

Phòng ngừa đột quỵ trên bệnh nhân rung nhĩ không do bệnh van tim: Cập nhật các khuyến cáo mới

PGS. TS. BS Phạm Nguyễn Vinh

BV Tim Tâm Đức

Viện Tim TP. HCM

ĐH Y Khoa Phạm Ngọc Thạch

ĐH Y Khoa Tân Tạo



2016 ESC Guidelines for the management of atrial fibrillation developed in collaboration with EACTS

The Task Force for the management of atrial fibrillation of the European Society of Cardiology (ESC)

Developed with the special contribution of the European Heart Rhythm Association (EHRA) of the ESC

Endorsed by the European Stroke Organisation (ESO)

Authors/Task Force Members: Paulus Kirchhof* (Chairperson) (UK/Germany), Stefano Benussi*¹ (Co-Chairperson) (Switzerland), Dipak Kotecha (UK), Anders Ahlsson¹ (Sweden), Dan Atar (Norway), Barbara Casadei (UK), Manuel Castella¹ (Spain), Hans-Christoph Diener² (Germany), Hein Heidbuchel (Belgium), Jeroen Hendriks (The Netherlands), Gerhard Hindricks (Germany), Antonis S. Manolis (Greece), Jonas Oldgren (Sweden), Bogdan Alexandru Popescu (Romania), Ulrich Schotten (The Netherlands), Bart Van Putte¹ (The Netherlands), and Panagiotis Vardas (Greece)



ESC

European Society
of Cardiology

European Heart Journal (2018) **00**, 1–64

doi:10.1093/eurheartj/ehy136

SPECIAL ARTICLE

The 2018 European Heart Rhythm Association Practical Guide on the use of non-vitamin K antagonist oral anticoagulants in patients with atrial fibrillation

**Jan Steffel^{1*}, Peter Verhamme², Tatjana S. Potpara³, Pierre Albaladejo⁴,
Matthias Antz⁵, Lien Desteghe⁶, Karl Georg Haeusler⁷, Jonas Oldgren⁸,
Holger Reinecke⁹, Vanessa Roldan-Schilling¹⁰, Nigel Rowell¹¹, Peter Sinnaeve²,
Ronan Collins¹², A. John Camm¹³, and Hein Heidbüchel^{6,14}**



Pham
Nguyen
Vinh

Dịch tễ của rung nhĩ

- 2010: 20,9 triệu/nam và 12,6 triệu/nữ bị RN/thế giới.
- 2030: 14 – 17 triệu b/n RN/Châu Âu
- 1/4 người trung niên ở châu Âu và Mỹ bị RN

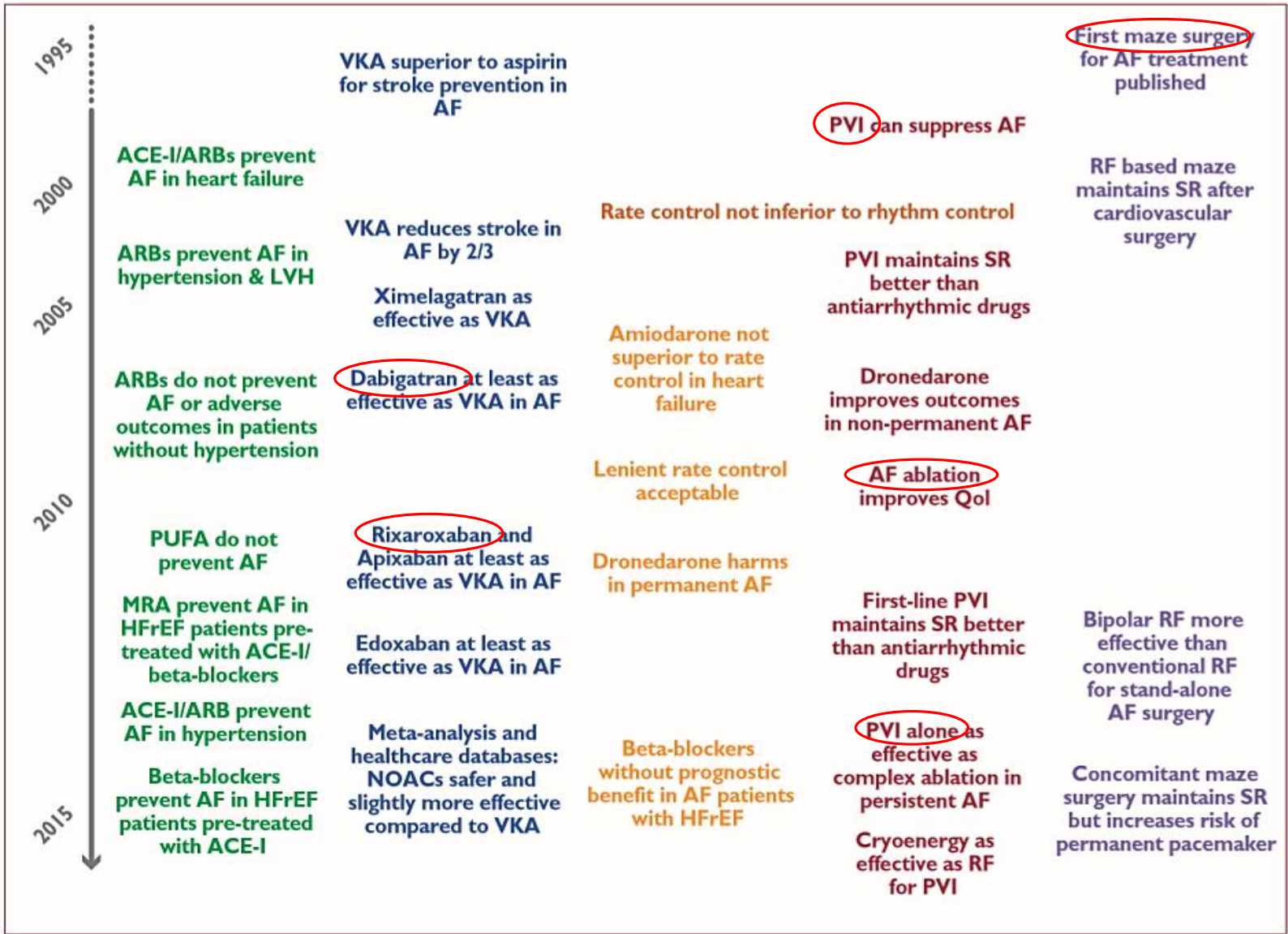
Cardiovascular morbidity and mortality associated with atrial fibrillation

TL: Kirchhof P et al. 2016 ESC Guidelines for the management of AF. Eur H J, Aug 2016.

