How to Manage NOACs in Clinical Practice

Walid Amara, MD

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- Consulting and Speaker's fees from Bayer, BMS, Pfizer, Boehringer Ingelheim, Biotronik, Medtronic, Boston Scientific, Saint Jude Medical, Sorin Group, MEDA, Novartis, Servier

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Une cardioversion…

François

- 78 ans
- 65 kg, 1,72 cm
- Ramipril 5mg

Sous apixaban 2.5 mg x 2 / jours depuis 3 semaines

Mis sous amiodarone 1/j

ETT OG modérément dilatée. FEVG conservée

Adressé pour cardioversion électrique

1. faites-vous la cardioversion ?
2. Faites-vous une ETO ?
3. Modifications thérapeutiques

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CKD-EPI; Chronic Kidney Disease Epidemiology Collaboration; MDRD, Modification of Diet in Renal Disease

How to Evaluate Renal Function ?

A. Cockcroft–Gault
B. MDRD
C. CKD-EPI

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CLAIRANCE DE LA CRÉATININE

Commentaires Références

CLAIRANCE ESTIMÉE DE LA CRÉATININE (COCKROFT)

Choisissez : (•) Masculin ( ) Féminin

Entrez l'âge en années : 78

Entrez le poids en Kg : 65

Entrez la créatinine : 111 µmol/L

RÉSULTAT :

La clairance calculée est de 44.6 ml/min

CALCULER R.A.Z. QUITTER

COMMENTAIRES

La trés connue formule de Cockroft et Gault permet de façon rapide et fiable, d'estimer la clearance de la créatinine lorsqu'on ne peut disposer des urines des 24 heures. La fiabilité de cette formule est suffisante pour peut qu'on l'utilise sur des sujets adultes (20 à 100 ans) dont le poids est compris entre 50 et 75 Kg. Voici cette formule :

$$Cl_{(H)} = 1,23 \times P \times (140 - Age)/Créat_m$$
$$Cl_{(F)} = 1,04 \times P \times (140 - Age)/Créat_m$$

avec Age en années, P en Kg, $Créat_m$ en µmol/L, et le résultat en ml/min.

INTERPRETATION :

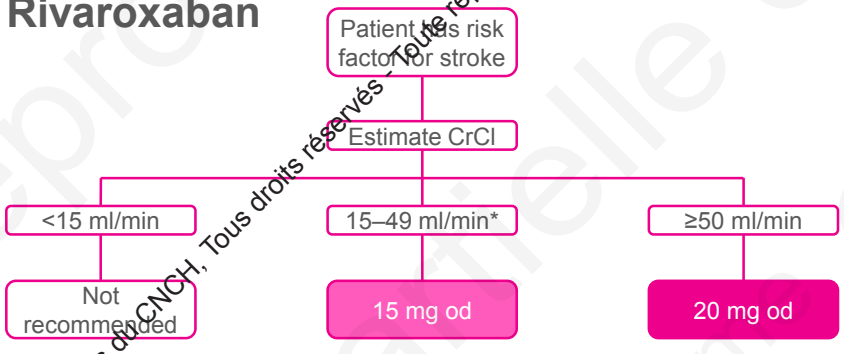
Normal de 95 pour les femmes à 120 pour les hommes +ou- 20 ml/min

RÉFÉRENCES

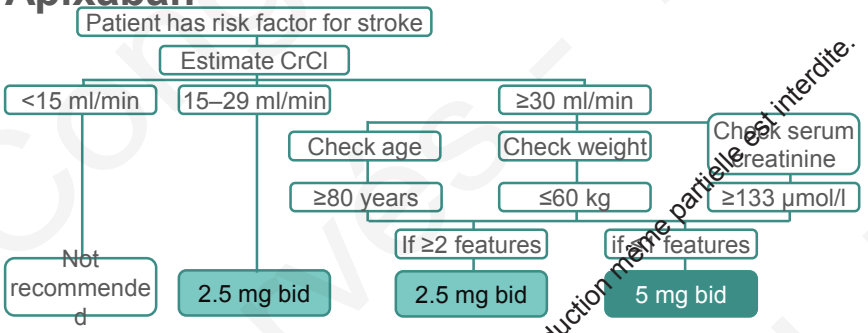
• Messaï E. "Guide des chiffres et formules utiles en pratique médicale" Ed. Arnette Blackwell (Paris) 1995. ISBN : 0184-0770-0
• Cockcroft D. Gault M.H. Nephron. 1976 ; 16 : 31-41

Dose Adjustments in Non-valvular AF

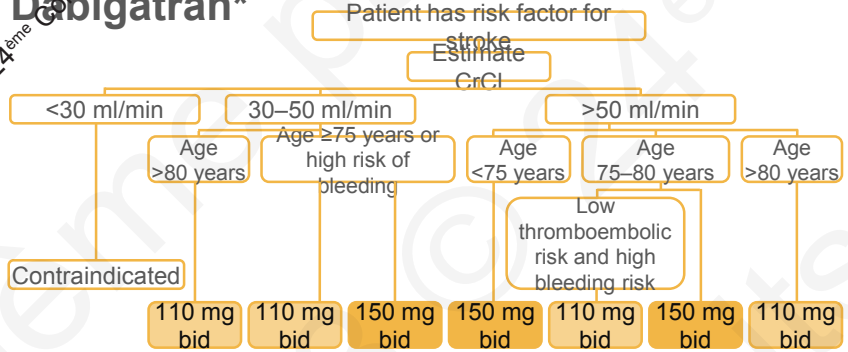
Rivaroxaban



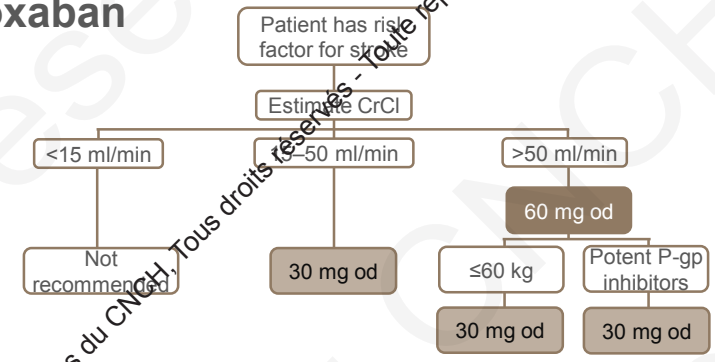
Apixaban



Dabigatran*



Edoxaban

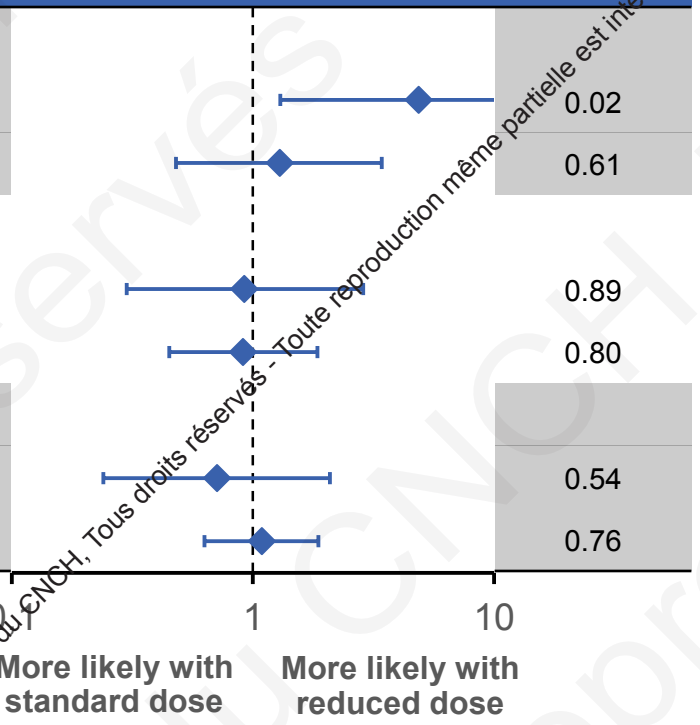


*Patients receiving concomitant dabigatran and verapamil should reduce their dabigatran dose to 110 mg bid

*1. Rivaroxaban SmPC; 2. Apixaban SmPC; 3. Dabigatran SmPC; 4. Edoxaban SmPC

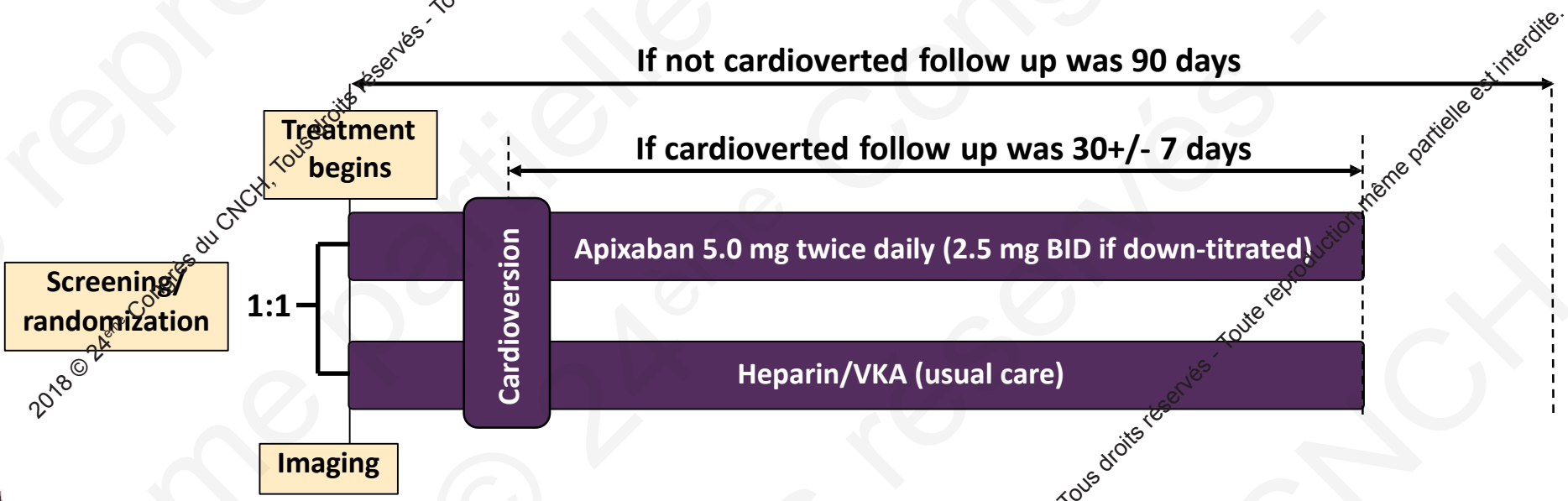
Reduced Dose NOACs in Patients Without Severe Renal Disease

	Reduced dose %/year	Standard dose %/year	HR	95% CI	*p*-value
Apixaban					
Stroke/SE	2.57	0.54	4.87	1.30–18.26	0.02
Major bleeding	6.01	4.64	1.29	0.48–3.42	0.61
Dabigatran					
Stroke/SE	1.64	1.75	0.92	0.30–2.87	0.89
Major bleeding	4.99	5.54	0.91	0.45–1.85	0.80
Rivaroxaban					
Stroke/SE	1.23	1.65	0.71	0.24–2.09	0.54
Major bleeding	5.42	4.90	1.09	0.63–1.87	0.76

