"Symposium on Atrial Fibrillation"

Anesthetic Implications of Atrial Fibrillation Therapy

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June, 17 2018

CHUM

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NO CONFLICT OF INTERESTS

OBJECTIVES

- Address the anesthetic considerations related to the various pharmacologic agents used in the treatment of atrial fibrillation (AF)
  - Anesthetic considerations of antiarrhythmic agents
  - Implications of direct oral anticoagulants (DOACs) on anesthesia, especially regional anesthesia

OVERVIEW

- Introduction of AF therapy
- **Antiarrhythmics**
  - classification and mechanism of action
  - adverse effects
  - drug interactions and considerations in anesthesia
- **Anticoagulants**
  - stroke prevention
  - Direct Oral AntiCoagulants (DOACS)
  - regional anesthesia
- Conclusions

Pharmacological treatment of AF

- AF is the most common cardiac arrhythmia
- Estimated prevalence of 33.5 million individuals
  - affected individuals with AF is expected to double in the next several decades because of older population

- What to address?
  - thromboembolism prophylaxis when AF is detected
  - treatment options fall into 2 broad overlapping categories: rate or rhythm control

Management of atrial fibrillation (AF)

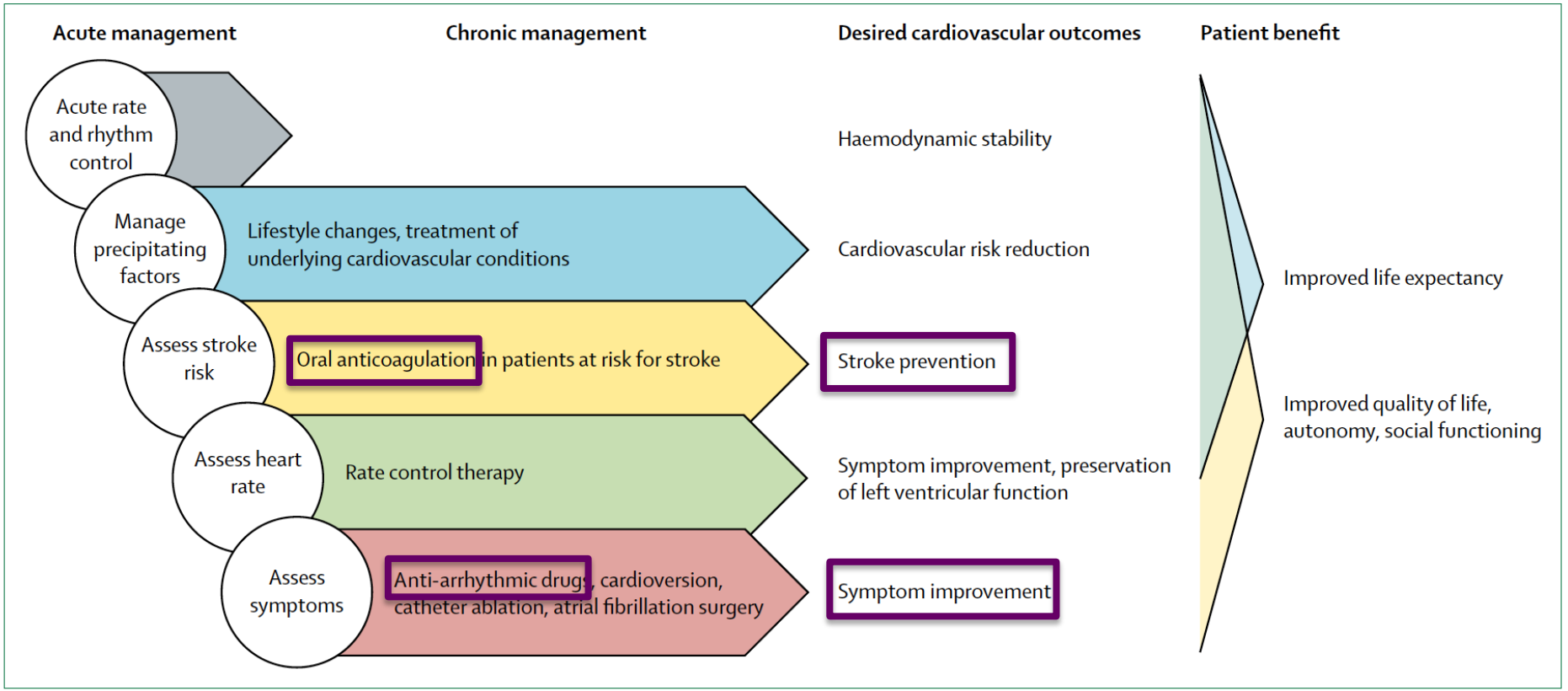

***Figure 1*: The five domains of atrial fibrillation management**

Kirchhof *Lancet* 2016

Rate and rhythm control in AF

- **Rate control** often use for initial treatment
  - use of negatively chronotropic drugs (eg, β-blockers or calcium channel blockers)
- **Rhythm control** involves the use of pharmacological, electrical, or surgical cardioversion to convert AF to normal sinus rhythm
- Drug choice is often dictated by safety concerns (toxicities and proarrhythmic adverse effects) as well as patient characteristics and comorbidities