Event	Association with AF
Death	Increased mortality, especially cardiovascular mortality due to sudden death, heart failure or stroke.
Stroke	20–30% of all strokes are due to AF. A growing number of patients with stroke are diagnosed with 'silent', paroxysmal AF.
Hospitalizations	10–40% of AF patients are hospitalized every year.
Quality of life	Quality of life is impaired in AF patients independent of other cardiovascular conditions.
Left ventricular dysfunction and heart failure	Left ventricular dysfunction is found in 20–30% of all AF patients. AF causes or aggravates LV dysfunction in many AF patients, while others have completely preserved LV function despite long-standing AF.
Cognitive decline and vascular dementia	Cognitive decline and vascular dementia can develop even in anticoagulated AF patients. Brain white matter lesions are more common in AF patients than in patients without AF.

AF = atrial fibrillation; LV = left ventricular.

Timeline of findings from landmark trials in AF management



PUFA = polyunsaturated fatty acid; PVI = pulmonary vein isolation; QoL = quality of life; RF = radiofrequency; SR = sinus rhythm

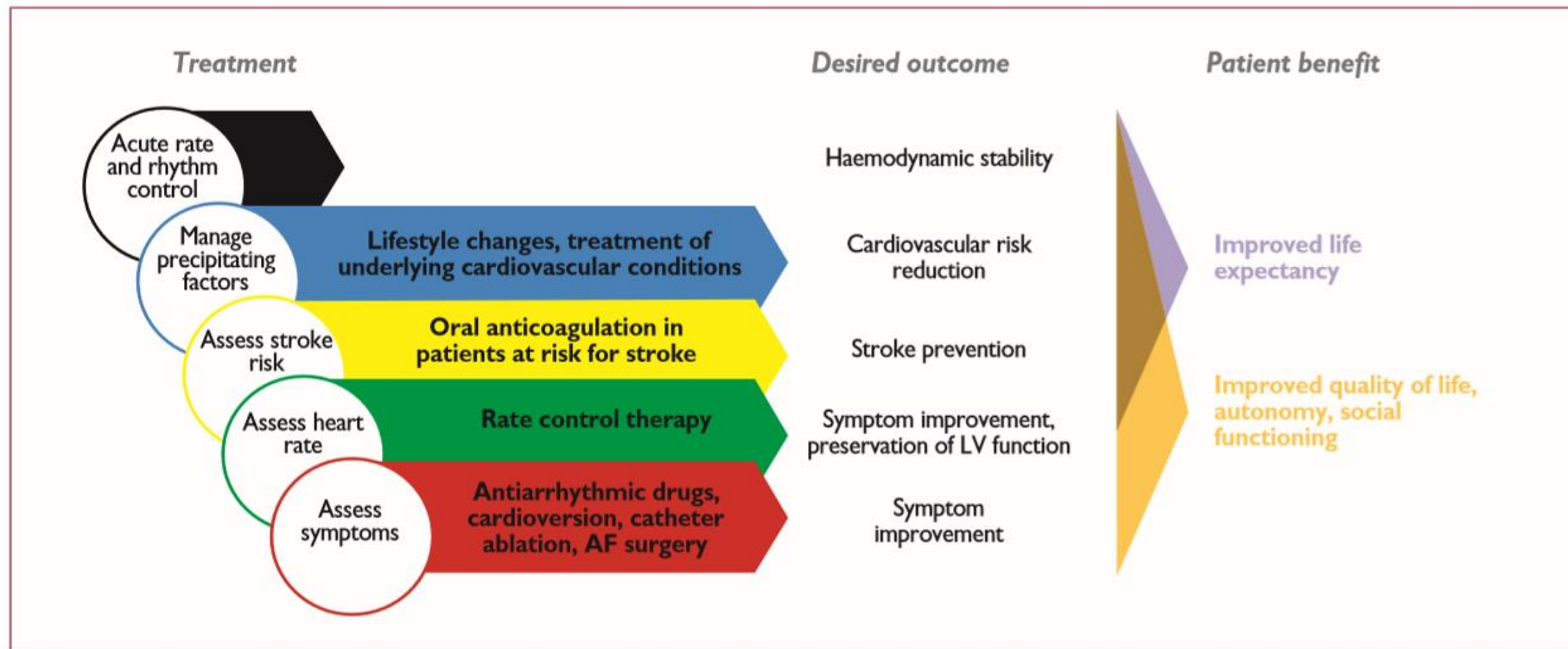
Patterns of atrial fibrillation

AF pattern	Definition
First diagnosed AF	AF that has not been diagnosed before, irrespective of the duration of the arrhythmia or the presence and severity of AF-related symptoms.
Paroxysmal AF	Self-terminating, in most cases within 48 hours. Some AF paroxysms may continue for up to 7 days. ^a AF episodes that are cardioverted within 7 days should be considered paroxysmal. ^a
Persistent AF	AF that lasts longer than 7 days, including episodes that are terminated by cardioversion, either with drugs or by direct current cardioversion, after 7 days or more.
Long-standing persistent AF	Continuous AF lasting for ≥ 1 year when it is decided to adopt a rhythm control strategy.
Permanent AF	AF that is accepted by the patient (and physician). Hence, rhythm control interventions are, by definition, not pursued in patients with permanent AF. Should a rhythm control strategy be adopted, the arrhythmia would be re-classified as 'long-standing persistent AF'.

AF = atrial fibrillation.

^aThe distinction between paroxysmal and persistent AF is often not made correctly without access to long-term monitoring.¹⁶³ Hence, this classification alone is often insufficient to select specific therapies. If both persistent and paroxysmal episodes are present, the predominant pattern should guide the classification.