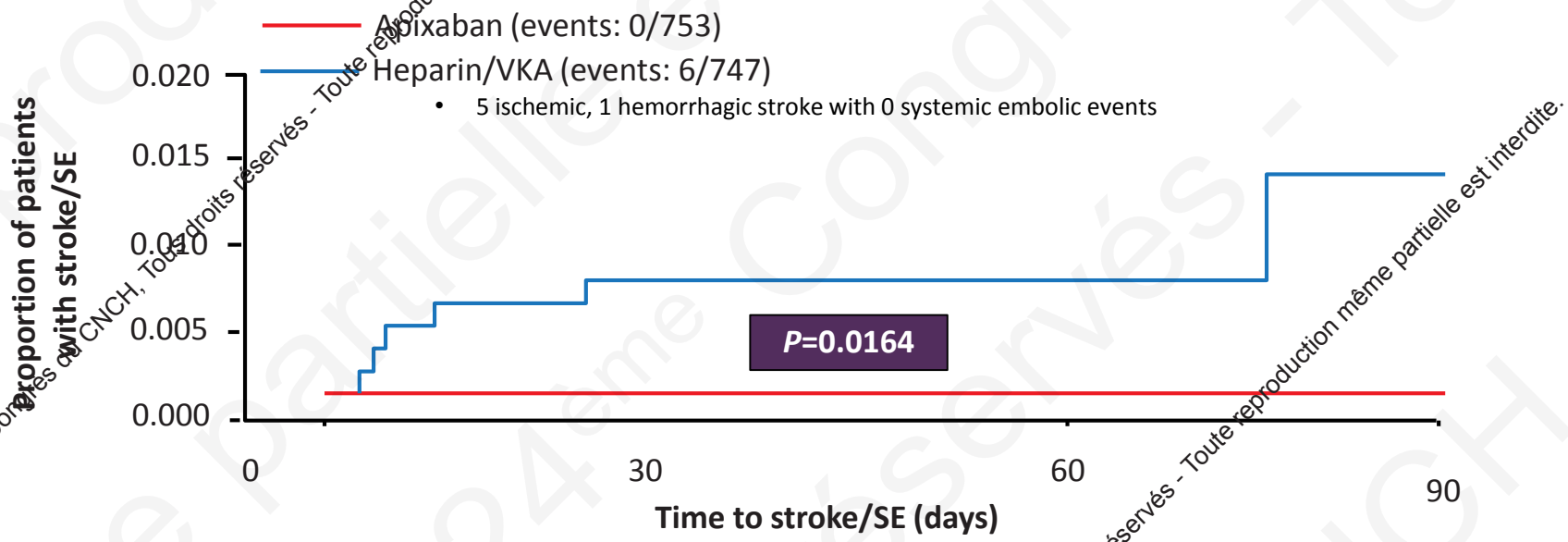


Yao X *et al. Value in Health* 2016;19:3,A2 [Presented at ISPOR 2016]

Study Design



Stroke/Systemic Embolic Outcomes



- 5 ischemic, 1 hemorrhagic stroke with 0 systemic embolic events

Number at risk

Apixaban	752	6145	199	55
Heparin/VKA	747	65	231	88

One patient's adjudicated stroke date was one day prior to randomization; thus at Day 0, only 1499 were at risk for stroke. No patients had SE.
ITT population. SE = systemic embolism

2016 ESC Guidelines

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 (2016) 37, 2893–2962

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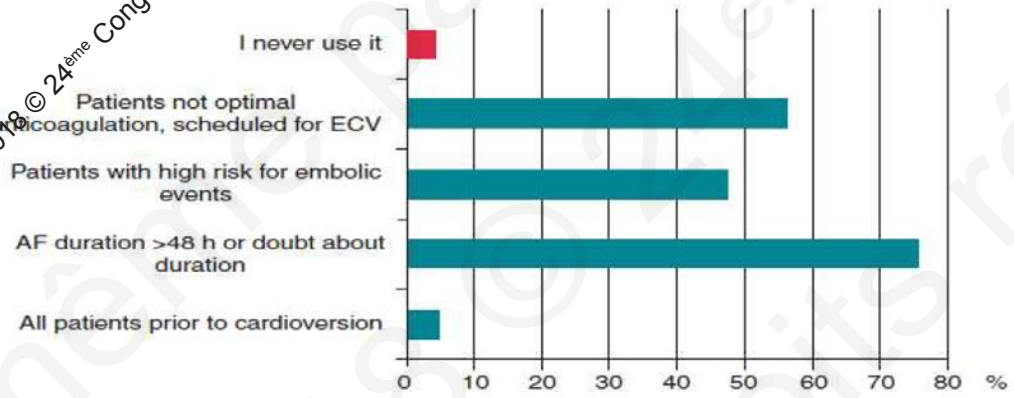
Europace (2013) 15, 915–918
doi:10.1093/europace/eut143

Cardioversion for atrial fibrillation in current European practice: results of the European Heart Rhythm Association survey

Antonio Hernández-Madrid[1]*, Jesper Hastrup Svendsen[2,3], Gregory Y.H. Lip[4], Isabelle C. Van Gelder[5], Dan Dobreanu[6], and Carina Blomstrom-Lundqvist[7] conducted by the Scientific Initiatives Committee, European Heart Rhythm Association (EHRA)

Alliance Day

Utilisation de l'ETO



- **ETO dans 48% des centres chez le patient à haut risque quelque soit durée FA**

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Feriez-vous la cardioversion en urgence ?

François

- 78 ans
- 64 kg, 1,72 cm
- Ramipril 5mg

Consulte pour palpitations évoluant depuis 2 heures responsables d'un malaise sans PC

ECG : FA. Fréquence ventriculaire à 200 bpm

1. faites-vous la cardioversion aux urgencies ?
2. Quel anticoagulant ?
3. Quelle cardioversion médicamenteuse ?

CKD-EPI; Chronic Kidney Disease Epidemiology Collaboration; MDRD, Modification of Diet in Renal Disease

Apixaban Loading Dose Option

- In patients randomized to apixaban, cardioversion could be performed 2 hours after a loading dose of 10 mg (reduced to 5 mg if 2 of the following present: age ≥ 80, weight ≤ 60 kg, serum creatinine ≥ 1.5 mg/dl [133 micromol/L).

Et s'il avait une angioplastie ?

François

- 78 ans
- 64 kg, 1,72 cm
- Ramipril 5mg

Sous apixaban 5 mg x 2 / jour

Sous FLECAINE

Angor d'effort recent. Ischémie myocardiaque en antérieur en scinti d'effort

Rentre pour coronarographie

1. Quel traitement la veille de la coro ?
2. Quel traitement à la sortie ?

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Cas

Le patient est hospitalisé la veille de sa coronarographie. Prescrivez-vous

A. Uniquement Aspirine
B. Aspirine et dose de charge de clopidogrel
C. Aspirine et dose de charge de ticagrelor
D. Un inhibiteur de la pompe à proton

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Strategies to avoid bleeding complications in patients treated with oral anticoagulant

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- Assess ischaemic and bleeding risks using validated risk predictors (e.g. CHA_2DS_2-VASc, ABC, HAS-BLED) with a focus on modifiable risk factors.
- Keep triple therapy duration as short as possible; dual therapy after PCI (oral anticoagulant and clopidogrel) to be considered instead of triple therapy.
- Consider the use of NOACs instead of VKA when NOACs are not contra-indicated.
- Consider a target INR in the lower part of the recommended target range and maximize time in therapeutic range (i.e. >65–70%) when VKA is used.
- Consider the lower NOAC regimen tested in approval studies and apply other NOAC regimens based on drug-specific criteria for drug accumulation.
- Clopidogrel is the $P2Y_{12}$ inhibitor of choice.
- Use low-dose (≤100 mg daily) aspirin.
- Routine use of PPIs.

2017 ESC Focused Update on DAPT in Coronary Artery Disease, developed in collaboration with EACTS
(European Heart Journal 2017 - doi:10.1093/eurheartj/ehx419)

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Algorithm for dual antiplatelet therapy (DAPT) in patients with an indication for oral anticoagulation Undergoing percutaneous coronary intervention (PCI)

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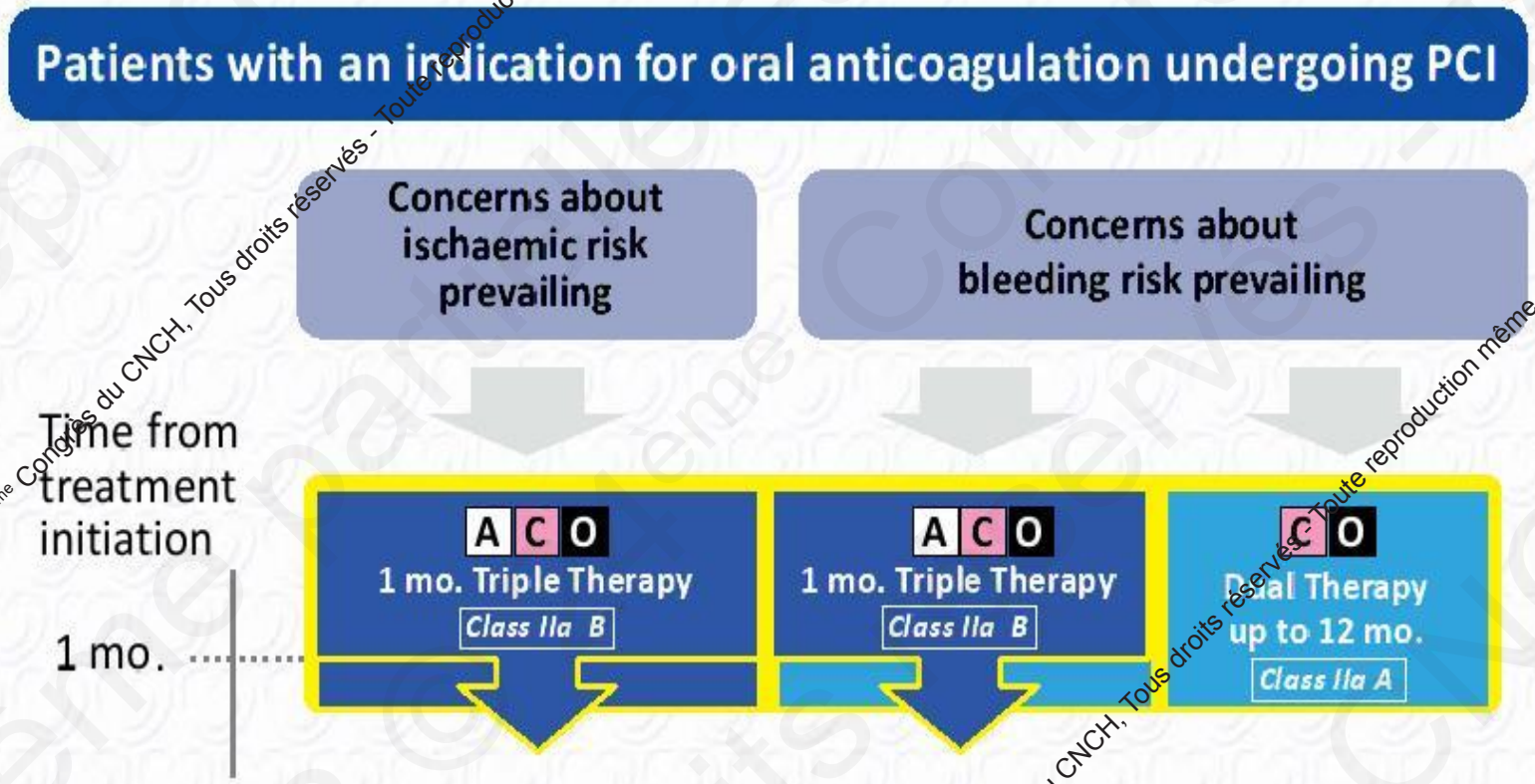

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High-risk features of stent-driven recurrent ischaemic events

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- Prior stent thrombosis on adequate antiplatelet therapy.
- Stenting of the last remaining patent coronary artery.
- Diffuse multivessel disease especially in diabetic patients.
- Chronic kidney disease (i.e. creatinine clearance <60 mL/min).
- At least three stents implanted.
- At least three lesions treated.
- Bifurcation with two stents implanted.
- Total stent length >60 mm.
- Treatment of a chronic total occlusion.

Unfavourable patient profile for a combination of oral anticoagulant and antiplatelet therapy

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- Short life expectancy.
- Ongoing malignancy.
- Poor expected adherence.
- Poor mental status.
- End stage renal failure.
- Advanced age.
- Prior major bleeding/prior haemorrhagic stroke.
- Chronic alcohol abuse.
- Anaemia.
- Clinically significant bleeding on dual antithrombotic therapy.