Antiarrhythmic drugs (AAD)

- Vaughan-Williams classification according to their mechanism of action:
  - sodium channel blockers (**class I**)
  - β-blockers (**class II**)
  - potassium channel blockers (**class III**)
  - calcium channel blockers (**class IV**)

- Furthermore, class I drugs are subdivided on the basis of drug affinity for sodium channels into *class IA, class IB, and class IC*

Vaughan-Williams classification

Table 1 Vaughan-Williams classification of currently used antiarrhythmic agents

Class	Example drugs	Mechanism of action	Limitations
Ia	Quinidine Procainamide Disopyramide	I_{Na} inhibition (intermediate kinetics), I_{Kr} inhibition	Risk of Torsades de pointes, associated with possible increased mortality
Ib	Lidocaine Mexiletine	I_{Na} inhibition (fast kinetics)	No efficacy in atrial arrhythmias
Ic	Flecainide Propafenone	I_{Na} inhibition (slow kinetics)	Contraindicated in coronary artery disease and structural heart disease
II	Beta blockers (propranolol, atenolol, metoprolol)	Beta adrenergic receptor competitive antagonist	Hypotension and bradycardia
III	Amiodarone Dronedarone Dofetilide Sotalol	Multichannel blocker I_{Kr} inhibition I_{Kr} inhibition	Extra-cardiac side effects Risk of Torsades de pointes, dependent on renal clearance
IV	Non-dihydropyridine calcium channel blockers (verapamil, diltiazem)	$I_{ca,L}$ inhibition	Hypotension and bradycardia