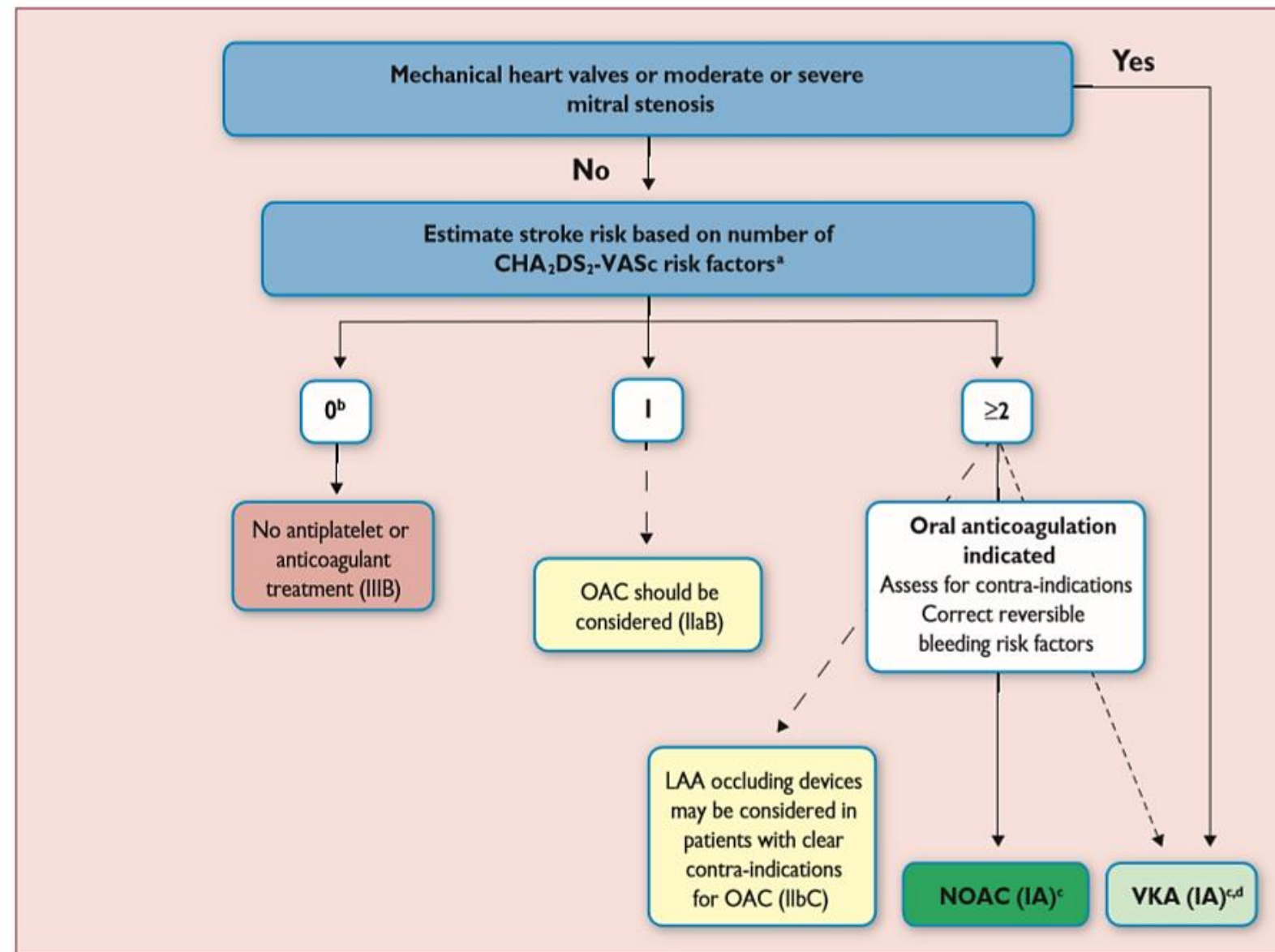
Acute and chronic management of AF patients: desired cardiovascular outcomes and patient benefits



AF = atrial fibrillation; LV = left ventricular.

Điều trị phòng ngừa đột quỵ/b/n RN không do van nhân tạo hay hẹp 2 lá hậu thấp

Stroke prevention in atrial fibrillation.



TL: Kirchhof P et al. 2016 ESC Guidelines for the management of AF. Eur H J, Aug 2016.

AF = atrial fibrillation; LAA = left atrial appendage; NOAC = non-vitamin K antagonist oral anticoagulant; OAC = oral anticoagulation; VKA = vitamin K antagonist.

^aCongestive heart failure, Hypertension, Age ≥75 years (2 points), Diabetes, prior Sstroke/TIA/embolus (2 points), Vascular disease, age 65–74 years, female Sex.

^bIncludes women without other stroke risk factors.

^cIIaB for women with only one additional stroke risk factor.

^dIB for patients with mechanical heart valves or mitral stenosis.

Clinical risk factors for stroke, transient ischaemic attack, and systemic embolism in the CHA₂DS₂-VASc score

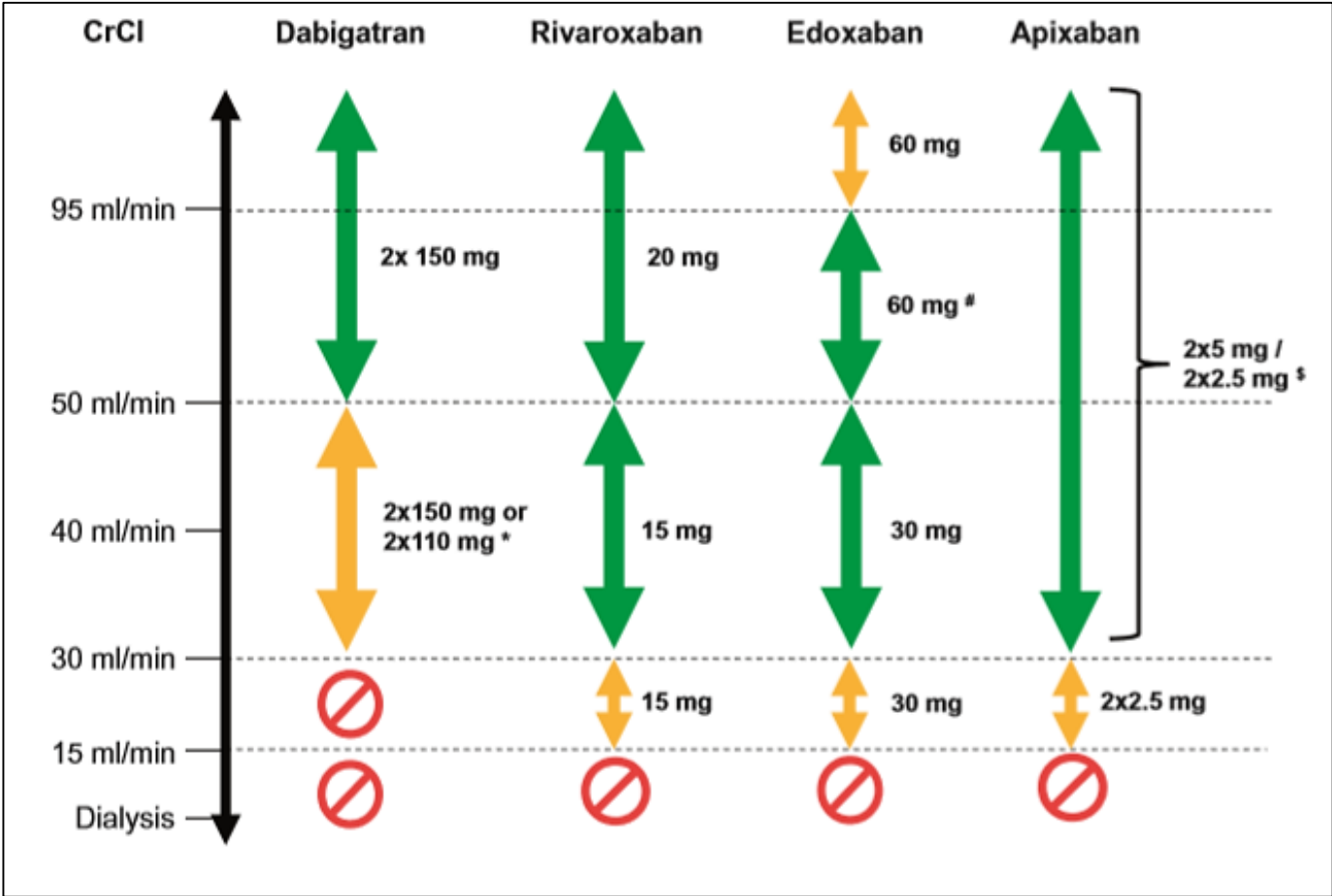
TL: Kirchhof P et al. 2016 ESC Guidelines for the management of AF. Eur H J, Aug 2016.