2017 ESC Focused Update on DAPT in Coronary Artery Disease, developed in collaboration with EACTS (European Heart Journal 2017 - doi:10.1093/eurheartj/ehx419)

Dual antiplatelet therapy duration in patients with indication for oral anticoagulation

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Recommendations	Class	Level
It is recommended to administer periprocedurally aspirin and clopidogrel in patients undergoing coronary stent implantation.	I	C
In patients treated with coronary stent implantation, triple therapy with aspirin, clopidogrel and OAC should be considered for 1 month, irrespective of the type of stent used.	IIa	B
Triple therapy with aspirin, clopidogrel and OAC for longer than 1 month and up to 6 months should be considered in patients with high ischaemic risk due to ACS or other anatomical/procedural characteristics, which outweigh the bleeding risk.	IIa	B
Dual therapy with clopidogrel 75 mg/day and OAC should be considered as an alternative to 1-month triple antithrombotic therapy in patients in whom the bleeding risk outweighs the ischaemic risk.	IIa	A

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Patients With Atrial Fibrillation Undergoing Coronary Stent Placement: PIONEER AF-PCI

- 2100 patients with NVAF
- Coronary stenting
- No prior stroke/TIA, GI bleeding, Hb<10, CrCl<30

≤72 hours
After Sheath removal

RANDOMIZE

End of treatment 12 months

Rivaroxaban 15 mg qd*
Clopidogrel 75 mg qd†
WOEST Like

⊢1,6, or 12 months⊣
Pre randomization MD Choice

Rivaroxaban 2.5 mg bid
Clopidogrel 75 mg qd†
Aspirin 75-100 mg qd‡

Rivaroxaban 15mg QD
Aspirin 75-100 mg qd
ATLAS Like

⊢1,6, or 12 months⊣
Pre randomization MD Choice

VKA$^{\Delta}$ (target INR 2.0-3.0)
Clopidogrel 75 mg qd†
Aspirin 75-100 mg qd

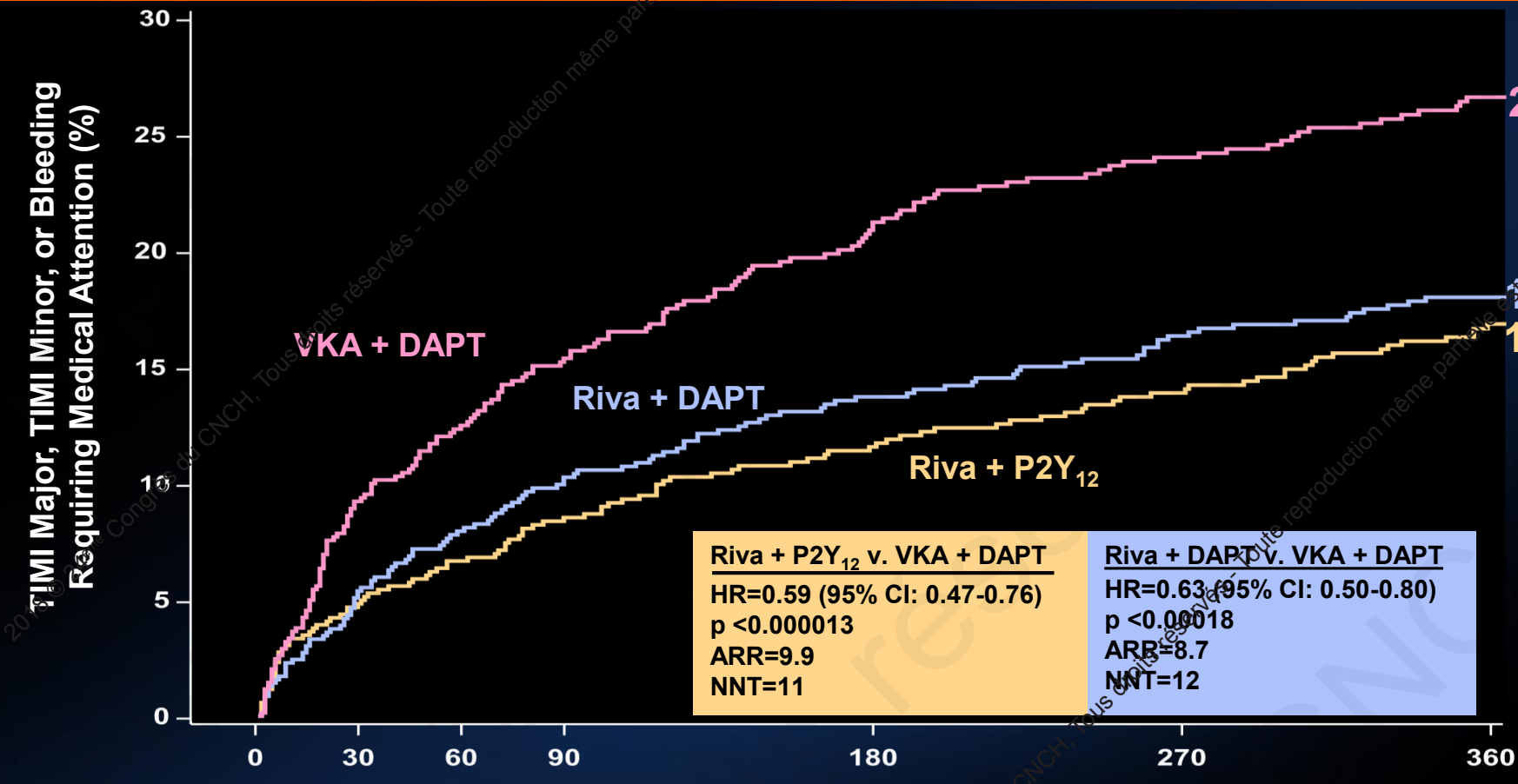
VKA$^{\Delta}$ (target INR 2.0-3.0)
Aspirin 75-100 mg qd
Triple Therapy

- **Primary endpoint: TIMI major + minor + bleeding requiring medical attention**
- **Secondary endpoint: CV death, MI, and stroke** (Ischemic, Hemorrhagic, or Uncertain Origin)

*Rivaroxaban dosed at 10 mg once daily in patients with CrCl of 30 to <50 mL/min.
†Alternative $P2Y_{12}$ inhibitors: 10 mg once-daily prasugrel or 90 mg twice-daily ticagrelor.
‡Low-dose aspirin (75-100 mg/d). Δ Open label VKA

Gibson et al. AHA 2016

Kaplan-Meier Estimates of First Occurrence of Clinically Significant Bleeding Events



No. at risk

Riva + P2Y$_{12}$	696	628	606	585	543	510	389
Riva + DAPT	696	696	666	579	563	500	409
VKA + DAPT	697	593	555	521	461	426	329

Treatment-emergent period: period starting after the first study drug administration following randomization and ending 2 days after stop of study drug.
Clinically significant bleeding is the composite of TIMI major, TIMI minor, and BRMA.
Hazard ratios as compared to the VKA group are based on the (stratified, only for Overall, 2.5 mg BID/15 mg QD comparing VKA) Cox proportional hazards model.
Log-Rank P-values as compared to VKA group are based on the (stratified, only for Overall, 2.5 mg BID/15 mg QD comparing VKA) two-sided log rank test.

Gibson et al. AHA 2016

Major Adverse Cardiac Events
All Strata

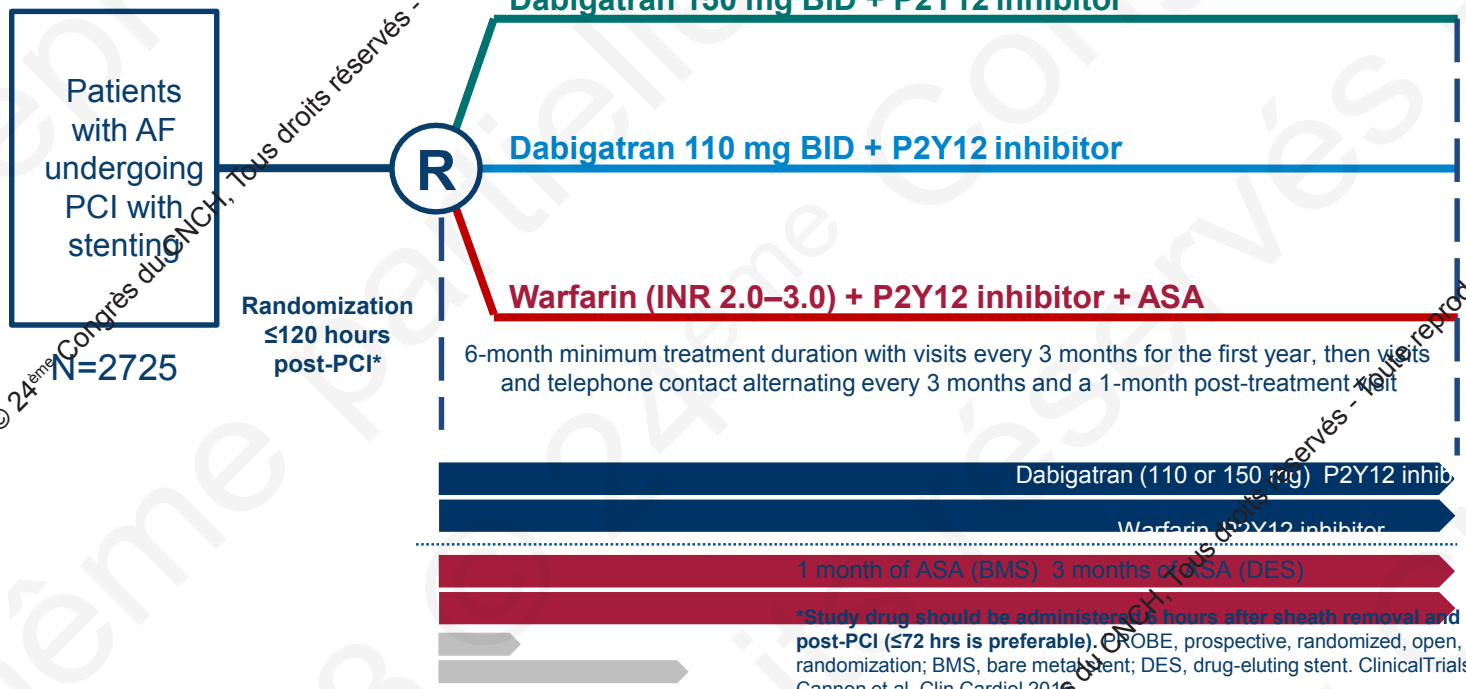
	Kaplan-Meier Estimates			Hazard Ratio (95% CI)	
Overall	Riva + $P2Y_{12}$ (N=694)	Riva + DAPT (N=704)	VKA + DAPT (N=695)	Riva + $P2Y_{12}$ vs. VKA + DAPT	Riva + DAPT vs. VKA + DAPT
Adverse CV Event	41 (6.5%)	36 (5.6%)	36 (6.0%)	1.08 (0.69-1.68) p=0.750	0.93 (0.59-1.48) p=0.765
CV Death	15 (2.4%)	14 (2.2%)	11 (1.9%)	1.29 (0.59-2.80) p=0.523	1.19 (0.54-2.62) p=0.664
MI	19 (3.0%)	17 (2.7%)	21 (3.5%)	0.86 (0.46-1.59) p=0.625	0.75 (0.40-1.42) p=0.374
Stroke	8 (1.3%)	10 (1.5%)	7 (1.2%)	1.07 (0.39-2.96) p=0.891	1.36 (0.52-3.58) p=0.530
Stent Thrombosis	5 (0.8%)	6 (0.9%)	4 (0.7%)	1.20 (0.32-4.45) p=0.790	1.44 (0.40-5.09) p=0.574
Adverse CV Events + Stent Thrombosis	41 (6.5%)	36 (5.6%)	36 (6.0%)	1.08 (0.69-1.68) P=0.750	0.93 (0.59-1.48) p=0.765

Treatment-emergent period: period starting after the first study drug administration following randomization and ending 2 days after stop of study drug.
A subject could have more than component event. n = number of subjects with events, N = number of subjects at risk, % = KM estimate at the end of study.
Hazard ratios as compared to VKA group are based on the (stratified, only for Overall, 2.5 mg BID/15 mg QD comparing VKA) Cox proportional hazards model.
Log-Rank p-values as compared to VKA group are based on the (stratified, only for Overall 2.5 mg BID/15 mg QD comparing VKA) two-sided log rank test.
CI = confidence interval, DAPT = dual antiplatelet therapy, HR = hazard ratio, VKA = vitamin K antagonist
6 Subjects were excluded from all efficacy analyses because of violations in Good Clinical Practice guidelines.

