Pirogov Russian National Research Medical University

Choosing of the anticoagulant in patients with atrial fibrillation and different conditions

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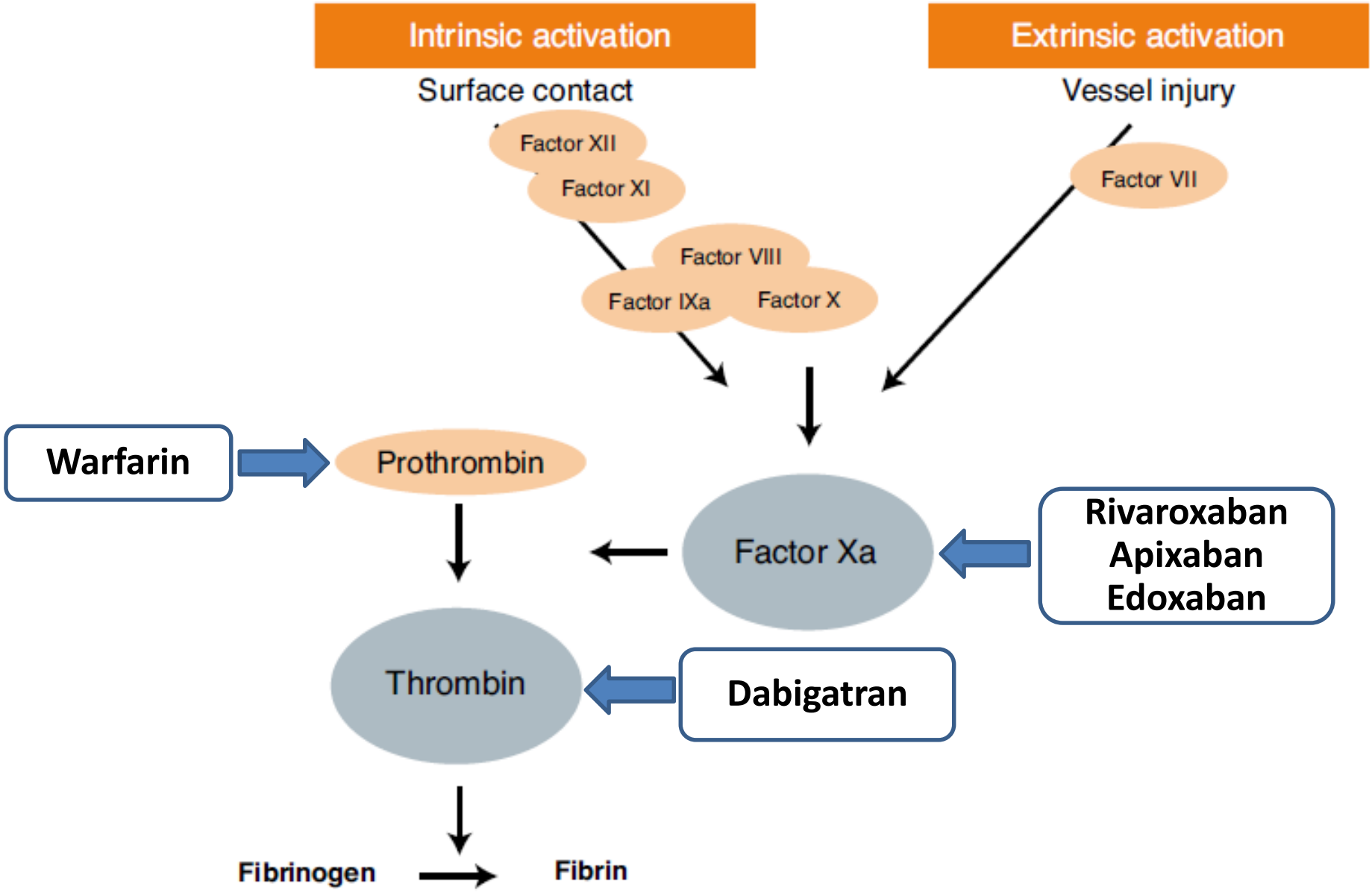
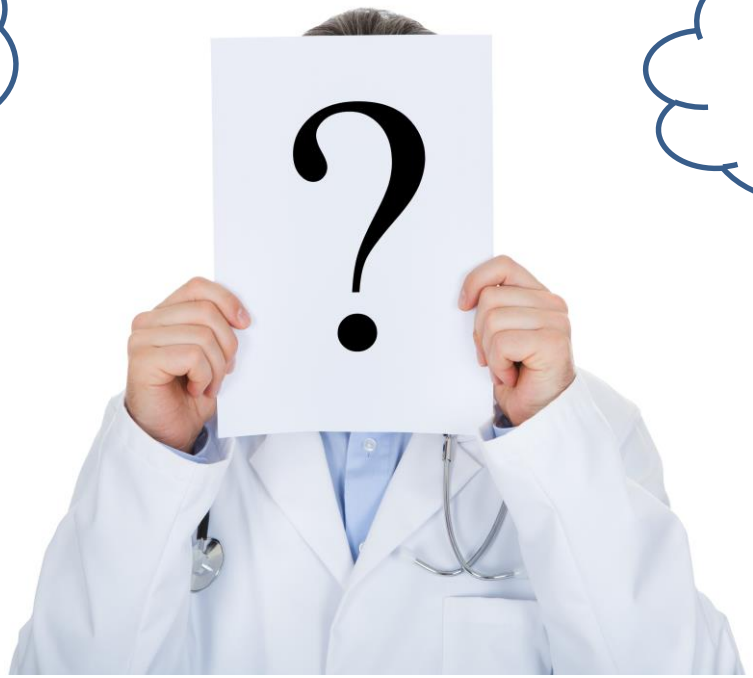
European School of Internal Medicine (ESIM)
Riga, 09 February 2017

Oral anticoagulants: mechanism of action



Patient with AF: which anticoagulant to choose?



Dabigatran

Warfarin

Rivaroxaban

Heparins

Apixaban

Aspirin

Edoxaban

Choosing OAC in AF patients: Game of the thrones

Dabigatran

Warfarin

Rivaroxaban

Apixaban

Case 1. Simple one

Patient, 60 years old male with permanent AF during last 3 years, without any CV history.

Which anticoagulant to choose:

- *Heparin or LMWH*
- *VKA*
- *Factor Xa inhibitors*
- *Direct thrombin inhibitors*
- *None*

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Patient, 60 years old male with permanent AF during last 3 years, without any CV history.

Which anticoagulant to choose:

- *Heparin or LMWH*
- *VKA*
- *Factor Xa inhibitors*
- *Direct thrombin inhibitors*
- ✓ ***None***

Clinical risk factors for stroke, transient ischaemic attack, and systemic embolism

CHA_2DS_2-VASc risk factor	Points
Congestive heart failure Signs/symptoms of heart failure or objective evidence of reduced left-ventricular ejection fraction	1
Hypertension Resting blood pressure >140/90 mmHg on at least two occasions or current antihypertensive treatment	1
Age 75 years or older	2
Diabetes mellitus Fasting glucose >125 mg/dL (7 mmol/L) or treatment with oral hypoglycaemic agent and/or insulin	1
Previous stroke, transient ischaemic attack, or thromboembolism	2
Vascular disease Previous myocardial infarction, peripheral artery disease, or aortic plaque	1
Age 65–74 years	1
Sex category (female)	1

European Heart Journal - doi:10.1093/eurheartj/ehw210

Oral anticoagulants in atrial fibrillation

Recommendations	Class	Level
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
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
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
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

European Heart Journal - doi:10.1093/eurheartj/ehw210

Case 2. High risk

Patient, 70 y.o. male with paroxysmal AF and arterial hypertension. Never used OAC before. What is the best option?