CHA ₂ DS 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

Dose adjustment for NOACs as evaluated in the PHASE III trials

	Dabigatran (RE-LY) ^{318, 425}	Rivaroxaban (ROCKET-AF) ^{320, 426}	Apixaban (ARISTOTLE) ^{319, 427}	Edoxaban (ENGAGE AF-TIMI 48) ³²¹
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	15 mg once daily if CrCl <30–49 mL/min	2.5 mg twice daily if serum creatinine ≥1.5 mg/dL (133 µmol/L) plus age ≥80 years or weight ≤60 kg	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 <u>eGFR >80 mL/min</u> with either dose	Major haemorrhage similar	Reduction in major haemorrhage with apixaban	NA

Use of non-vitamin K antagonist oral anticoagulants according to renal function



*in patients at high risk of bleeding (per SmPc). # Other dose reduction criteria may apply (weight <_60kg, concomitant potent P-Gp inhibitor therapy). \$ only if at least two out of three fulfilled: age >_80years, body weight <_60kg, creatinine >1.5mg/dL. Orange arrows indicate cautionary use (dabigatran in moderate renal insufficiency, Fxa inhibitors in severe renal insufficiency, edoxaban in 'supranormal' renal function)

Calculation of the Child-Turcotte-Pugh score and use of NOACs in hepatic insufficiency

Parameters	1 point	2 points	3 points
Encephalopathy	No	Grade 1–2 (suppressed with medication)	Grade 3–4 (refractory/chronic)
Ascites	No	Mild (diuretic-responsive)	Moderate–severe (diuretic-refractory)
Bilirubin	<2 mg/dL	2–3 mg/dL	>3 mg/dL
	<34 μ mol/L	34–50 μ mol/L	>50 μ mol/L
Albumin	>3.5 g/dL	2.8–3.5 g/dL	<2.8 g/dL
	>35 g/L	28–35 g/L	<28 g/dL
INR	<1.7	1.71–2.30	>2.30

Child–Pugh category	Dabigatran	Apixaban	Edoxaban	Rivaroxaban
A (5–6 points)	No dose reduction	No dose reduction	No dose reduction	No dose reduction
B (7–9 points)	Use with caution	Use cautiously	Use cautiously	Do not use
C (10–15 points)	Do not use	Do not use	Do not use	Do not use

Plasma levels and coagulation assays in patients treated with non-VKA oral anticoagulants

	Dabigatran ^{229,230}	Apixaban ²³¹ , SmPc	Edoxaban ^{184,232}	Rivaroxaban ^{131,186}
Expected plasma levels of NOACs in patients treated for AF (based on dTT/ECA for dabigatran and anti-FXa activity for Xa inhibitors)				
Expected range of plasma levels <i>at peak</i> for standard dose (ng/mL) ^a	64–443	69–321	91–321	184–343
Expected range of plasma levels <i>at trough</i> for standard dose (ng/mL) ^a	31–225	34–230	31–230	12–137
Expected impact of NOACs on routine coagulation tests				
PT	↑	(↑)	↑(↑)	↑↑(↑)
aPTT	↑↑(↑)	(↑)	↑	↑
ACT	↑(↑)	↑	↑	↑
TT	↑↑↑↑	—	—	—

Possible measures to take in case of bleeding (1)