Gibson et al. AHA 2016

Study Design: Multicenter, randomized, open-label trial following a PROBE design

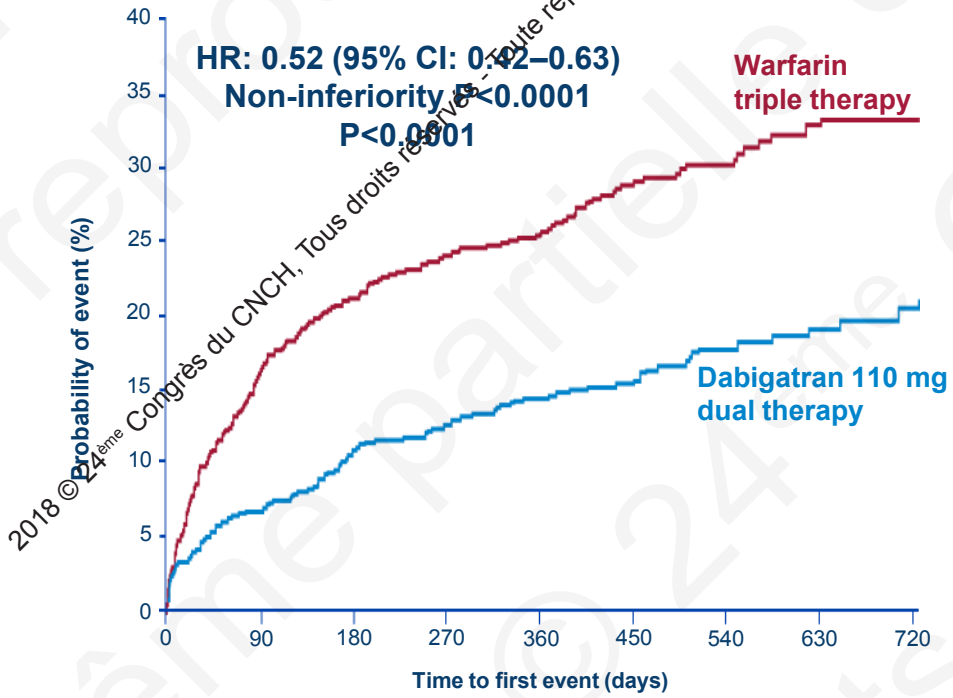
RE-DUAL PCI
Study in NVAF patients undergoing PCI

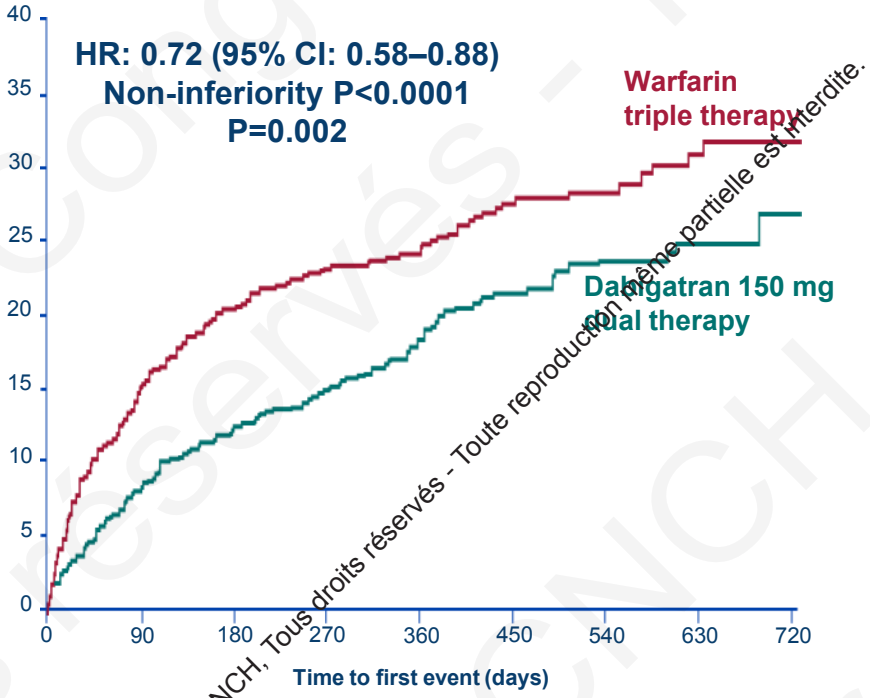


*Study drug should be administered 6 hours after sheath removal and no later than ≤120 hrs post-PCI (≤72 hrs is preferable). PROBE, prospective, randomized, open, blinded end-point; R, randomization; BMS, bare metal stent; DES, drug-eluting stent. ClinicalTrials.gov: NCT02164864; Cannon et al. Clin Cardiol 2016

Primary Endpoint: Time to first ISTH major or clinically relevant non-major bleeding event

RE-DUAL PCI
Study in NVAF patients undergoing PCI





Full analysis set presented. HRs and Wald CIs from Cox proportional-hazard model. For the dabigatran 110 mg vs warfarin comparison, the model is stratified by age, non-elderly vs elderly (<70 or ≥70 in Japan and <80 or ≥80 years old elsewhere). For the dabigatran 150 mg vs warfarin comparison, an unstratified model is used, elderly patients outside the USA are excluded. Non-inferiority P value is one sided (alpha=0.025). Wald two-sided P value from (stratified) Cox proportional-hazard model (alpha=0.05)

Apixaban Versus Warfarin in Patients with AF and ACS or PCI: The AUGUSTUS Trial

Inclusion
- AF (prior, persistent, or >6 hrs duration)
- Physician decision that oral anticoag is indicated
- ACS and/or PCI with planned P2Y12 inhibitor for 6 months

Randomize
n =4,600
Patients

Exclusion
- Contraindication to DAPT
- Other reason for warfarin (prosthetic valve, mod/sev MS)

Apixaban | **Warfarin**

P2Y12 inhibitor for all patients x 6 months
Aspirin for all on the day of ACS or PCI
Aspirin versus placebo after randomization

ASA | **placebo** | **ASA** | **placebo**

Primary outcome: major/clinically relevant bleeding (through 6 months)

Secondary objective: Death, MI, stroke, stent thrombosis

Cas

Le coronarographiste recommande ensuite une bithérapie. Pour quelle durée ?

A. 1 mois
B. 3 mois
C. 6 mois
D. 12 mois

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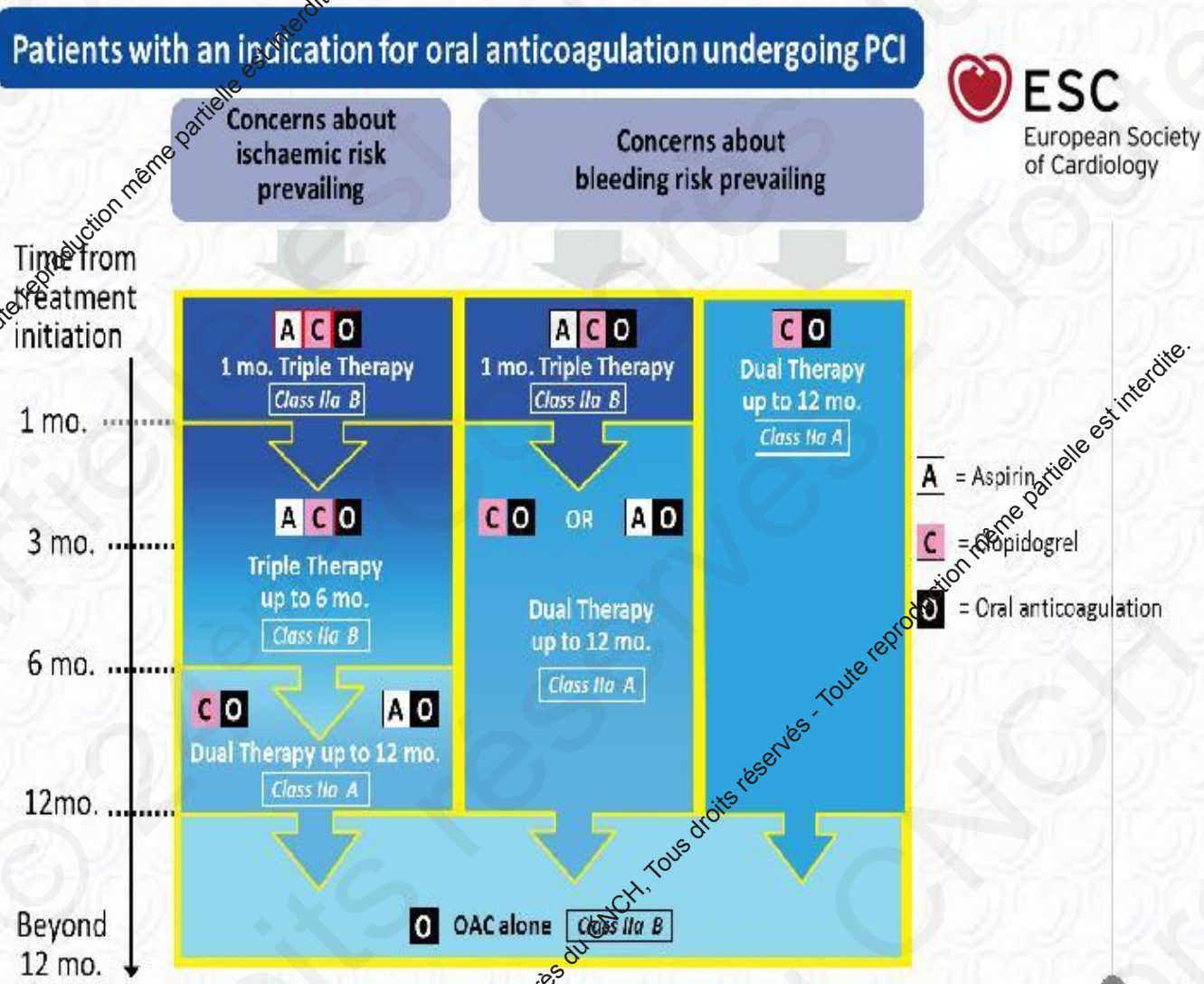
Algorithm for dual antiplatelet therapy (DAPT) in patients with an indication for oral anticoagulation undergoing percutaneous coronary intervention (PCI)



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Dual antiplatelet therapy duration in patients with indication for oral anticoagulation *(continued)*

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Recommendations	Class	Level
Discontinuation of antiplatelet treatment in patients treated with OAC should be considered at 12 months.	IIa	B
In patients with an indication for VKA in combination with aspirin and/or clopidogrel, the dose intensity of VKA should be carefully regulated with a target INR in the lower part of the recommended target range and a time in the therapeutic range >65–70%.	IIa	B
When a NOAC is used in combination with aspirin and/or clopidogrel, the lowest approved dose effective for stroke prevention tested in AFib trials should be considered.	IIa	C
When rivaroxaban is used in combination with aspirin and/ or clopidogrel, rivaroxaban 15 mg *q.d.* may be used instead of rivaroxaban 20 mg *q.d.*	IIb	B
The use of ticagrelor or prasugrel is not recommended as part of triple antithrombotic therapy with aspirin and OAC.	III	C

2017 ESC Focused Update on DAPT in Coronary Artery Disease, developed in collaboration with EACTS (European Heart Journal 2017 - doi:10.1093/eurheartj/ehx419)

Dual antiplatelet therapy duration in patients with indication for oral anticoagulation *(continued)*

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Recommendations	Class	Level
Discontinuation of antiplatelet treatment in patients treated with OAC should be considered at 12 months.	IIa	B
In patients with an indication for VKA in combination with aspirin and/or clopidogrel, the dose intensity of VKA should be carefully regulated with a target INR in the lower part of the recommended target range and a time in the therapeutic range >65–70%.	IIa	B
When a NOAC is used in combination with aspirin and/or clopidogrel, the lowest approved dose effective for stroke prevention tested in AFib trials should be considered.	IIa	C
When rivaroxaban is used in combination with aspirin and/ or clopidogrel, rivaroxaban 15 mg *q.d.* may be used instead of rivaroxaban 20 mg *q.d.*	IIb	B
The use of ticagrelor or prasugrel is not recommended as part of triple antithrombotic therapy with aspirin and OAC.	III	C

2017 ESC Focused Update on DAPT in Coronary Artery Disease, developed in collaboration with EACTS (European Heart Journal 2017 - doi:10.1093/eurheartj/ehx419)

Le dentiste envisage une extraction dentaire :

François

- 78 ans
- 64 kg, 1,72 cm
- Ramipril 5mg

Sous apixaban 5 mg x 2 / jour et bêtablooquant

?