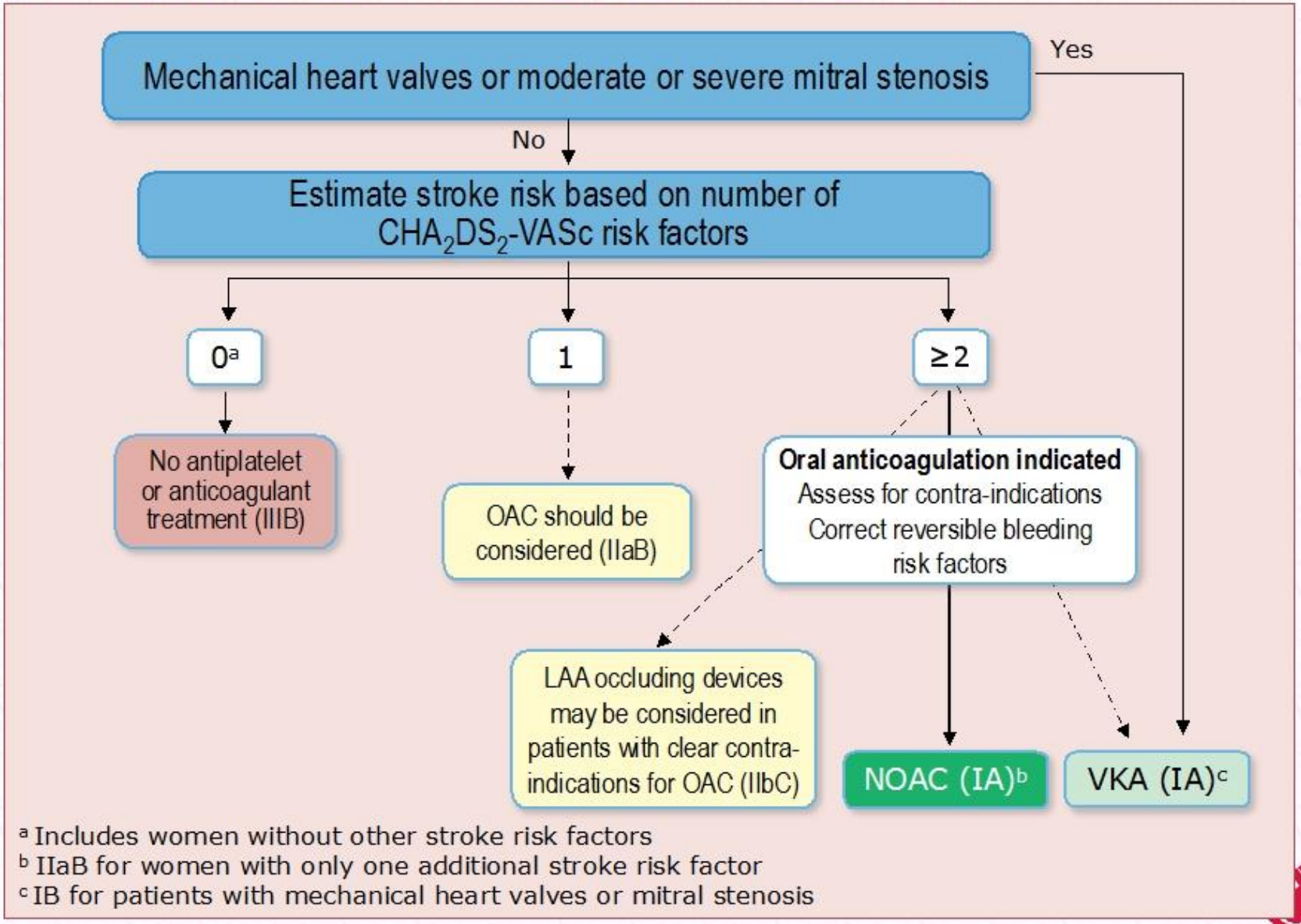
- *Heparin or LMH*
- *VKA*
- *Factor Xa inhibitors*
- *Direct thrombin inhibitors*
- *None*

Case 2. High risk

Patient, 70 y.o. male with paroxysmal AF and arterial hypertension. Never used OAC before. What is the best option?

- *Heparin or LMH*
- *VKA*
- ✓ ***Factor Xa inhibitors***
- ✓ ***Direct thrombin inhibitors***
- *None*

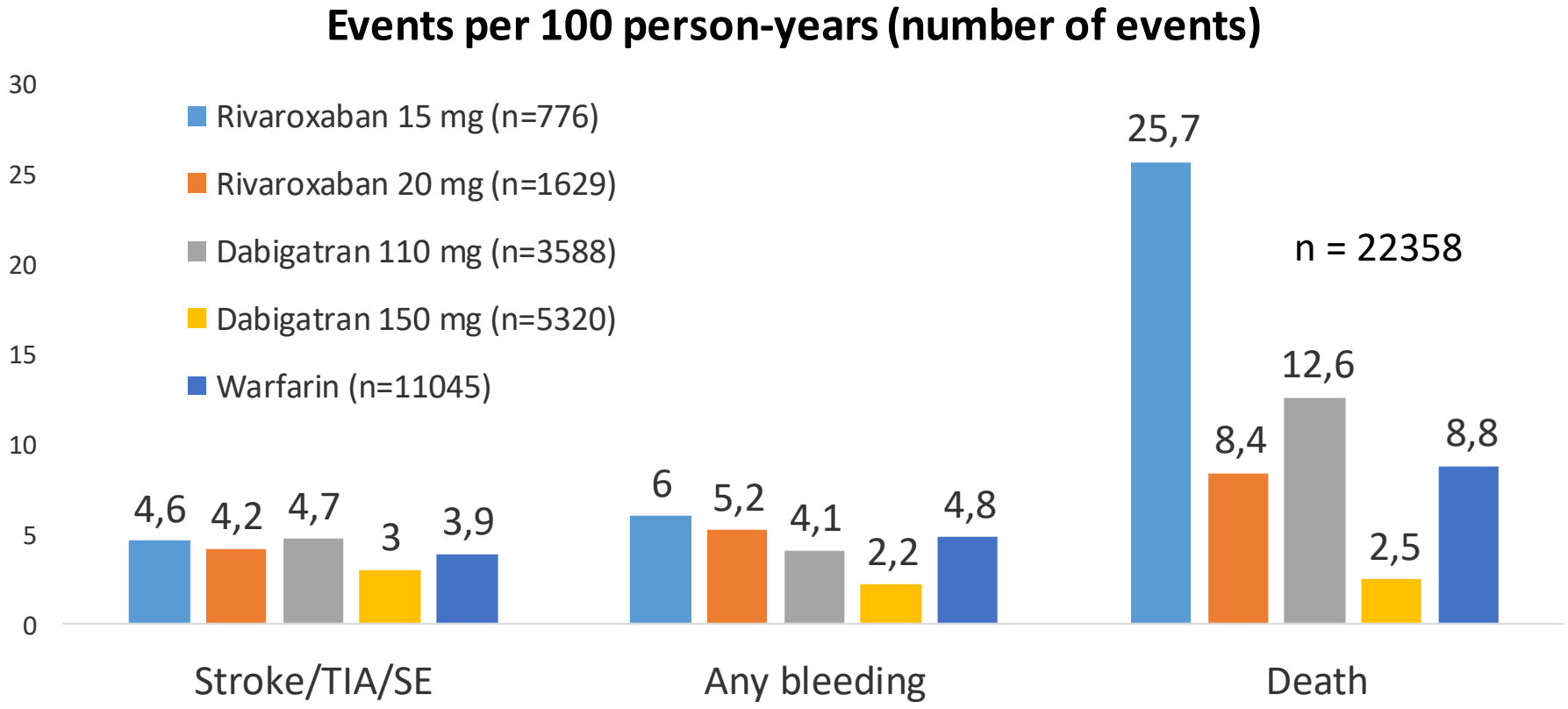
Stroke prevention in atrial fibrillation