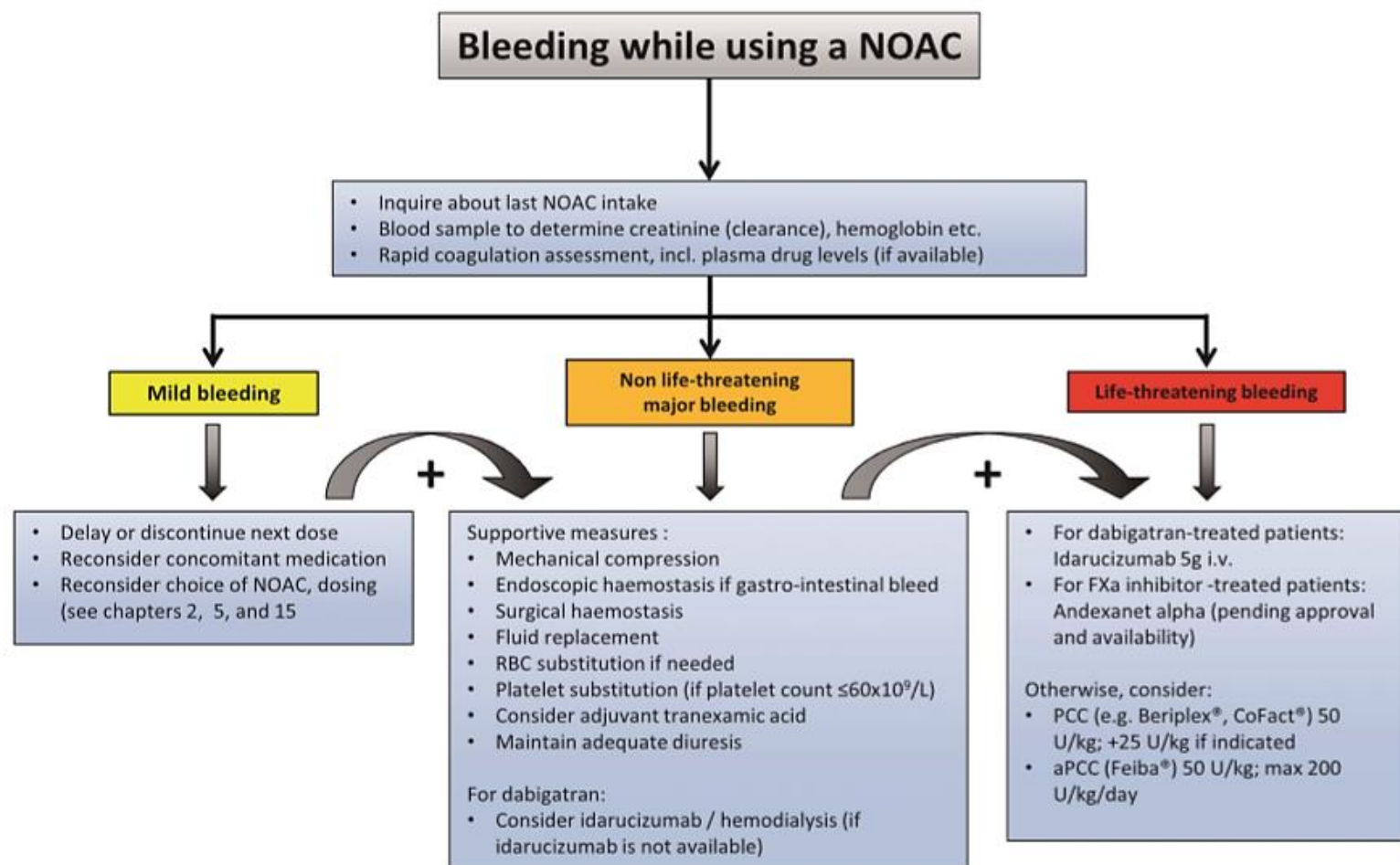
	Direct thrombin inhibitors (dabigatran)	FXa inhibitors (apixaban, edoxaban, rivaroxaban)
Non life-threatening major bleeding	● Inquire about last intake + dosing regimen ● Local haemostatic measures ● Fluid replacement ● RBC substitution, if necessary ● Platelet substitution (in case of thrombocytopenia $\leq 60 \times 10^9/L$ or thrombopathy) ● Fresh frozen plasma not as reversal agent (may be considered as plasma expander) ● Tranexamic acid can be considered as adjuvant (1 g i.v., repeat every 6 h, if necessary) ● Desmopressin can be considered in special cases such as coagulopathy or thrombopathy; 0.3 $\mu\text{g/kg}$ i.v. infusion (max dose 20 μg)	
	● Estimate normalization of plasma levels: ● Normal renal function: 12–24 h ● CrCl 50–80 mL/min: 24–36 h ● CrCl 30–50 mL/min: 36–48 h ● CrCl <30 mL/min: ≥ 48 h ● Maintain diuresis ● Consider idarucizumab (see below)	● Normalization of plasma levels: 12–24 h

Possible measures to take in case of bleeding (2)

	Direct thrombin inhibitors (dabigatran)	FXa inhibitors (apixaban, edoxaban, rivaroxaban)
Life-threatening bleeding	• All of the above • Direct reversal: Idarucizumab 5 g i.v. in two doses a 2.5 g i.v. no more than 15 min apart	• All of the above • Direct reversal: Andexanet alpha (if available and approved)^a • Bolus over 15–30 min, followed by 2-h infusion • Rivaroxaban (last intake >7 h before) or apixaban: 400 mg bolus, 480 mg infusion @ 4 mg/min • Rivaroxaban (last intake <7 h before or unknown) or enoxaparin or edoxaban: 800 mg bolus, 960 mg infusion @ 8 mg/min
	• Prothrombin complex concentrate (PCC) 50 U/kg (with additional 25 U/kg if clinically needed) • Activated PCC 50 U/kg; max 200 U/kg/day): no strong data about additional benefit over PCC. Can be considered before PCC, if available	

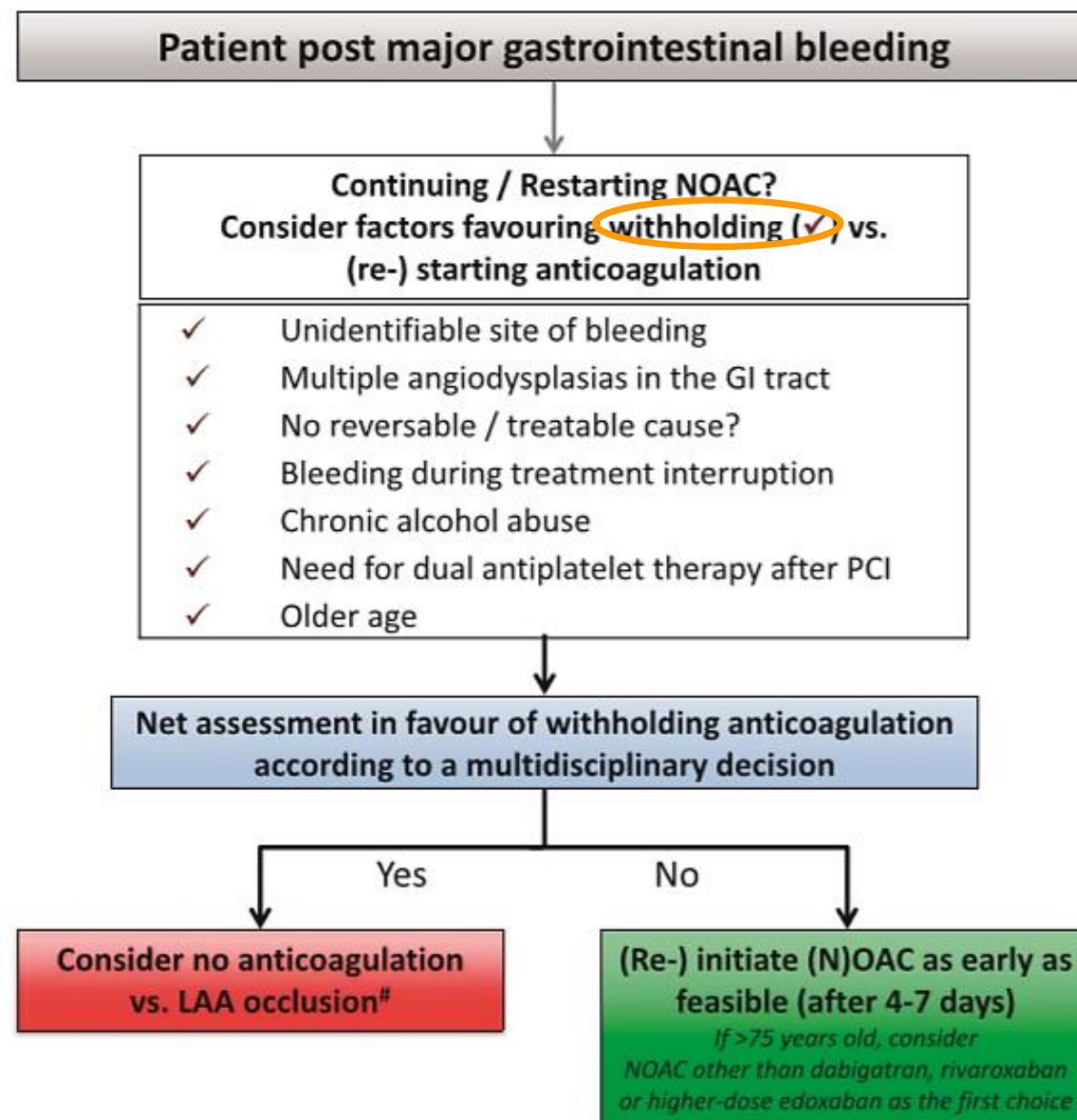
RBC, red blood cells; CrCl, creatinine clearance; PCC, prothrombin complex concentrate. ^aAndexanet alpha is currently neither approved nor available and final results of the ANNEXA-4 study are pending

