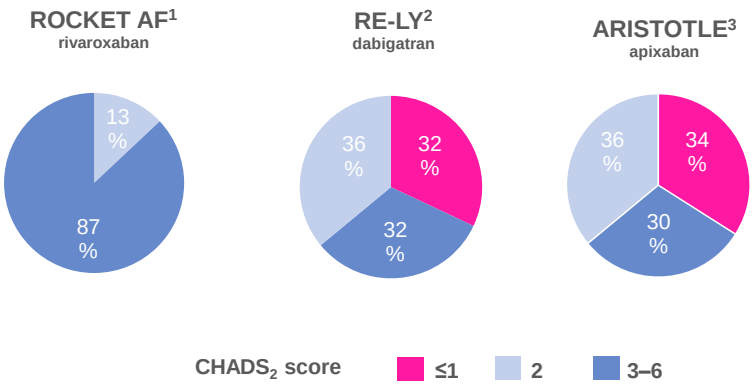
Kirchhof P *et al, Eur Heart J* 2016; doi:10.1093/eurheartj/ehw210

2019 AHA/ACC/HRS Focused Update of the 2014 AHA/ACC/HRS Guideline for the Management of Patients With Atrial Fibrillation

I	A	2. NOACs (dabigatran, rivaroxaban, apixaban, and edoxaban) are recommended over warfarin in NOAC-eligible patients with AF (except with moderate-to-severe mitral stenosis or a mechanical heart valve) (S4.1.1-8–S4.1.1-11). NEW: Exclusion criteria are now defined as moderate-to-severe mitral stenosis or a mechanical heart valve. When the NOAC trials are considered as a group, the direct thrombin inhibitor and factor Xa inhibitors were at least noninferior and, in some trials, superior to warfarin for preventing stroke and systemic embolism and were associated with lower risks of serious bleeding.

Are all NOACs the same when considering giving them to an elderly patient?

Different $CHADS_2$-Score patient distribution in phase III RCT



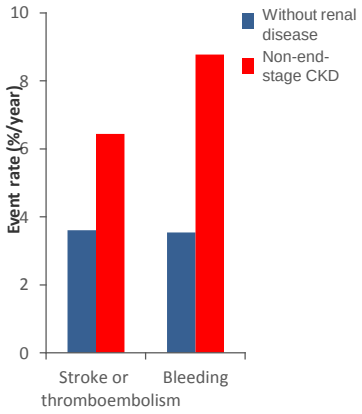
1. Patel MR et al. N Engl J Med. 2011;365(10):883-891; 2. Connolly SJ et al. N Engl J Med. 2009;361(12):1139-1151;
3. Granger CB et al. N Engl J Med. 2011;365(11):981-992; 4. Giugliano RP et al. N Engl J Med. 2013;369(22):2093-2104

Is the assessment of renal function in patients with atrial fibrillation important?

Background: AF Patients With Moderate Renal Impairment

- Every third patient with AF has chronic kidney disease (CKD)[1]
- Patients with AF and renal impairment are at higher risk for bleeding and stroke[2]
- Patient with AF and renal impairment were more often undertreated with warfarin than those with normal renal function[3]

Danish registry[2] (N=132,372)
(~28% of patients received warfarin)



1. Hart RG et al. Can J Cardiol. 2013;23:S71-S78; 2. Olesen JB et al. N Engl J Med. 2012;367(7):625-35;
3. Capodanno D et al. Circulation 2012;125(21):2649-2661

Recommendations for patients with kidney disease and atrial fibrillation

Recommendations	Class[a]	Level[b]	Ref[c]
The assessment of kidney function by serum creatinine or creatinine clearance is recommended in all AF patients to detect kidney disease and to support correct dosing of AF therapy.	I	A	316, 318–321
All AF patients treated with oral anticoagulation should be considered for at least yearly renal function evaluation to detect chronic kidney disease.	IIa	B	

ESC guidelines 2016

Given the renal function, what would be your strategy for stroke prevention in this elderly patient with renal impairment?