[a] Includes women without other stroke risk factors
[b] IIaB for women with only one additional stroke risk factor
[c] IB for patients with mechanical heart valves or mitral stenosis

European Heart Journal - doi:10.1093/eurheartj/ehw210

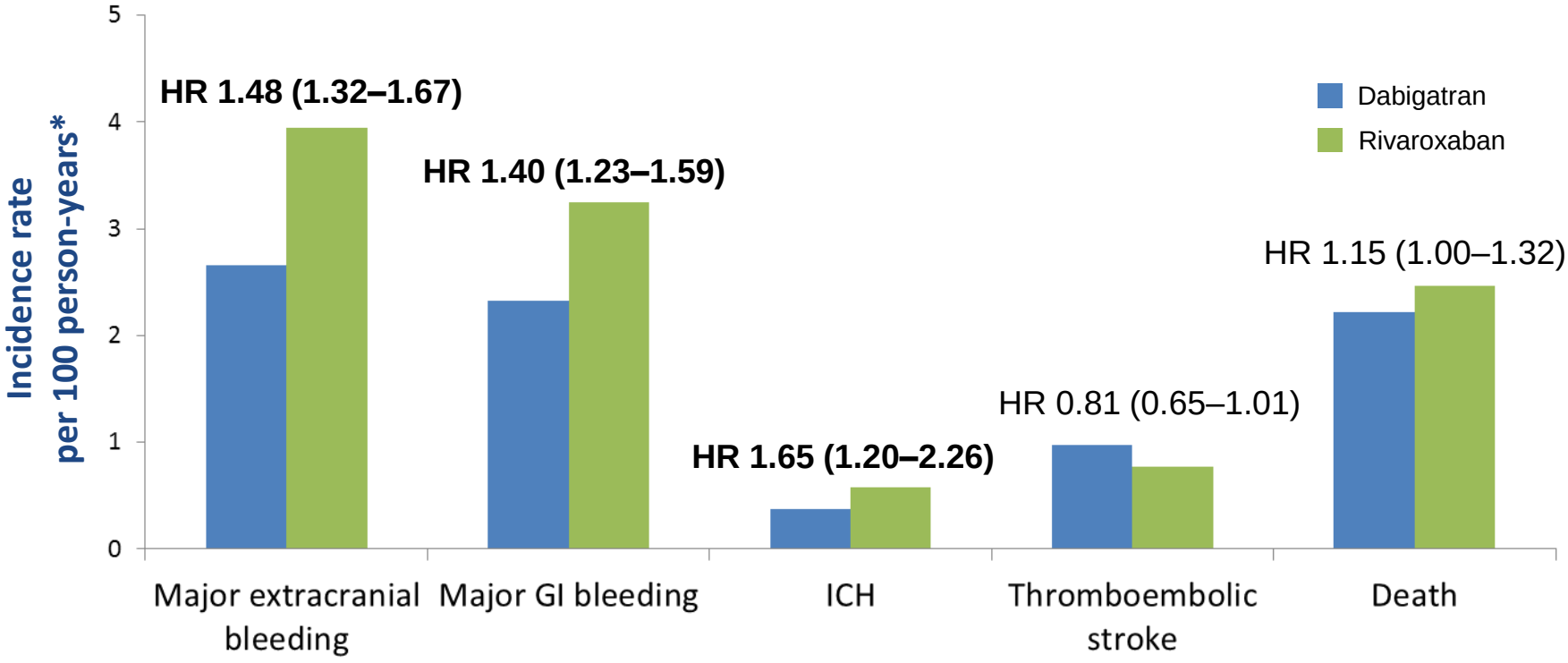
Efficacy and safety of rivaroxaban, dabigatran and warfarin in AF in real practice



Conclusions: Rivaroxaban was associated with similar or lower stroke rates, but higher bleeding and mortality rates. Channeling of rivaroxaban towards elderly and less healthy patients may have generated residual confounding.

Gorst-Rasmussen A. et al. Pharmacoepidemiology and Drug Safety, 2016 DOI: 10.1002/pds

An independent FDA study of >118 000 Medicare patients compared dabigatran 150 mg BID with rivaroxaban 20 mg OD



Dabigatran was associated with a statistically significantly lower risk of major extracranial bleeding, major GI bleeding and ICH compared with rivaroxaban

*Incidence rates are unadjusted; hazard ratios (HR) are adjusted HR (95% CI) comparing inverse probability of treatment-weighted new-user cohorts; bold values indicate statistical significance; average follow-up duration <4 months;
ICH, intracranial haemorrhage; GI, gastrointestinal.

Graham DJ et al. JAMA Intern Med 2016; doi:10.1001/jamainternmed.2016.5954

FDA Medicare study Editorial

Commentary to the manuscript: Editors´note

"… rivaroxaban was associated with a statistically significant increase in bleeding, with more intracranial and major extracranial bleeding, including major gastrointestinal bleeding."…

"… ***it offers important guidance to consumers on relative efficacy and safety profiles that drive NOAC selection, particularly for those at greatest risk of hemorrhage.*****"…**

Editor's note: "*The additional information should lead us to prescribe dabigatran over rivaroxaban for patients with atrial fibrillation."*

Parks AL et Redberg RF, JAMA Intern Med, 2016, Editorial, Oct 3

Case 3. Obese patient

Patient, 29 y.o. male with persistent AF, arterial hypertension, diabetes mellitus type 1 & obesity (BMI 42 kg/m^2). Never used OAC before. Which OAC should be chosen?

- *Warfarin*
- *Rivaroxaban*
- *Apixaban*
- *Dabigatran*
- *None*

Case 3. Obese patient

Patient, 29 y.o. male with persistent AF, arterial hypertension, diabetes mellitus type 1 & obesity (BMI 42 kg/m^2). Never used OAC before. Which OAC should be chosen?

- ✓ ***Warfarin***
- *Rivaroxaban*
- *Apixaban*
- *Dabigatran*
- *None*

Use of direct oral anticoagulants in obese patients

- In patients with AF or VTE and body weight <120 kg or BMI <40 kg/m^2 - **standard doses** of DOAC.
- In patients with body weight >120 kg or BMI >40 kg/m^2 - DOACs **should not be used**.
- If already given in extremely obese, serum level of DOAC should be evaluated, and if below of therapeutic ranges, patients **should be rather given VKA**.

Martin K et al. J Thromb Haemost 2016; 14: 1308–13.

Case 4. Chronic kidney disease

Patient, 58 y.o. male with permanent AF, hypertension, diabetes type 2 and diabetic nephropathy (CrCl 26 ml/min). Which anticoagulant will you choose?

- *Heparin or LMWH*
- *Warfarin*
- *Apixaban*
- *Rivaroxaban*
- *Dabigatran*

Case 4. Chronic kidney disease

Patient, 58 y.o. male with permanent AF, hypertension, diabetes type 2 and diabetic nephropathy (CrCl 26 ml/min). Which anticoagulant will you choose?