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Classification of elective surgical interventions according to bleeding risk

Interventions with minor bleeding risk
Dental interventions
Extraction of 1–3 teeth
Paradontal surgery
Incision of abscess
Implant positioning
Cataract or glaucoma intervention
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Pacemaker or ICD implantation (unless complex anatomical setting, e.g. congenital heart disease)

Interventions with high bleeding risk (i.e. frequent and/or with high impact)
Complex endoscopy (e.g. polypectomy, ERCP with sphincterotomy etc.)
Spinal or epidural anaesthesia; lumbar diagnostic puncture
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Abdominal surgery
Major orthopaedic surgery
Liver biopsy
Transurethral prostate resection
Kidney biopsy
Extracorporeal shockwave lithotripsy (ESWL)
Interventions with high bleeding risk AND increased thromboembolic risk
Complex left-sided ablation (pulmonary vein isolation; some VT ablations)

For each patient, individual factors relating to bleeding and thromboembolic risk need to be taken into account, and be discussed with the operating physician.

Steffel et al., EHRA Practical Guide, European Heart Journal 2018

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Perioperative management of NOACs

Table 11 Timing of last non-vitamin K antagonist oral anticoagulant intake before start of an elective intervention

	Dabigatran		Apixaban – Edoxaban – Rivaroxaban	
	No important bleeding risk and/or adequate local haemostasis possible: perform at trough level (i.e. 12 h or 24 h after last intake)			
	Low risk	High risk	Low risk	High risk
CrCl ≥80 mL/min	≥24 h	≥48 h	≥24 h	≥48 h
CrCl 50–79 mL/min	≥36 h	≥72 h	≥24 h	≥48 h
CrCl 30–49 mL/min	≥48 h	≥96 h	≥24 h	≥48 h
CrCl 15–29 mL/min	Not indicated	Not indicated	≥36 h	≥48 h
CrCl <15 mL/min	No official indication for use			
No bridging with LMWH/UFH				
Resume full dose of NOAC ≥24 h post-low bleeding risk interventions and 48 (–72) h post-high bleeding risk interventions (see also *Figure 8*)				
Patients undergoing a planned intervention should receive a written note indicating the anticipated date and time of their intervention, and the date and time of the last intake of their NOAC (and any other medication)				

Low risk: with a low frequency of bleeding and/or minor impact of a bleeding; high risk: with a high frequency of bleeding and/or important clinical impact. See also *Table 12*.
CrCl, creatinine clearance; LMWH, low molecular weight heparin; UFH, unfractionated heparin.

Steffel et al., EHRA Practical Guide, European Heart Journal 2018

Collège National des Cardiologues des Hôpitaux

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 Verhamme[2], Tatjana S. Potpara[3], Pierre Albaladejo[4], Matthias Antz[5], Lien Desteghe[6], Karl Georg Haeusler[7], Jonas Oldgren[8], Holger Reinecke[9], Vanessa Roldan-Schilling[10], Nigel Rowell[11], Peter Sinnaeve[2], Ronan Collins[12], A. John Camm[13], and Hein Heidbüchel[6,14]

Back up

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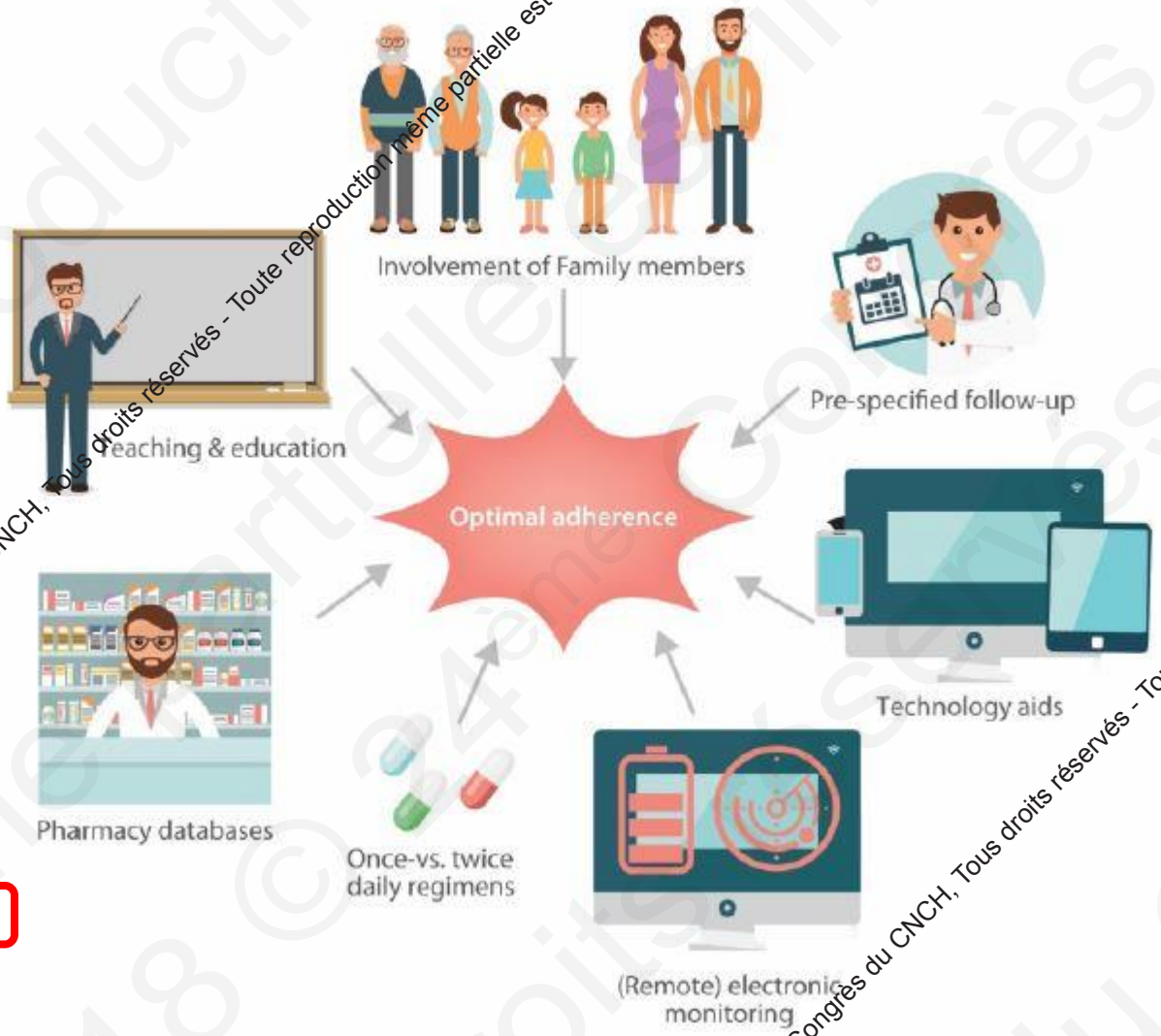
Practical considerations to ensure adherence



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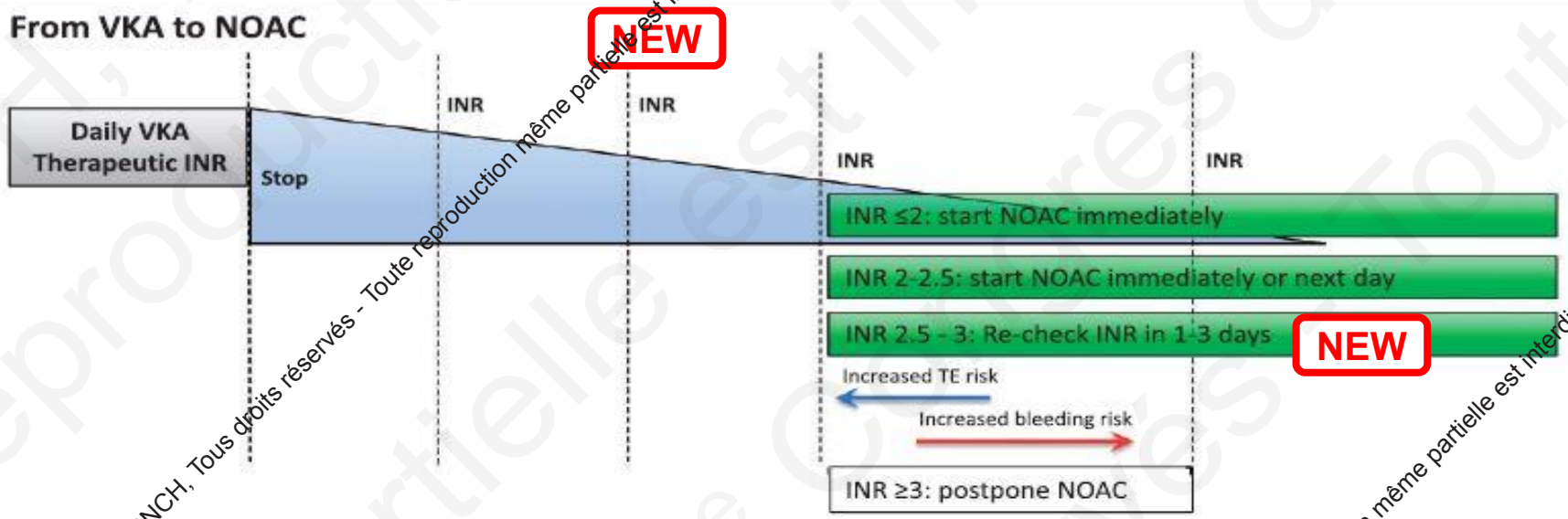
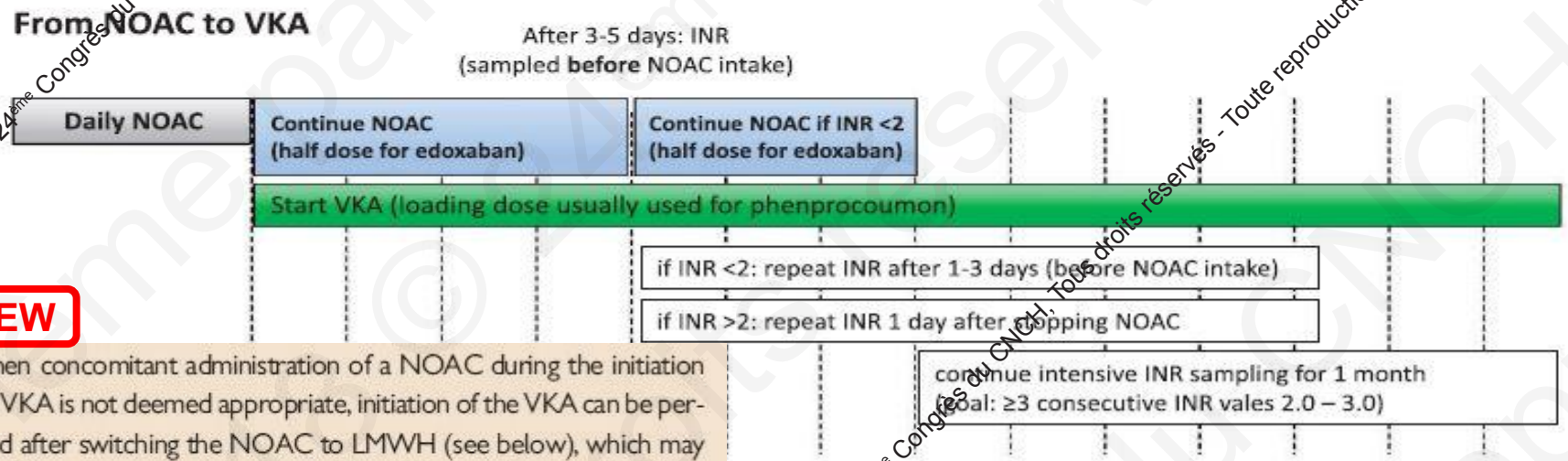
Switching between anticoagulant regimens





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When concomitant administration of a NOAC during the initiation of the VKA is not deemed appropriate, initiation of the VKA can be performed after switching the NOAC to LMWH (see below), which may be considered especially in patients with a high thromboembolic risk.