Management of bleeding in patients taking non-vitamin antagonist oral anticoagulants

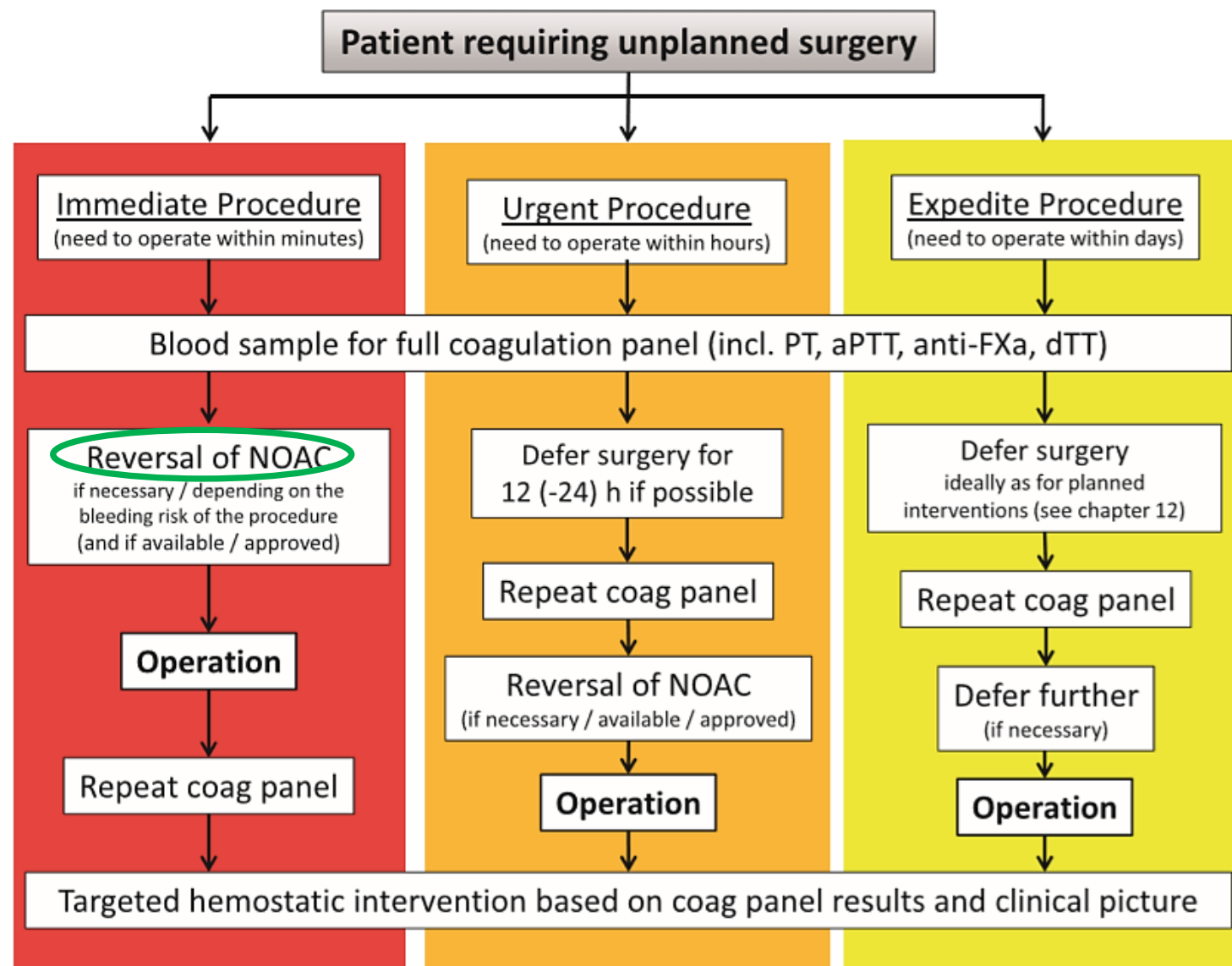


Re-initiation of anticoagulation post-gastrointestinal bleeding

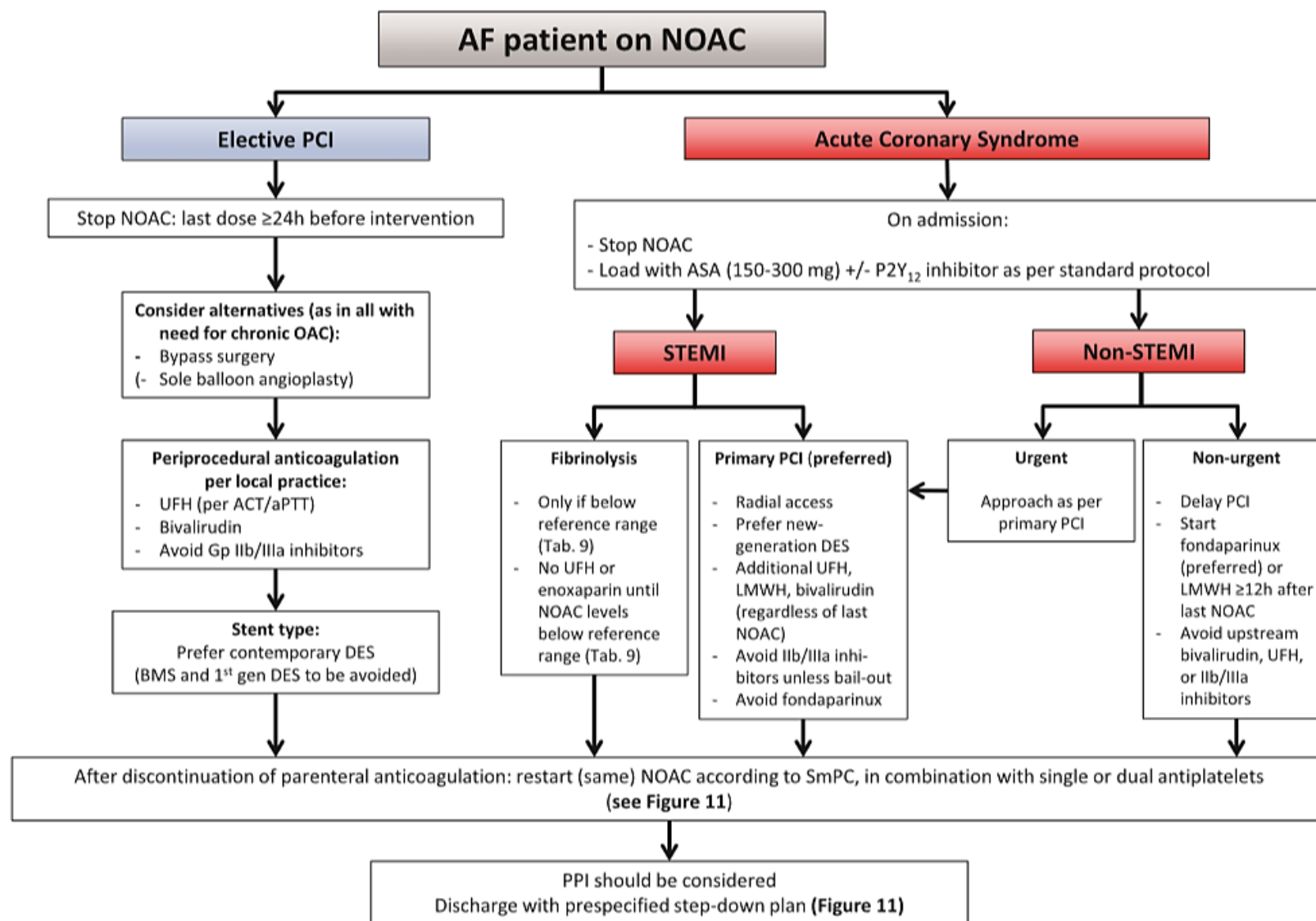