- *Heparin or LMWH*
- ✓ ***Warfarin***
- ✓ ***Apixaban***
- *Rivaroxaban*
- *Dabigatran*

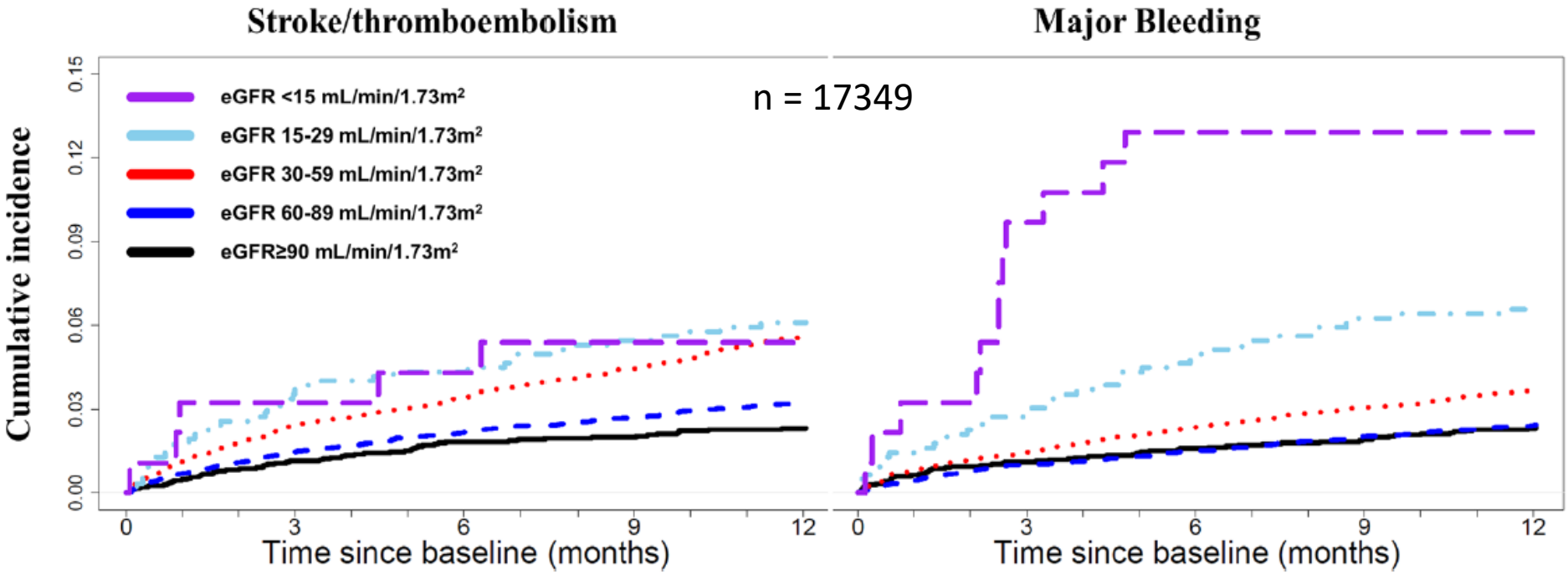
Assessment of kidney function in atrial fibrillation

Recommendations	Class	Level
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
All AF patients treated with oral anticoagulation should be considered for at least yearly renal function evaluation to detect chronic kidney disease.	IIa	B

- Almost 40% of AF patients have CKD stage III-V
- Nearly 20% of CKD patients have atrial fibrillation
- Although an estimated creatinine clearance (CrCl) rate of <60 mL/min is indicative of CKD, a number of trials in AF patients have used CrCl <50 mL/min to adapt NOAC dosage, usually estimated using the Cockroft–Gault formula.

European Heart Journal - doi:10.1093/eurheartj/ehw210

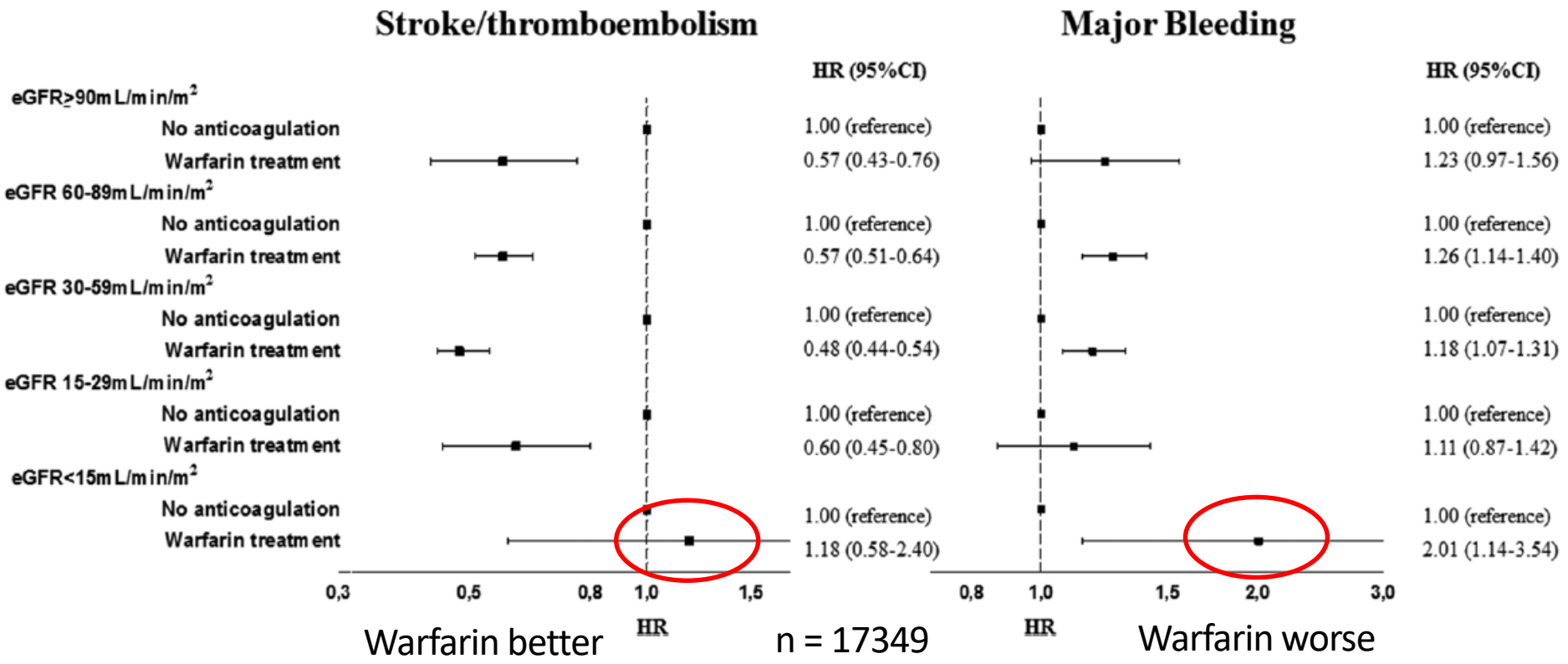
Incidence of stroke/thromboembolism and major bleeding according to eGFR in AF patients



Conclusion: In AF patients, risk of stroke/thromboembolism and major bleeding were significantly associated with the level of renal function.

Bonde A.N. et al. Stroke. 2016;47:2707-2713

Stroke/thromboembolism and major bleeding according to eGFR and warfarin treatment



Conclusion: Warfarin treatment was associated with higher risk of bleeding in all eGFR groups and lower risk of stroke/thromboembolism in patients with eGFR >15 mL/min per 1.73 m^2.