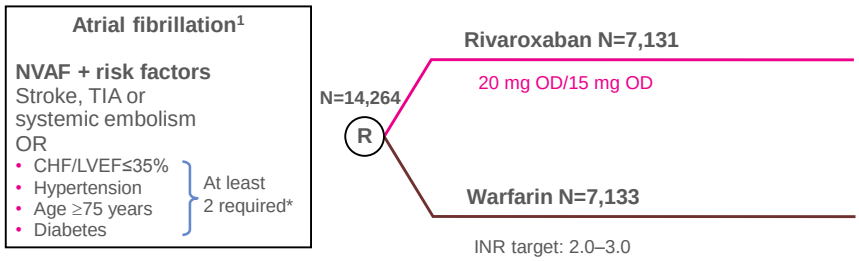
A) Dabigatran 110 mg BID.

B) Apixaban 2.5 mg BID.

C) Rivaroxaban 15 mg OD.

Is there any data that a specific NOAC has subanalysis data on AF patients with renal impairment?

ROCKET AF Prospectively Tested a Reduced Dose in AF Patients With Renal Impairment



- **AF patients with moderate renal impairment (CrCl 30-49 ml/min) received a reduced dose of rivaroxaban 15 mg OD (21%)[1,2]**
- **Primary efficacy endpoint: stroke or non-CNS systemic embolism**
- **Primary safety endpoint: major or NMCR bleeding**

*Enrolment of patients without prior stroke, TIA or systemic embolism and only two factors capped at 10%.
LVEF, left ventricular ejection fraction; NVAF, non-valvular atrial fibrillation

1. Patel MR et al. N Engl J Med. 2011;365(10):883-891; 2. Fox KA et al. Eur Heart J. 2011;32(19):2387-2394

Differences in patient characteristics between phase lll clinical trials

		ROCKET AF[1] (n=14,264)	ARISTOTLE[2] (n=18,201)	RE-LY[4,5] (n=18,113)
Mean $CHADS_2$-Score		3.5	2.1	2.1
C	**CHF***	62%	35%	32%
H	**Hypertension**	91%	87%	79%
A	**Age ≥75 years**	43%	31%	40%
D	**Diabetes mellitus**	40%	25%	23%
S_2	**Prior stroke or TIA#**	55%	19%	20%
Moderate renal impairment		**21%**	**15%**	**19%**
Specific dose studied prospectively		✓	✘	✘

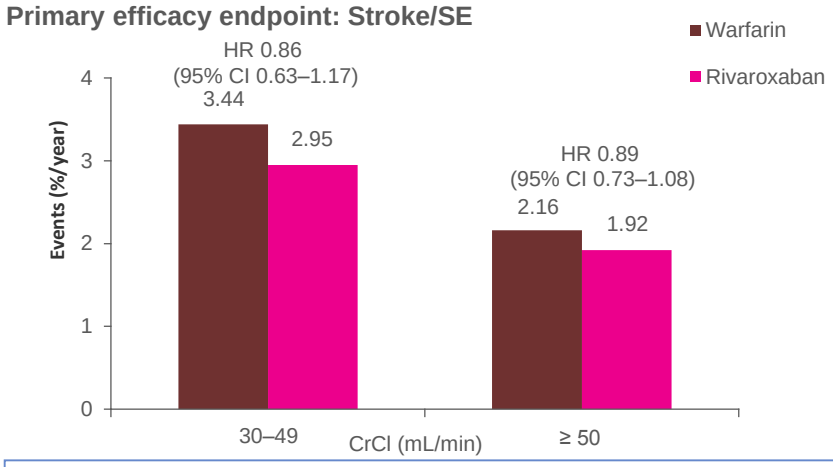
* LVEF <40%; #Data include patients with systemic embolism

AF Patients studied in ROCKET AF had higher risk of stroke than patients in other phase III trials with novel OACs.