#Without evidence; ideally include patient in ongoing trial



Non-VKA oral anticoagulant management in the setting of unplanned surgery

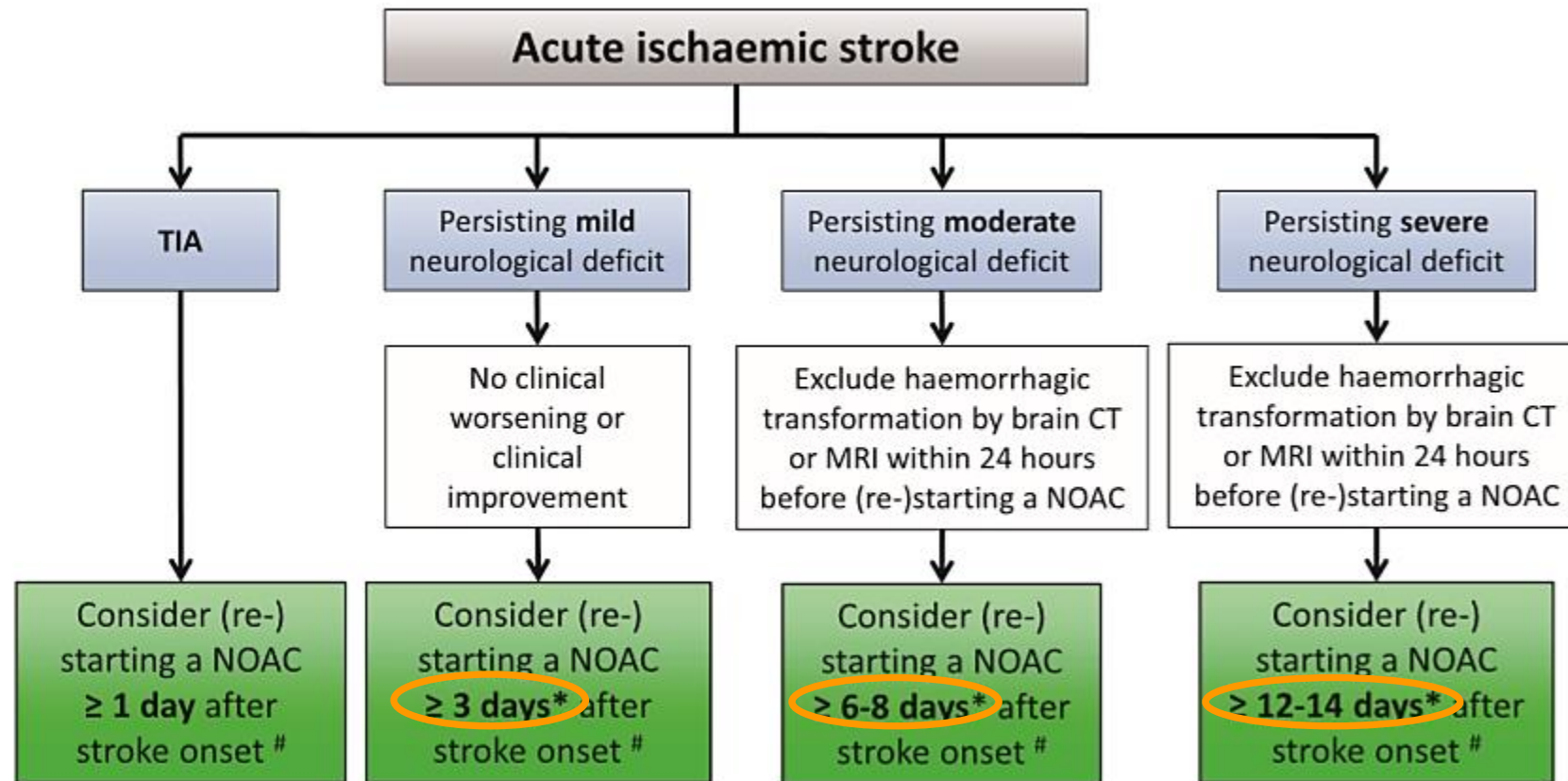


Acute management of elective PCI or ACS in AF patients treated with non-VKA oral anticoagulant