Bonde A.N. et al. Stroke. 2016;47:2707-2713

Relevant clinical characteristics and dose adjustment in the four phase III NOAC trials in patients with atrial fibrillation

	Dabigatran (RE-LY)	Rivaroxaban (ROCKET-AF)	Apixaban (ARISTOTLE)	Edoxaban (ENGAGE AF-TIMI 48)
Renal clearance	80%	35%	25%	50%
Number of patients	18 113	14 264	18 201	21 105
Dose	150 mg or 110 mg twice daily	20 mg once daily	5 mg twice daily	60 mg (or 30 mg) once daily
Exclusion criteria for CKD	CrCl <30 ml/min	CrCl <30 mL/min	Serum creatinine >2.5 mg/dL or CrCl <25 mL/min	CrCl <30 mL/min
Dose adjustment with CKD	None	Rivaroxaban 15 mg once daily if CrCl 30–49 mL/min	Apixaban 2.5 mg twice daily if at least two of age ≥80 years, weight ≤60 kg, or serum creatinine ≥1.5 mg/dL (133 µmol/L)	Edoxaban 30 mg (or 15 mg) once daily if CrCl <50 mL/min
Percentage of patients with CKD	20% with CrCl 30-49 mL/min	21% with CrCl 30-49 mL/min	15% with CrCl 30-50 mL/dL	19% with CrCl <50 mL/min
Reduction of stroke and systemic embolism	No interaction with CKD status	No interaction with CKD status	No interaction with CKD status	NA
Reduction in major haemorrhages compared to warfarin	Reduction in major haemorrhage with dabigatran was greater in patients with eGFR >80 mL/min with either dose	Major haemorrhage similar	Reduction in major haemorrhage with apixaban	NA

European Heart Journal - doi:10.1093/eurheartj/ehw210

OAC in patients with AF and advanced or severe CKD

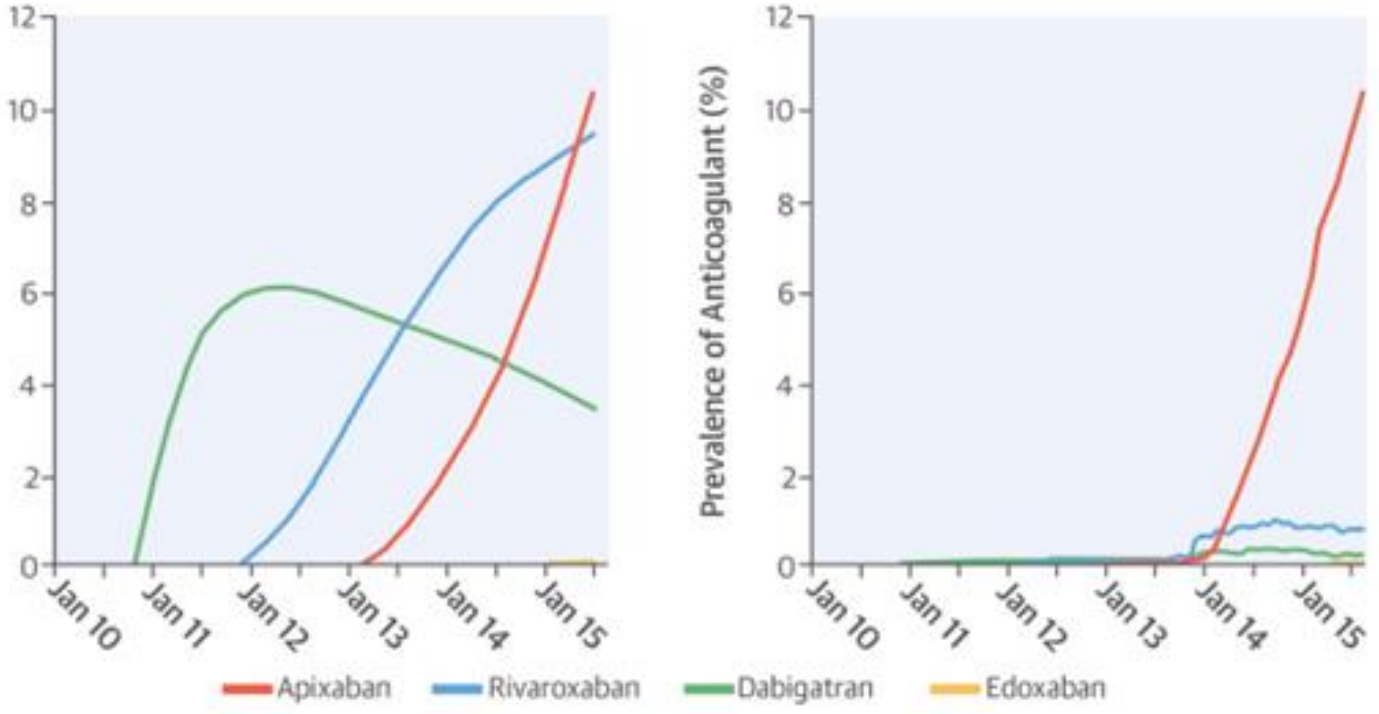
The use of NOACs has not been tested in patients with creatinine clearance <30 mL/min, and there is very little evidence on the effects of OAC in patients on hemodialysis or on other forms of renal replacement therapy. Studies evaluating OAC in patients with severe CKD are needed to inform the best management in this patient group at high risk for stroke and bleeding.

European Heart Journal - doi:10.1093/eurheartj/ehw210

Is it the same in USA?

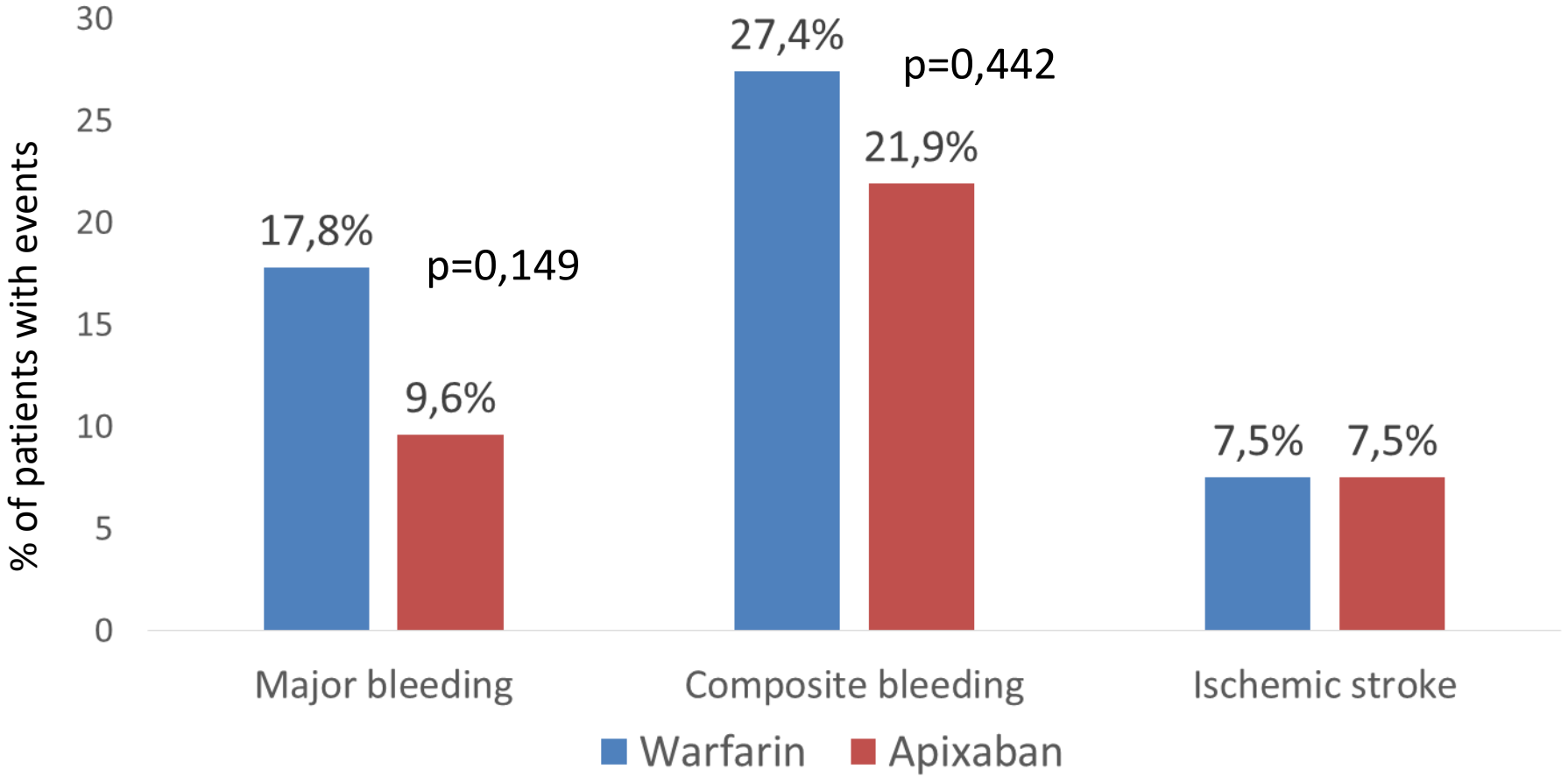
- FDA approved administration of DOACs in patients with CrCl 15-30 ml/min (apixaban 5 mg bid, rivaroxaban 15 mg OD and dabigatran 75 mg bid)