Figure 2 Switching between vitamin K antagonists and non-vitamin K antagonist oral anticoagulants and vice versa. TE, thromboembolic.

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Management of bleeding under NOAC therapy

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Management of bleeding under NOAC therapy

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Table 10 Possible measures to take in case of bleeding

	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 ≤60 × 109/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 µg/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

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)*
		  • 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 is available	

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

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Management of bleeding under NOAC therapy

New scheme on how to use reversal agents

(for andexanet alfa pending approval)

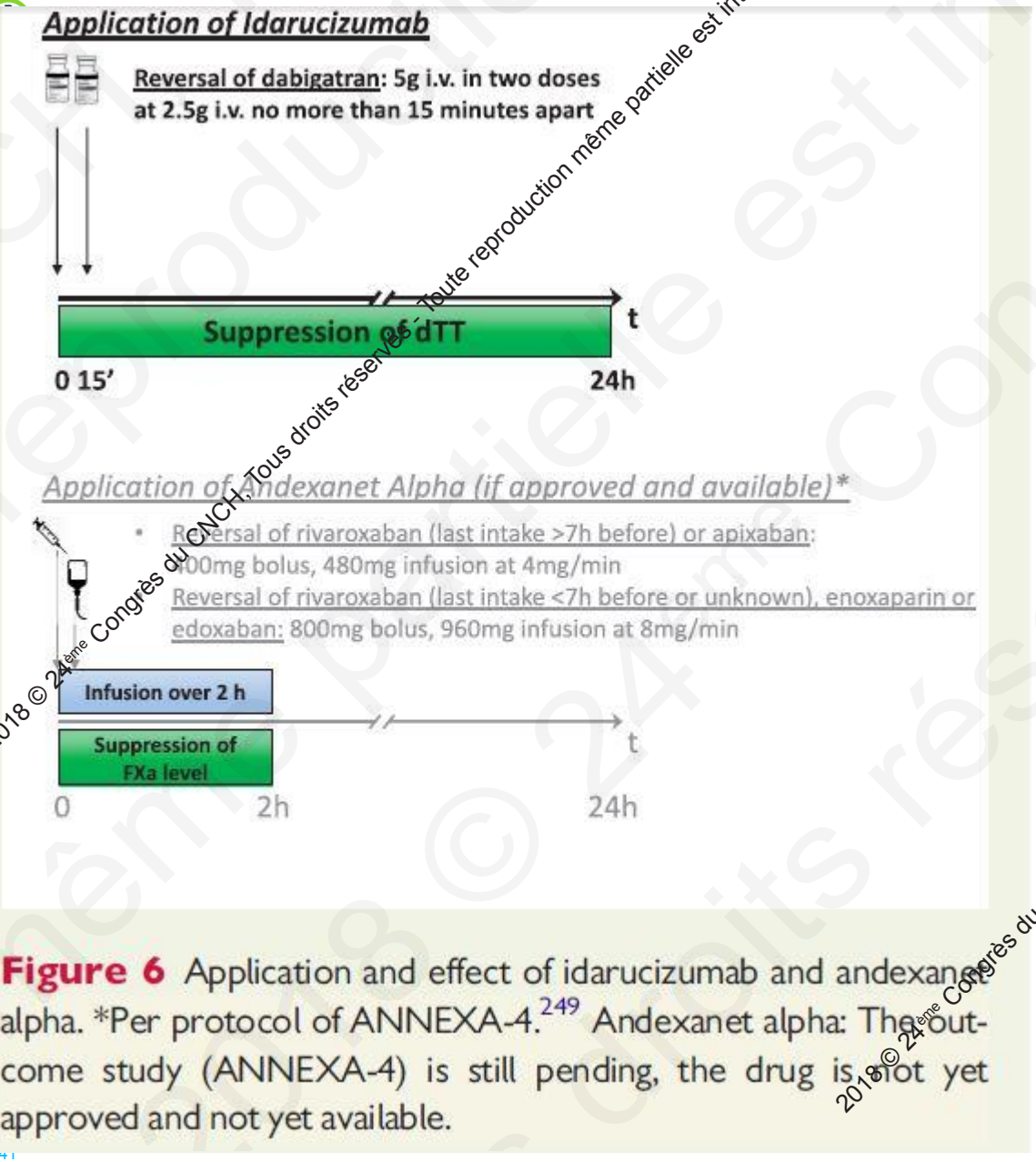

Figure 6 Application and effect of idarucizumab and andexanet alpha. *Per protocol of ANNEXA-4.[249] Andexanet alpha: The outcome study (ANNEXA-4) is still pending, the drug is not yet approved and not yet available.

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Management of bleeding under NOAC therapy

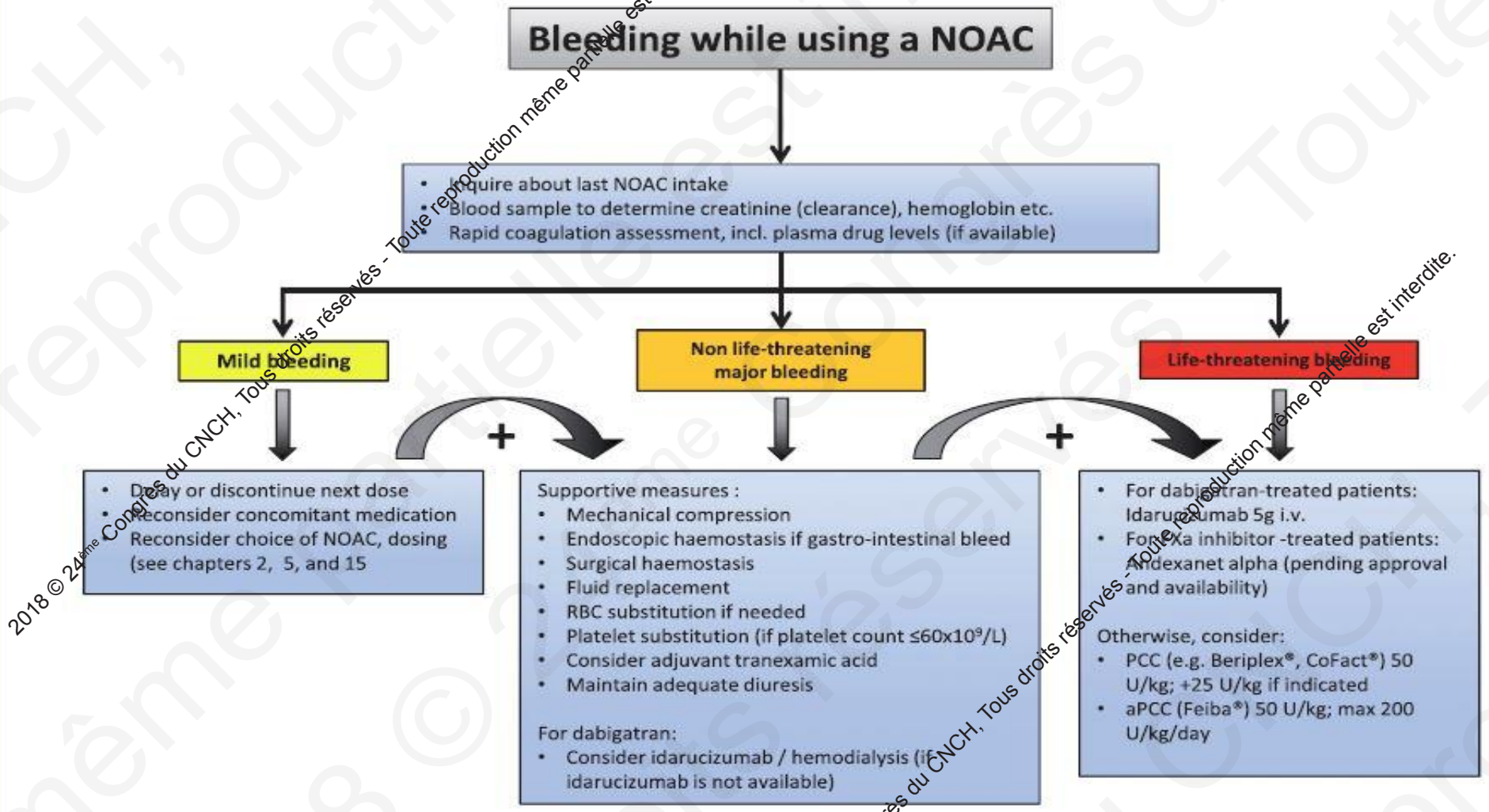

Figure 5 Management of bleeding in patients taking non-vitamin K antagonist oral anticoagulants.

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Patients undergoing a planned invasive procedure, surgery or ablation

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Special considerations for AF ablation

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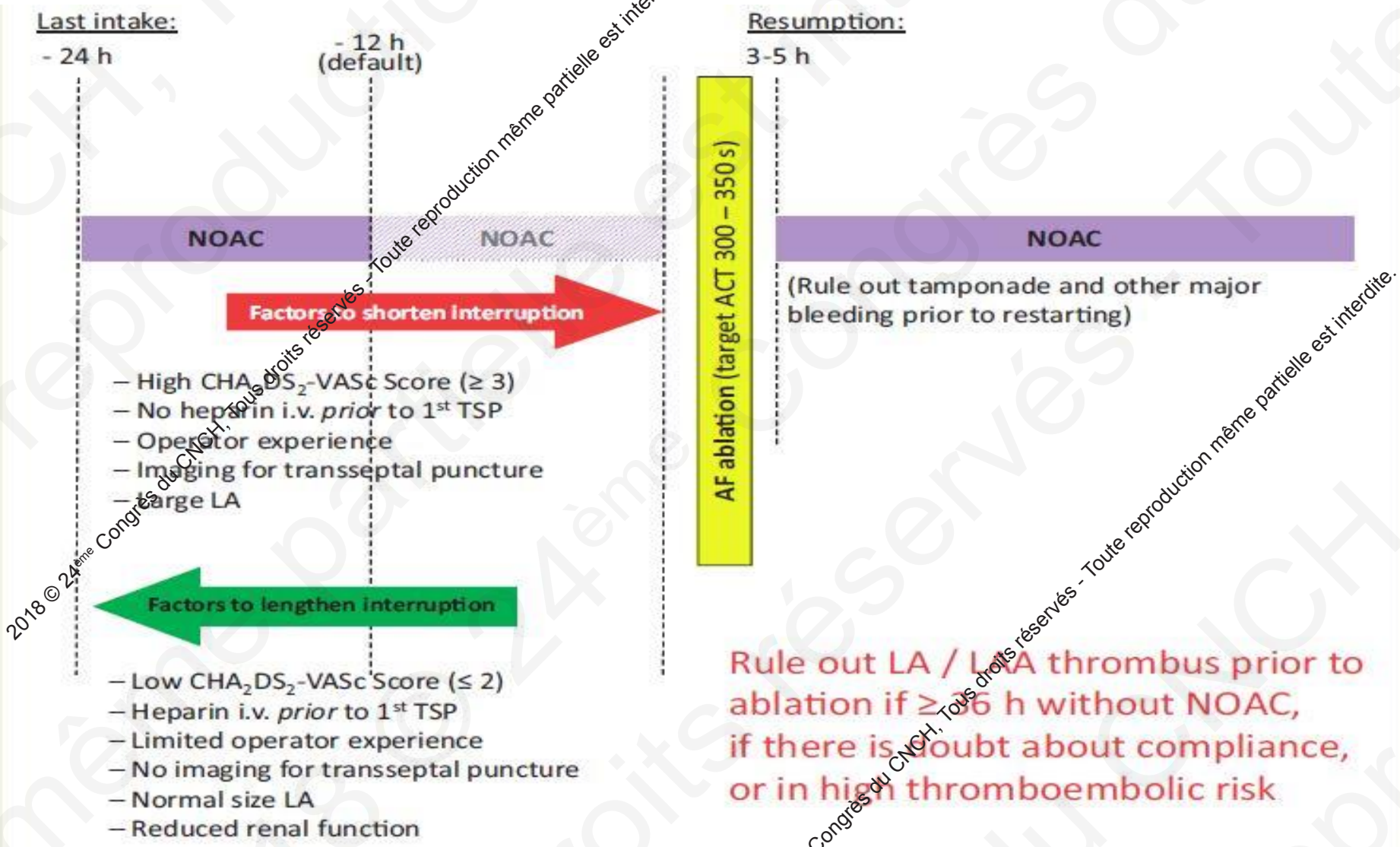

Figure 3 Non-vitamin K antagonist oral anticoagulant management before and after atrial fibrillation ablation. ACT, activated clotting time; AF, atrial fibrillation; LA, left atrium; LAA, left atrial appendage; NOAC, non-vitamin K antagonist oral anticoagulant; TSP, transseptal puncture.