1. Patel MR et al. N Engl J Med. 2011;365(10):883-891; 2. Granger CB et al. N Engl J Med. 2011;365(11):981-992; 3. Giugliano RP et al. N Engl J Med. 2013;369(22):2093-2104; 4. Connolly SJ et al. N Engl J Med. 2009;361(12):1139-1151; 5. Eikelboom JW et al. Circulation 2011;123(21):2363-2372

Rivaroxaban in Patients with Non-Valvular AF and Renal Impairment

ROCKET AF: Primary Efficacy Endpoint in Patients with Moderate Renal Impairment

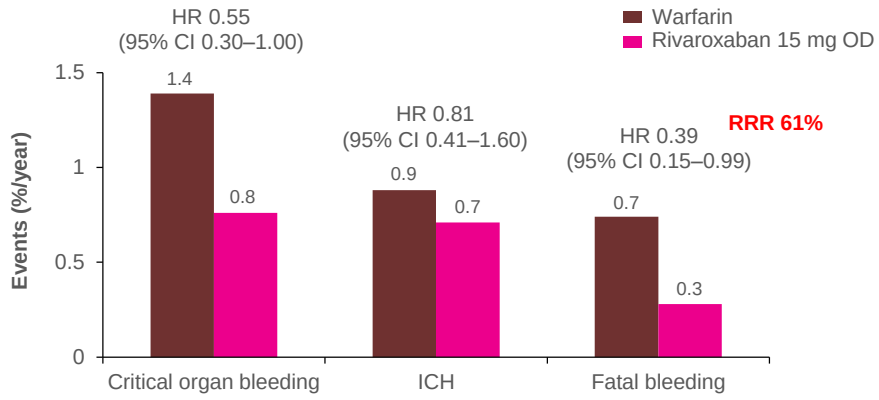


Consistent efficacy of rivaroxaban vs. warfarin in NVAF patients with moderate renal impairment

Intention-to-treat population

Fox KA et al. Eur Heart J. 2011;32(19):2387-2394

ROCKET AF: Consistent Safety Outcomes in NVAF Patients With Moderate Renal Impairment



Safety on-treatment population

Fox KA et al. Eur Heart J. 2011;32(19):2387-2394

Is there an evidence that rivaroxaban is nephroprotective in patients with NVAF?

AHA 2019 updated guidelines

4.2. Anticoagulant Options (Modified From Section 4.2., "Antithrombotic Options," in the 2014 AF Guideline)

Over time, NOACs (particularly dabigatran and rivaroxaban) may be associated with lower risks of adverse renal outcomes than warfarin in patients with AF (S4.2.2.2-16).

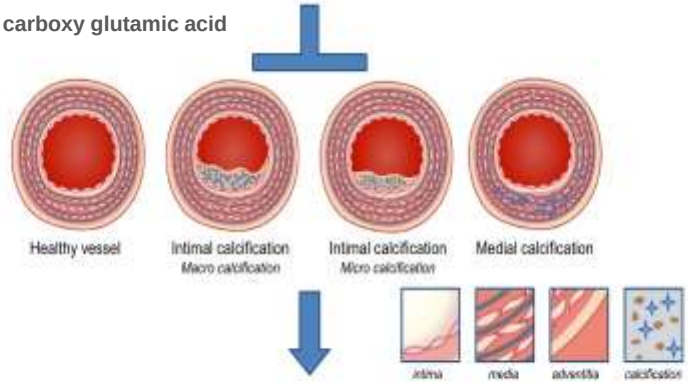
2019 AHA/ACC/HRS Focused Update of the 2014 AHA/ACC/HRS Guideline for the Management of Patients With Atrial Fibrillation

What is the evidence behind this?

Vascular injury, calcification and decline in renal function in CKD patients: role of VKDP

MGP is a VKDP and protects against vascular calcification

Gamma carboxy glutamic acid



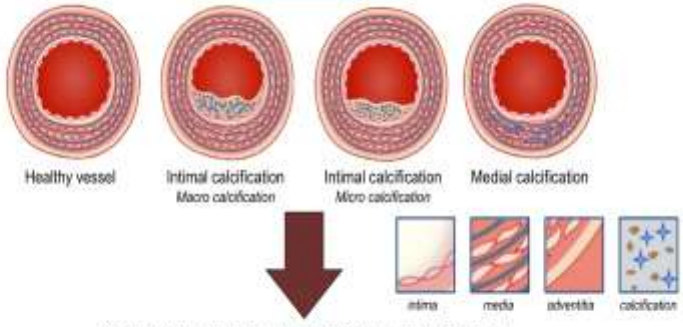
Advanced vascular disease and decline in renal function

MGP=Matrix Gla Protein; VKDP=Vitamin K dependent protein.
Willems BAG, et al. *Mol Nutr Food Res* 2014; 58:1620–1635. van Gorp RH & Schurgers LJ. *Nutrients* 2015; 7:9538–9557.