Off-label DOAC administration in patients with advanced CKD (n = 102 504) and on dialysis (n= 140 918)



Chan K.E. et al. J Am Coll Cardiol. 2016;67(24):2888-99.

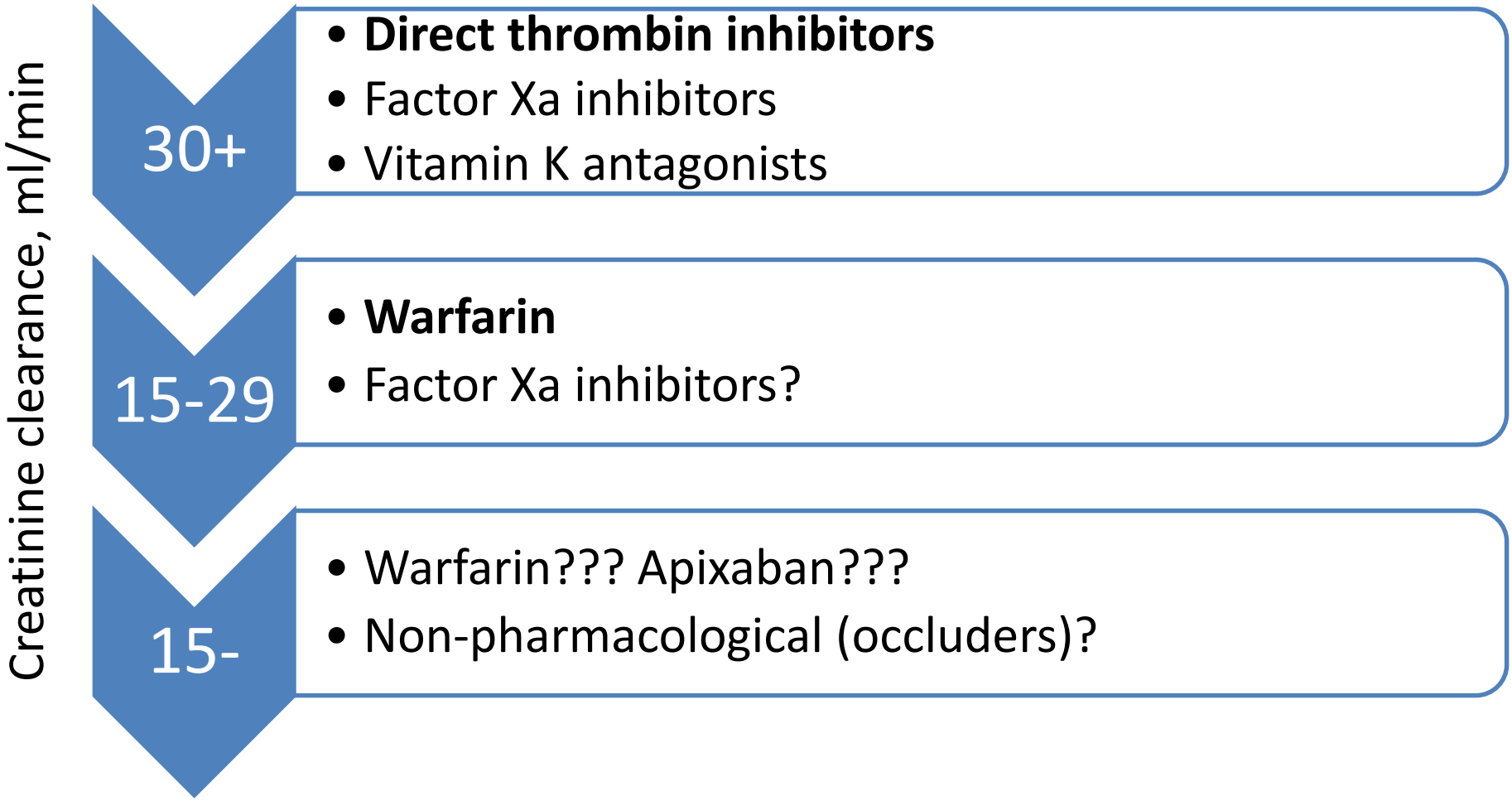
Is Apixaban an Appropriate Alternative to Warfarin in Patients with Severe Renal Impairment?



146 patients previously receiving warfarin with a CrCl <25mL/min or SCr >2.5mg/dL, or received peritoneal dialysis or hemodialysis.

Stanton B.E. et al. Pharmacotherapy. 2017; DOI: 10.1002/phar.1905

Selection of oral anticoagulant in accordance with renal function



Case 5. Pregnancy

Patient, 30 y.o. pregnant female with paroxysmal AF, DM and hypertension. Which anticoagulant should we choose?

- *Heparin or LMWH*
- *VKA*
- *Factor Xa inhibitors*
- *Direct thrombin inhibitors*
- *None*

Case 5. Pregnancy

Patient, 30 y.o. pregnant female with paroxysmal AF, DM and hypertension. Which anticoagulant should we choose?

- ✓ ***Heparin or LMWH***
- ✓ ***VKA***
- *Factor Xa inhibitors*
- *Direct thrombin inhibitors*
- *None*

Atrial fibrillation during pregnancy

Recommendations	Class	Level
Electrical cardioversion can be performed safely at all stages of pregnancy, and is recommended in patients who are haemodynamically unstable due to AF, and whenever the risk of ongoing AF is considered high for the mother or the foetus.	I	C
Anticoagulation is recommended in pregnant patients with AF at risk of stroke. To minimize teratogenic risk and intrauterine bleeding, dose-adjusted heparin is recommended during the first trimester of pregnancy and in the 2–4 weeks before delivery. Vitamin K antagonists or heparin can be used in the remaining parts of the pregnancy.	I	B
NOACs should be avoided in pregnancy and in women planning a pregnancy.	III (harm)	C

European Heart Journal - doi:10.1093/eurheartj/ehw210

Case 6. Mitral stenosis

Patient, 20 y.o. female with permanent AF and moderate mitral stenosis. Which anticoagulant will you choose?

- *Heparin or LMWH*
- *VKA*
- *Factor Xa inhibitors*
- *Direct thrombin inhibitors*
- *None*

Case 6. Mitral stenosis

Patient, 20 y.o. female with permanent AF and moderate mitral stenosis. Which anticoagulant will you choose?

- *Heparin or LMWH*
- ✓ ***VKA***
- *Factor Xa inhibitors*
- *Direct thrombin inhibitors*
- *None*

Stroke prevention in patients with atrial fibrillation (1)

Recommendations	Class	Level
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
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
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
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
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
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

European Heart Journal - doi:10.1093/eurheartj/ehw210

Case 7. After elective PCI

Patient, 78 y.o. female with paroxysmal AF, hypertension and heart failure underwent elective PCI. What should be the duration of triple antithrombotic therapy?