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Patient requiring an urgent surgical intervention

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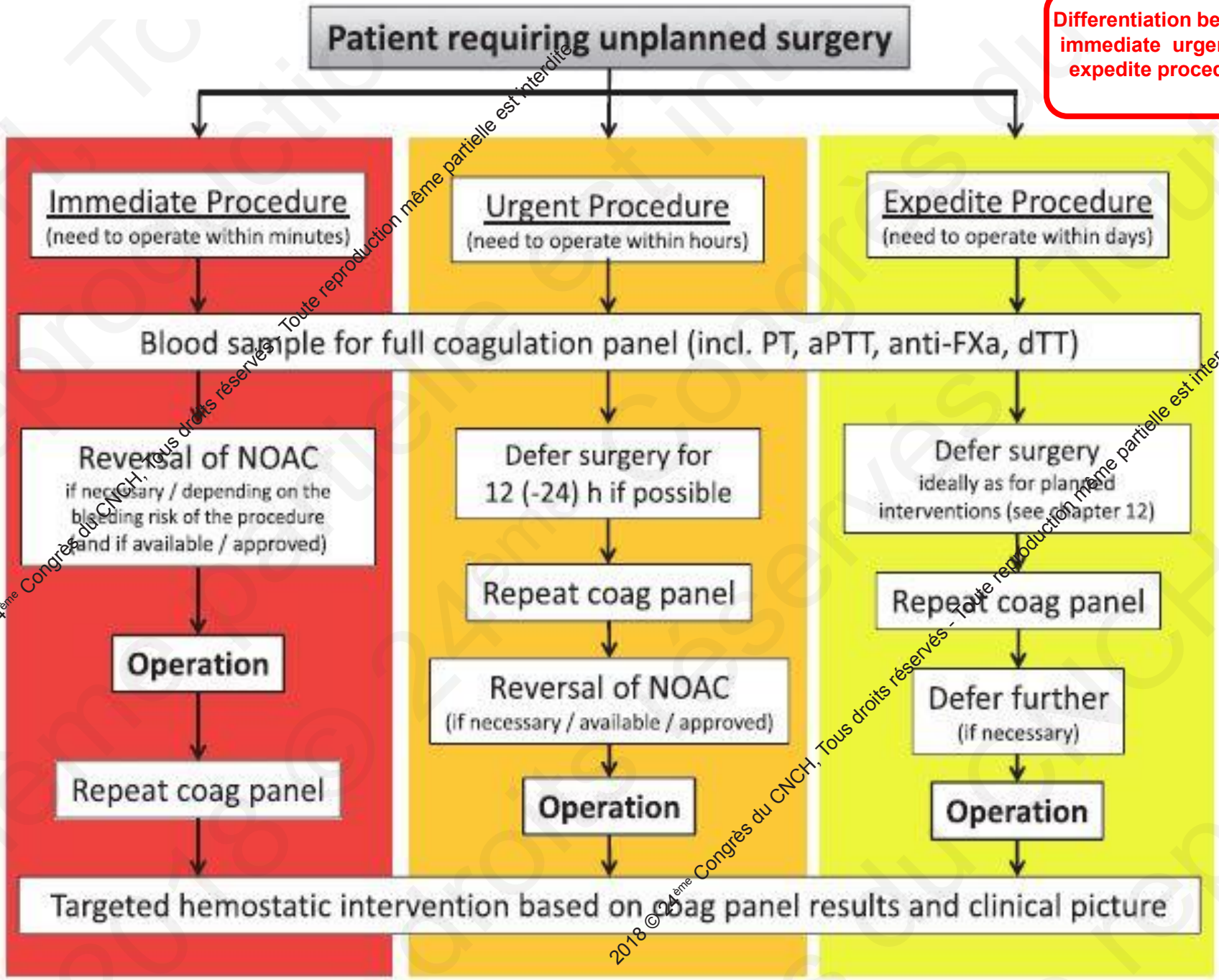

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Patient with AF and CAD

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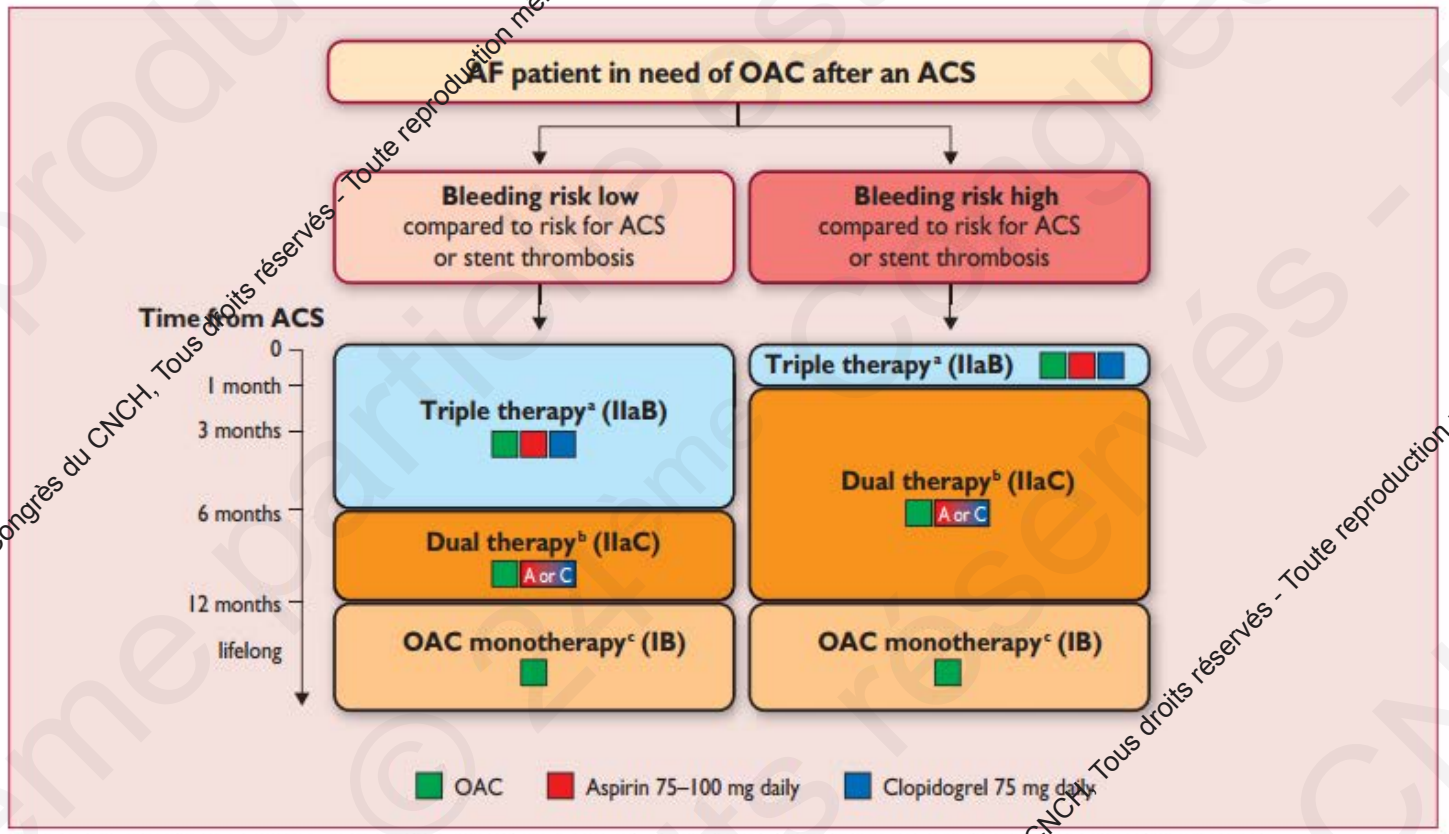

ACS = acute coronary syndrome; AF = atrial fibrillation; OAC = oral anticoagulation (using vitamin K antagonists or non-vitamin K antagonist oral anticoagulants); PCI = percutaneous coronary intervention.

[a]Dual therapy with OAC and aspirin or clopidogrel may be considered in selected patients, especially those not receiving a stent or patients at a longer time from the index event.

[b]OAC plus single antiplatelet.

[c]Dual therapy with OAC and an antiplatelet agent (aspirin or clopidogrel) may be considered in patients at high risk of coronary events.

Figure 12 Antithrombotic therapy after an acute coronary syndrome in atrial fibrillation patients requiring anticoagulation.