Vascular injury, calcification and decline in renal function in CKD patients: role of VKDP

MGP is a VKDP and protects against vascular calcification

Gamma carboxy glutamic acid **VKA**



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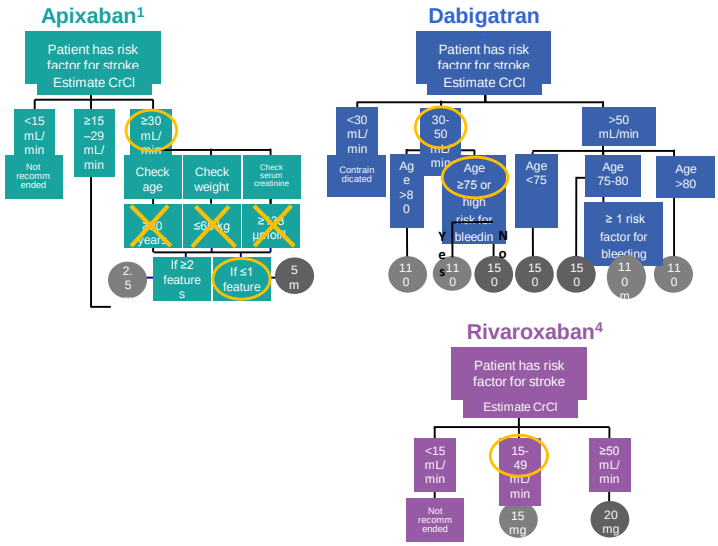
NOAC Dosing Algorithms in AF



1. Apixaban (Eliquis) Product Monograph; 2. Dabigatran (Pradaxa) Product Monograph; 3. Edoxaban (Savaysa) Product

Rivaroxaban for Stroke Prevention in Non-Valvular AF

- Indication: prevention of stroke and systemic embolism (SE) in adult patients with non-valvular AF with ≥1 risk factors, such as CHF, hypertension, age ≥75 years, diabetes mellitus or prior stroke/TIA

Rivaroxaban 20 mg OD

To be taken with food

In patients with moderate/severe renal impairment 15 mg OD*

To be taken with food

Continued long-term, benefit of prevention of stroke/SE outweighs bleeding risk

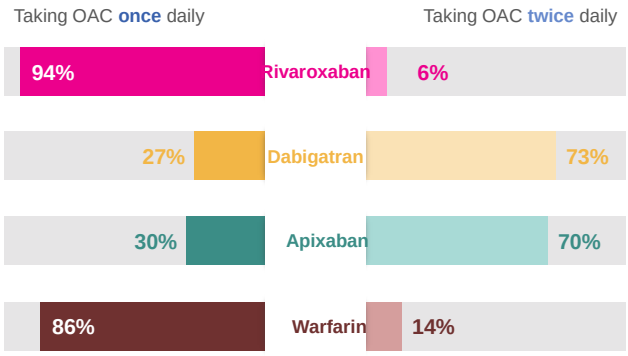
*Moderate renal impairment (CrCl 30-49 mL/min) – specific dose (15 mg OD) tested in ROCKET AF; Severe renal impairment (CrCl 15-29 mL/min) – use with caution; limited clinical data indicate that rivaroxaban plasma concentrations are significantly increased in these patients CrCl <15 mL/min – use not recommended

Rivaroxaban Summary of Product Characteristics as approved by the European Commission

Once vs twice daily: The compliance issue

One-Third of Twice-Daily Prescribed Medications Were Being Taken Once Daily

Therapy adherence
Self-reported patient survey (N=266)



Andrade JG *et al*, *Can J Cardiol* 2015;doi:0.1016/j.cjca.2015.09.023

Conclusion

In elderly AF patients with renal impairment and diabetes

- **Rivaroxaban is the only NOAC having a prespecified dose for AF patients with renal impairment which is 15 mg OD**
- **A specific subanlaysis was made on elderly AF patients as well as on patients with renal impairment in addition to those with diabetes from the ROCKET AF clinical trial showing better safety with rivaroxaban vs warfarin**
- **In prescribing an anticoagulant we have to stick to the approved indications and approved doses as well**

Thank you