- *1 month*
- *3 months*
- *6 months*
- *12 months*
- *Life-long*

Case 7. After elective PCI

Patient, 78 y.o. female with paroxysmal AF, hypertension and heart failure underwent elective PCI. What should be the duration of triple antithrombotic therapy?

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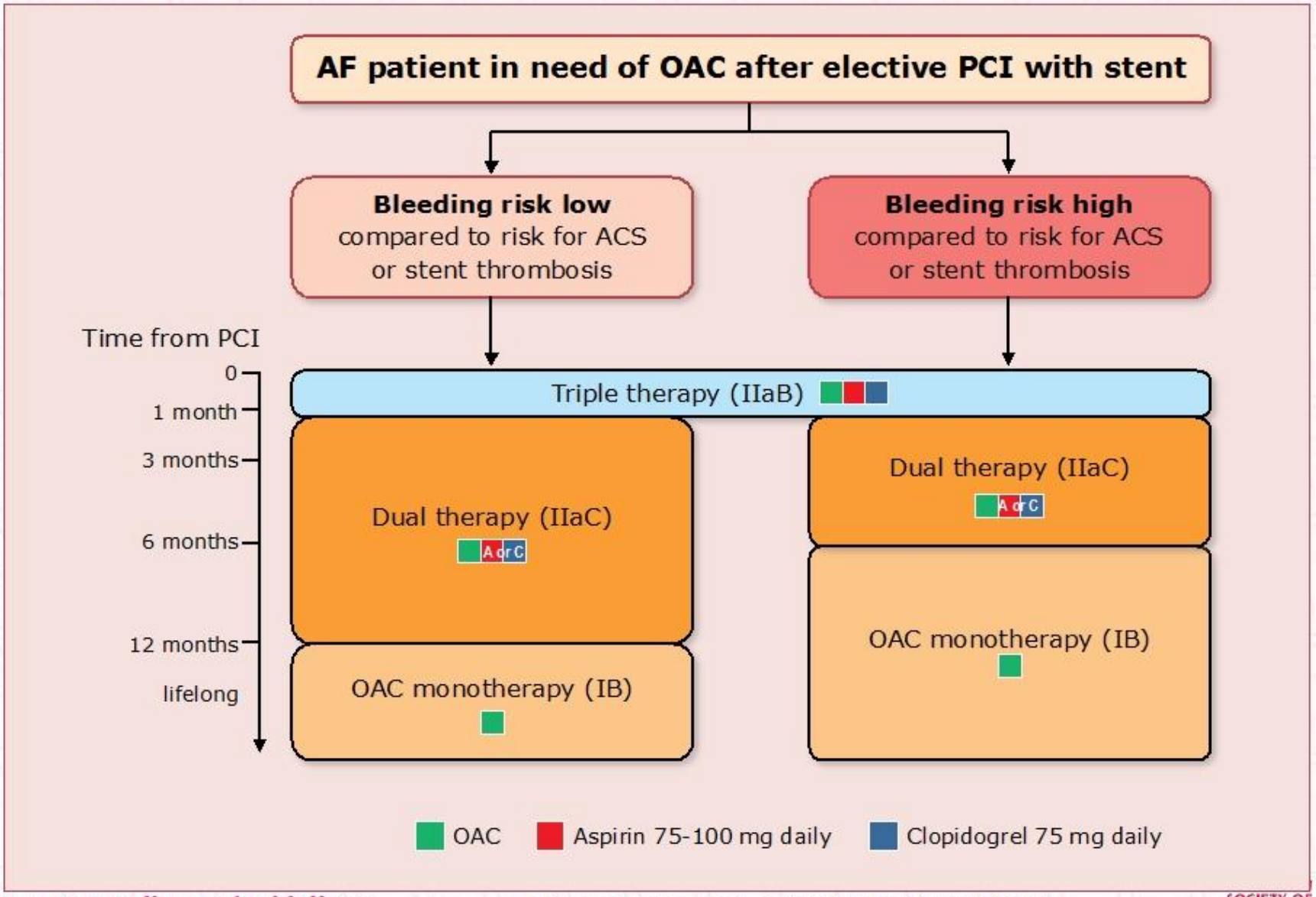
- *3 months*
- *6 months*
- *12 months*
- *Life-long*

Antithrombotic therapy after elective percutaneous intervention in atrial fibrillation patients requiring anticoagulation



European Heart Journal - doi:10.1093/eurheartj/ehw210

Modifiable and non-modifiable risk factors for bleeding in anticoagulated patients with AF

Modifiable bleeding risk factors:
Hypertension (especially when systolic blood pressure is >160 mmHg)
Labile INR or time in therapeutic range <60% in patients on vitamin K antagonists
Medication predisposing to bleeding, such as antiplatelet drugs and non-steroidal anti-inflammatory drugs
Excess alcohol (≥8 drinks/week)
Potentially modifiable bleeding risk factors:
Anaemia
Impaired renal function
Impaired liver function
Reduced platelet count or function

Non-modifiable bleeding risk factors:
Age (>65 years) (≥75 years)
History of major bleeding
Previous stroke
Dialysis-dependent kidney disease or renal transplant
Cirrhotic liver disease
Malignancy
Genetic factors
Biomarker-based bleeding risk factors:
High-sensitivity troponin
Growth differentiation factor-15
Serum creatinine/estimated CrCl

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Case 8. Perioperative management

Patient of 58 y.o. with permanent AF receiving rivaroxaban planning to undergo major surgery. Which will be the optimal anticoagulation strategy?

- *Stop rivaroxaban 5 days before surgery and bridge with LMWH before and after surgery*
- *Stop rivaroxaban 5 days before the procedure, measure anti-Xa factor activity level on the day of surgery; resume rivaroxaban 2-3 days later*
- *Stop rivaroxaban 2 days before and resume 2 or 3 days after the surgery*
- *Do not stop rivaroxaban at all*

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- ✓ ***Stop rivaroxaban 2 days before and resume 2 or 3 days after the surgery***
- *Do not stop rivaroxaban at all*

Perioperative management of patients receiving oral anticoagulants

	VKA	Dabigatran	Factor Xa inhibitors
Timing of cessation prior to procedure			
High bleeding risk	5 days with INR control on day before surgery.	≥2 days if CrCl >60 mL/min *OR* ≥4 days if CrCl 15-60 mL/min	≥2 days
Low bleeding risk	Proceed with surgery when the INR is ≤1.4	≥1 day if CrCl >60 mL/min *OR* ≥2 days if CrCl 15-60 mL/min	≥1 day *OR* ≥1,5 days if CrCl 15-30 mL/min
Resumption after procedure			
High bleeding risk	12 to 24 hours after surgery	2-3 days after surgery	
Low bleeding risk		1 day after surgery	

http://www.uptodate.com/contents/perioperative-management-of-patients-receiving-anticoagulants

Case 9. After stroke

Patient, 41 y.o. with persistent AF and diabetes suffered from severe ischemic stroke. When OAC should be started after acute event?