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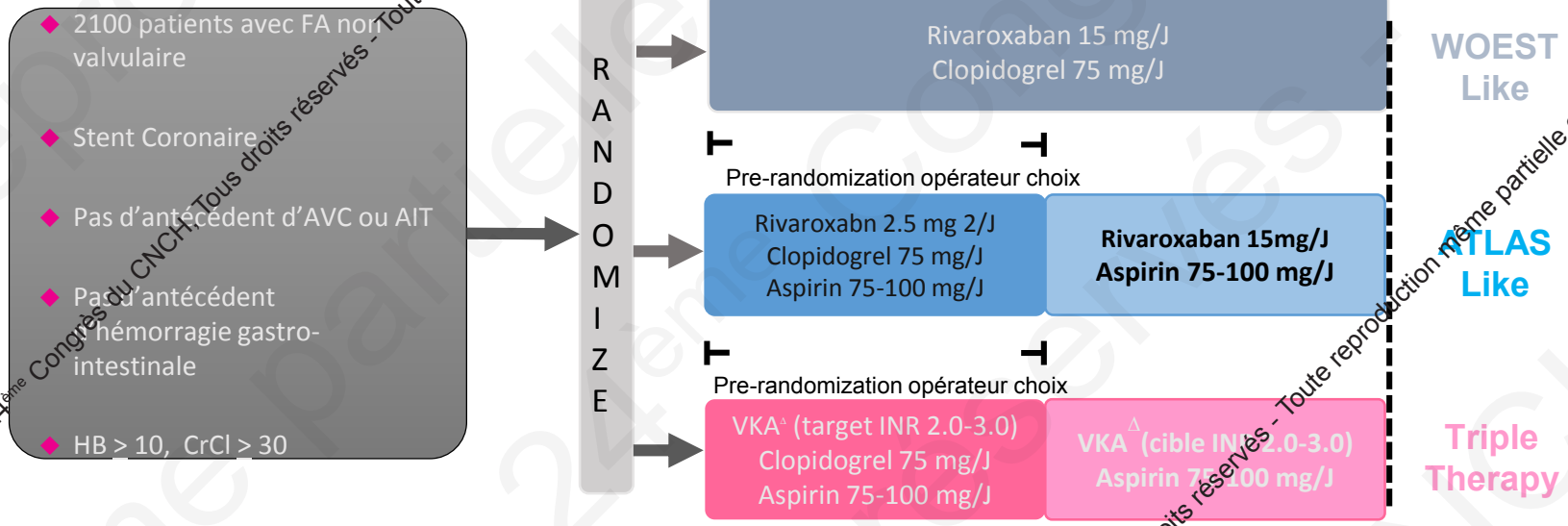
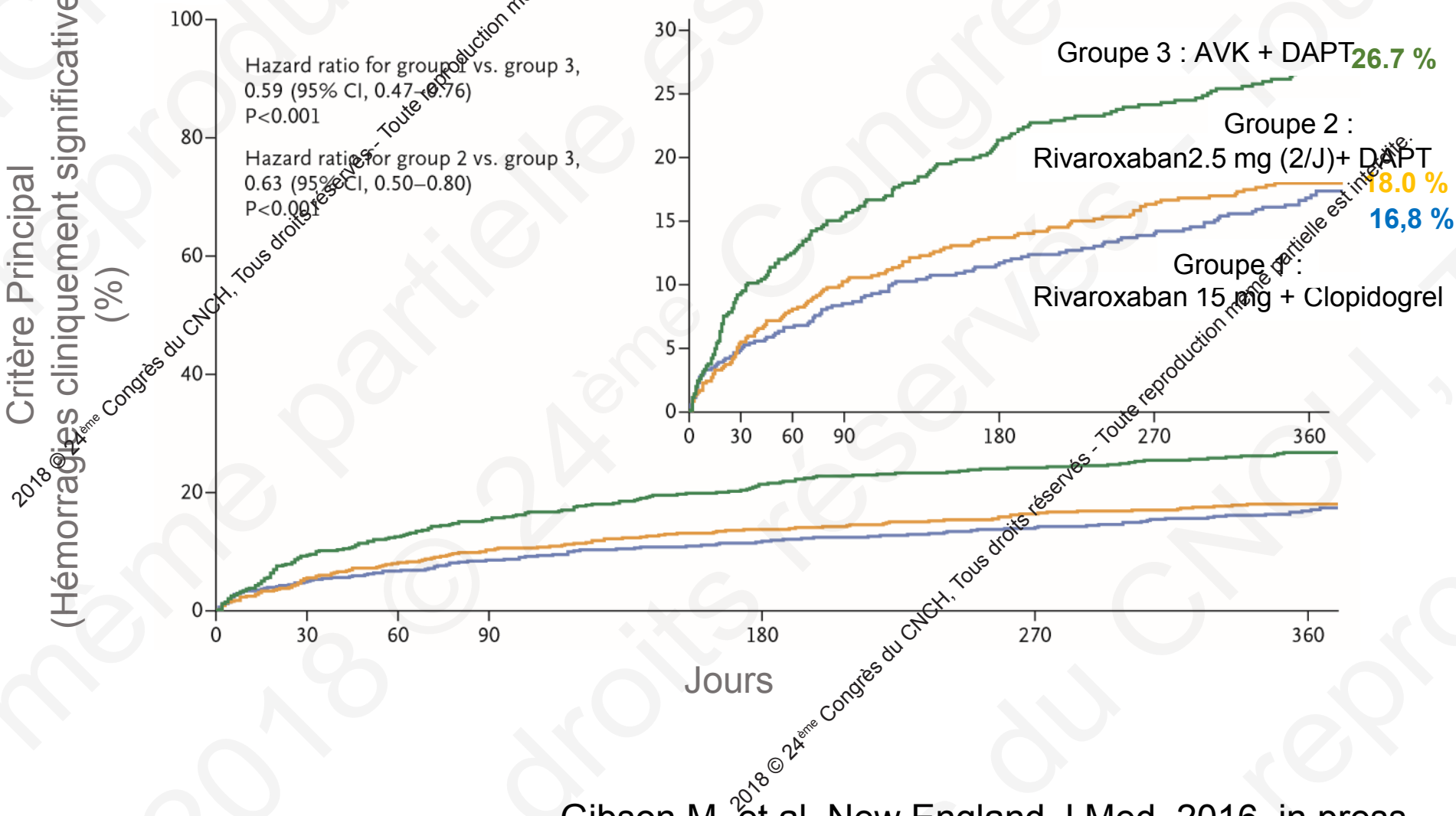
PIONEER AF-PCI

2124 Patients avec une fibrillation atriale ayant bénéficiés un stenting

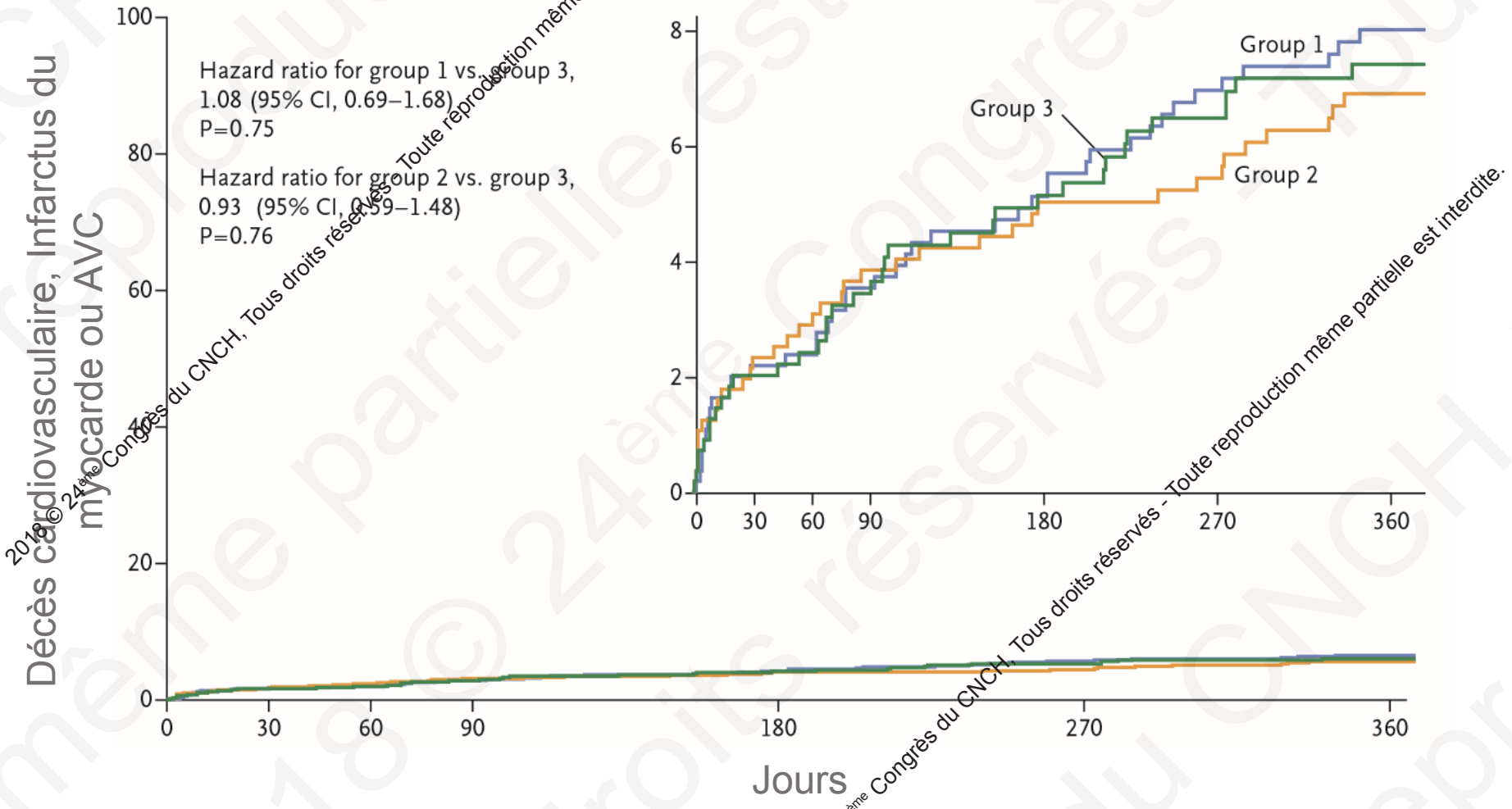


- Critère de Jugement : Hémorragie majeure selon TIMI + Hémorragie mineure ou hémorragie nécessitant une attention médicale
- Critère de jugement secondaire : Décès cardiovasculaire, infarctus du myocarde ou AVC (ischémique, hémorragique ou non déterminé)

Gibson M, et al. New England J Med. 2016. in press



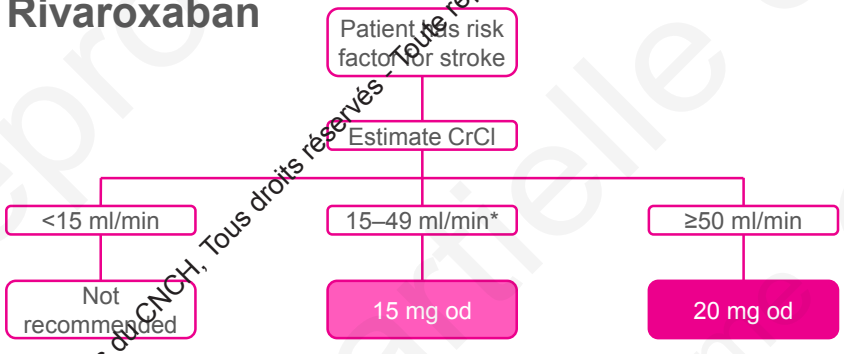
Gibson M, et al. New England J Med. 2016. in press



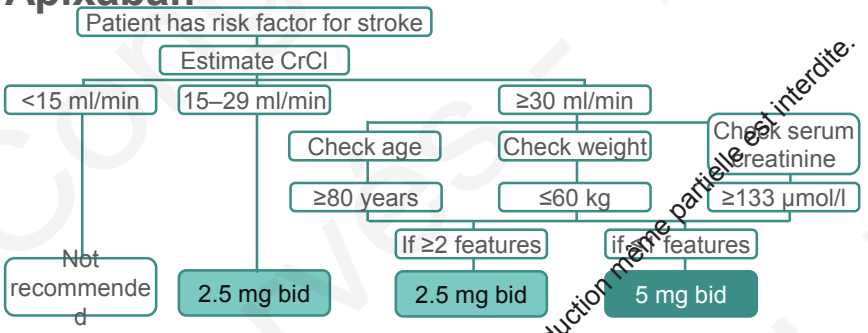
Gibson M, et al. New England J Med. 2016. in press

Dose Adjustments in Non-valvular AF

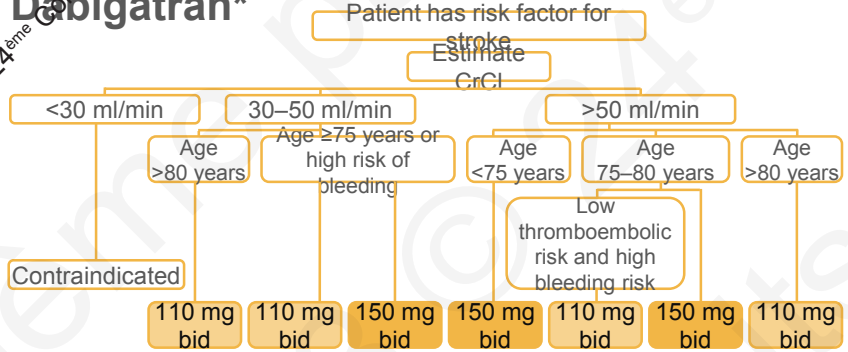
Rivaroxaban



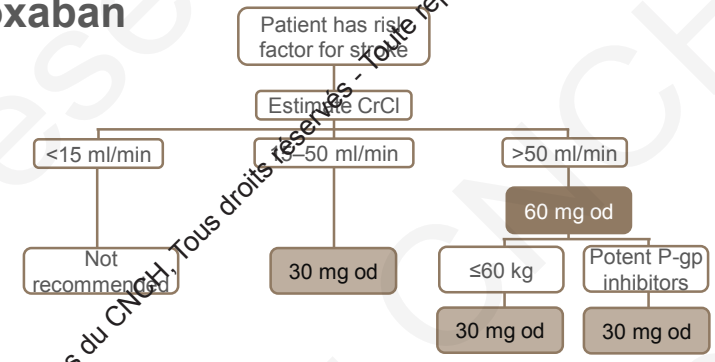
Apixaban



Dabigatran*



Edoxaban



*Patients receiving concomitant dabigatran and verapamil should reduce their dabigatran dose to 110 mg bid

*1. Rivaroxaban SmPC; 2. Apixaban SmPC; 3. Dabigatran SmPC; 4. Edoxaban SmPC

Conclusion

- NOACs demonstrated higher efficacy and safety in comparison with VKA in non valvular atrial fibrillation
- NOACs are used in different clinical situations
- The EHRA guide is useful and addresses all these practical situations and beyond

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