TL: Steffel J et al. The 2018 EHRA Practical Guide on the use of non-VKA oral anticoagulants in patients with AF. Eur H J, April 2018

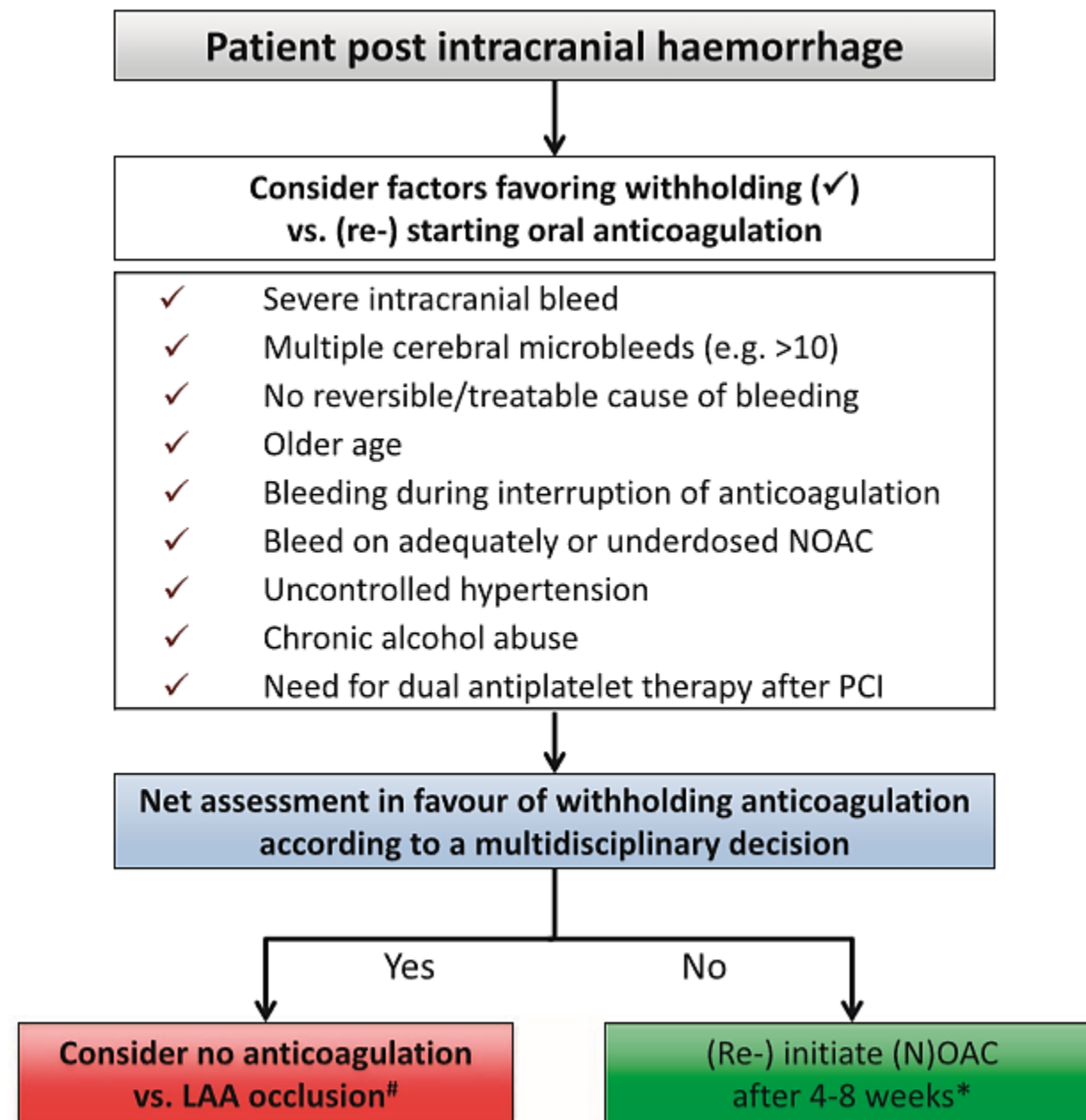
Re-initiation of anticoagulation after transient ischaemic attack/stroke



(Re-) start only in the absence of contraindications and if stroke size is not expected to substantially increase the risk of secondary haemorrhagic transformation. *Consider shorter delays to (re-) start a non-VKA oral anticoagulant if there is a very high risk of stroke recurrence (e.g. left atrial appendage thrombus) and no haemorrhagic transformation on follow-up brain imaging (using CT or MRI). Consider longer delays to (re-)start a non-VKA oral anticoagulant according to the recommendations made in the ESC AF Guidelines 2016. # Without proven evidence; consider inclusion of patient in an ongoing trial.

Re-initiation of anticoagulation post intracranial bleeding

Without evidence; ideally include the patient in an ongoing trial. *Brain imaging (CT/MRI) should be considered before (re-) initiation of (non)-VKA oral anticoagulant



Take home messages (1)

- NOACs: chống chỉ định/RN ở b/n mang van cơ học hoặc hẹp 2 lá hậu thấp
- Chức năng thận (Cockcroft-Gault) và chức năng gan: trước sử dụng NOACs
- Chuyển đổi thuốc kháng Vit K qua NOACs: bắt đầu khi INR < 2.5
- Tránh dùng đồng thời: dronedarone, rifampin, nhiều thuốc ức chế HIV protease, itraconazole, ketoconazole, voriconazole, St John's wort, dexamethasone, các thuốc nhóm P-glycoprotein, CYP3A4.

Take home messages (2)

- Sau XHTH nặng: bắt đầu lại NOACs sớm nhất khi có thể (4-7 ngày)
- XH đe dọa đến tính mạng:
 - Dabigatran: sử dụng thuốc đối kháng idarucizumab 5 mg TM x 2 (cách ≤ 15 phút).
 - Thuốc ức chế Xa: Prothrombin complex concentrate 50 UI/kg.
- B/n đang dùng NOACs bị HC/ĐMVC:
 - PCI ưu tiên đường mạch quay/NMCTSTCL
 - NMCT/KSTCL: trì hoãn can thiệp 24 – 48 giờ
- B/n NOACs bị đột quỵ TMCB:
 - Tiêu sợi huyết nếu nồng độ NOACs dưới ngưỡng thấp nhất hoặc liều cuối NOACs > 48 giờ.
 - Bắt đầu lại NOACs sau 3-14 ngày (dựa vào triệu chứng thần kinh và chuyển dạng xuất huyết)