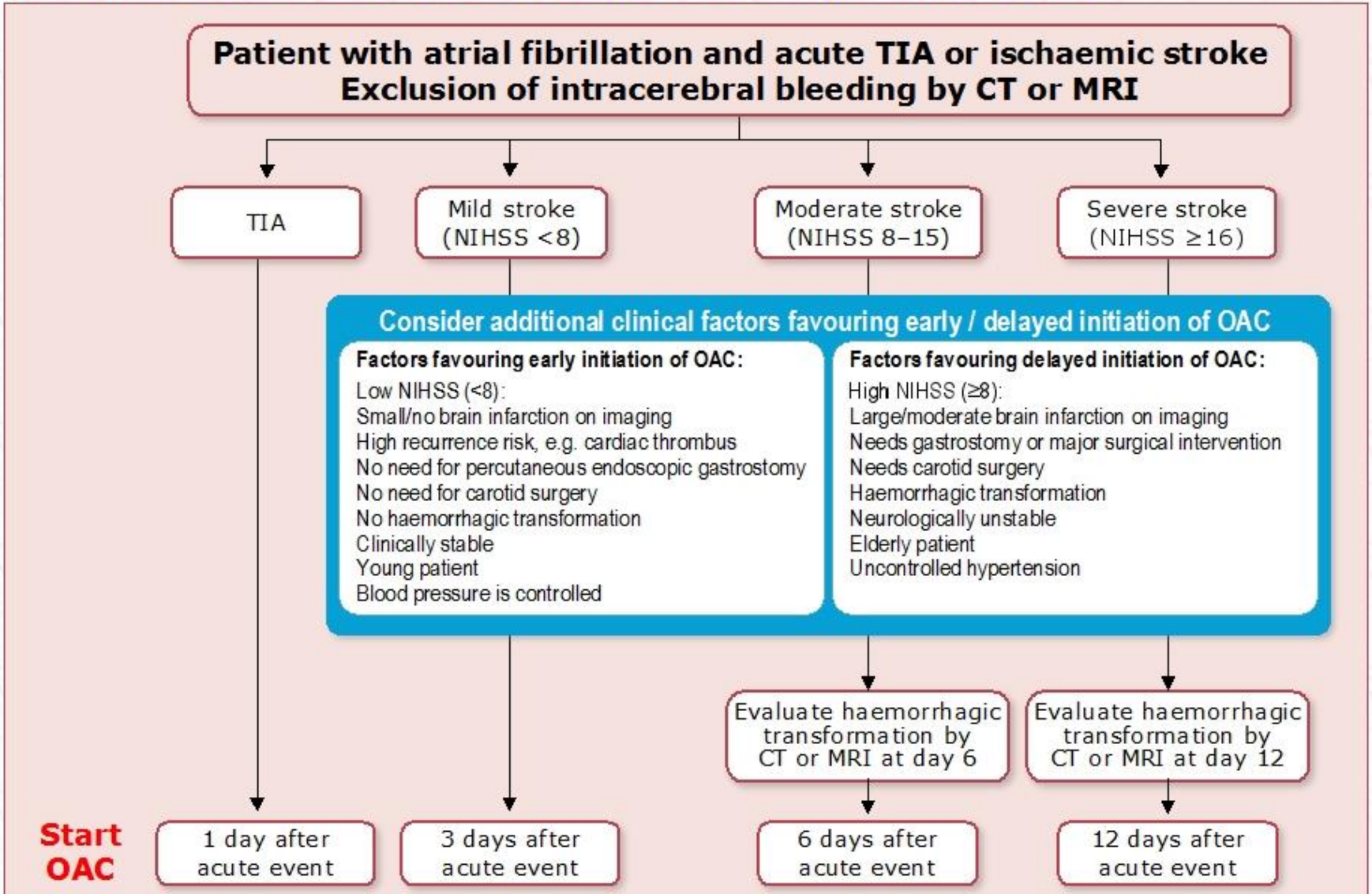
- *Immediately*
- *1 day after event*
- *3 days after event*
- *12 days after event*
- *Never*

Case 9. After stroke

Patient, 41 y.o. with persistent AF and diabetes suffered from severe ischemic stroke. When OAC should be started after acute event?

- *Immediately*
- *1 day after event*
- *3 days after event*
- ✓ ***12 days after event***
- *Never*

Initiation or continuation of anticoagulation in atrial fibrillation patients after a stroke or transient ischaemic attack



This approach is based on consensus within the Task Force, not on evidence.
NIHSS = National Institutes of Health Stroke Scale

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Case 10. Before cardioversion

Patient, 30 y.o. male with persistent AF is expected to undergo electrical cardioversion. How long anticoagulants should be started before?

- *≥ 3 days*
- *≥ 1 week*
- *≥ 2 weeks*
- *≥ 3 weeks*
- *Not necessary*

Case 10. Before cardioversion

* - in case of AF duration ≤ 48 hours

Patient, 30 y.o. male with persistent AF is expected to undergo electrical cardioversion. How long anticoagulants should be started before?

- *≥ 3 days*
- *≥ 1 week*
- *≥ 2 weeks*
- ✓ ***≥ 3 weeks***
- ✓ ***Not necessary****

Rhythm control therapy (3) – Stroke prevention

Recommendations	Class	Level
Stroke prevention in patients designated for cardioversion of AF		
Anticoagulation with heparin or a NOAC should be initiated as soon as possible before every cardioversion of AF or atrial flutter.	IIa	B
For cardioversion of AF/atrial flutter, effective anticoagulation is recommended for a minimum of 3 weeks before cardioversion.	I	B
Transoesophageal echocardiography (TOE) is recommended to exclude cardiac thrombus as an alternative to preprocedural anticoagulation when early cardioversion is planned.	I	B
Early cardioversion can be performed without TOE in patients with a definite duration of AF <48 hours.	IIa	B
In patients at risk for stroke, anticoagulant therapy should be continued long-term after cardioversion according to the long-term anticoagulation recommendations, irrespective of the method of cardioversion or the apparent maintenance of sinus rhythm. In patients without stroke risk factors, anticoagulation is recommended for 4 weeks after cardioversion.	I	B
In patients where thrombus is identified on TOE, effective anticoagulation is recommended for at least 3 weeks.	I	C
A repeat TOE to ensure thrombus resolution should be considered before cardioversion.	IIa	C

European Heart Journal - doi:10.1093/eurheartj/ehw210

Case 11. Atrial flutter

Patient, 47 years old male with persistent atrial flutter without any CV diseases. What is the best option?

- *Heparin or LMH*
- *VKA*
- *Xa factor inhibitors*
- *Direct thrombin inhibitors*
- *None*

Case 11. Atrial flutter

Patient, 47 years old male with persistent atrial flutter without any CV diseases. What is the best option?

- *Heparin or LMH*
- *VKA*
- *Xa factor inhibitors*
- *Direct thrombin inhibitors*
- ✓ ***None***

Management of atrial flutter

Recommendations	Class	Level
For patients with atrial flutter, antithrombotic therapy is recommended according to the same risk profile used for AF.	I	B
Overdrive atrial pacing of atrial flutter should be considered as an alternative to electrical cardioversion, depending on local availability and experience.	IIa	B
Management of typical atrial flutter with ablation of the cavotricuspid isthmus is recommended for patients failing antiarrhythmic drug therapy or as first-line treatment considering patient preference.	I	B
If atrial flutter has been documented before AF ablation, ablation of the cavotricuspid isthmus should be considered as part of the AF ablation procedure.	IIa	C

European Heart Journal - doi:10.1093/eurheartj/ehw210

Case 12. Bleeding

Patient, 59 y.o. male with permanent AF, who was taking dabigatran, and life-threating bleeding has developed. What should we do?

- *Discontinue dabigatran*
- *Idarucizumab*
- *Andexanet alfa*
- *Vitamin K*
- *Prothrombin complex concentrates*

Case 12. Bleeding

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- ✓ ***Discontinue dabigatran***
- ✓ ***Idarucizumab***
- *Andexanet alfa*
- *Vitamin K*
- ✓ ***Prothrombin complex concentrates***

What to do if the bleeding occurs?

VKA	• Vitamin K • Prothrombin complex concentrates or fresh frozen plasma
Dabigatran	• Idarucizumab • Prothrombin complex concentrates*
Xa factor inhibitors	• Prothrombin complex concentrates or fresh frozen plasma • Andexanet alfa???

Choosing of the anticoagulant in AF…

… is not a Game, but the real life!

Thanks for your attention!