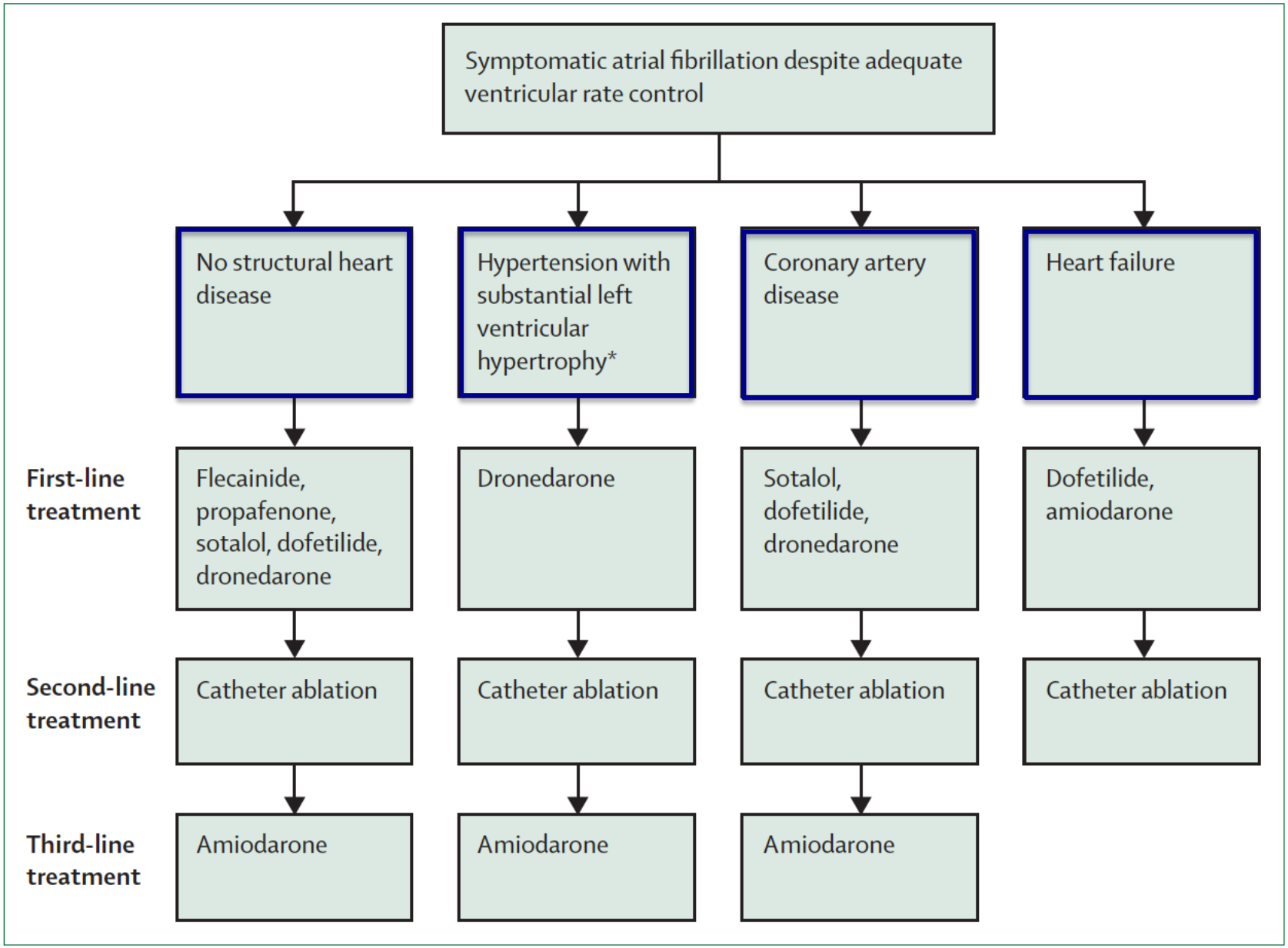

Figure 2: **Antiarrhythmic drug selection for the maintenance of sinus rhythm in patients with atrial fibrillation**

*Substantial left ventricular hypertrophy is defined as a wall thickness of more than 1·4 cm.

Piccini & Fauchier *Lancet* 2016

Pharmacokinetic characteristics of antiarrhythmic drugs

Drug	Oral bioavaila-bility (%)	Protein binding (%)	Vd (L/kg)	Metabolism	Half-life (hours)	Elimination (H/R, %)	C_{max} (μg/ml)	Active metabolites
Amiodarone (PO, IV)	35-65	99	66	CYP3A4 and 2C8	58 days	99/1	1-2.5	Desethylamiodarone
Dofetilide	95	65	3.4	CYP3A4	7-13	20/80	2.3	N-debutyl metabolite
Dronedarone	5	> 98	20	CYP3A4	13-19	84		
Flecainide	95	40-50	5.5-10	CYP2D6	20 (12-27)	10/85 (35*)	0.2-1	Meta-O-dealkylflecainide
Propafenone	5-30	95	2.5-4	CYP2D6 (3A4, 1A2)	2-10 EM; 10-32 PM	95/5 (1*)	0.2-3	5-OH-propafenone
Sotalol	90-100	0	1.5-2.5	Not metabolized	12 (7-18)	15/85*	< 5	

C_{max}, maximum plasma concentrations; H, hepatic; R, renal; PO, orally; IV, intravenous; EM, extensive metabolizer; PM, poor metabolizer.

* excreted unchanged in urine

Gheorghe et al. *Europace* 2018

TABLE. Interactions of Antiarrhythmic and Commonly Prescribed Drugs[17]

Variable	Class IA			Class IC		Class III		Class IC & III
	Quinidine	Procainamide	Disopyramide	Flecainide	Propafenone	Sotalol	Dofetilide	Amiodarone
Cardiovascular								
Warfarin	Level C	Level A	Level A	Level A	Level C	Level A	Level A	Level D
Lisinopril	Level A	Level A	Level B	Level A	Level A	Level C	Level A	Level C
Amlodipine	Level C	Level A	Level A	Level A	Level A	Level C	Level C	Level C
Hydrochlorothiazide	Level C	Level A	Level C	Level A	Level A	Level C	Level X	Level C
Furosemide	Level A	Level A	Level A	Level A	Level A	Level C	Level C	Level C
Spironolactone	Level C	Level A	Level A	Level A	Level A	Level C	Level A	Level C
Losartan	Level A	Level A	Level A	Level A	Level A	Level C	Level A	Level C
Metoprolol	Level D	Level A	Level C	Level A	Level C	Level C	Level A	Level C
Carvedilol	Level D	Level A	Level C	Level A	Level C	Level C	Level A	Level C
Labetalol	Level A	Level A	Level C	Level A	Level C	Level C	Level A	Level C
Atorvastatin	Level C	Level A	Level A	Level A	Level C	Level A	Level C	Level C
Rosuvastatin	Level A	Level A	Level A	Level A	Level A	Level A	Level A	Level B
Pravastatin	Level A	Level A	Level A	Level A	Level A	Level A	Level A	Level A
Simvastatin	Level A	Level A	Level A	Level A	Level A	Level A	Level A	Level D
Pulmonary								
Albuterol	Level D	Level D	Level D	Level C	Level C	Level X	Level D	Level D
Ipratropium (nasal)	Level C	Level A	Level C	Level A	Level A	Level A	Level A	Level A
Tiotropium	Level X	Level A	Level X	Level A	Level A	Level A	Level A	Level A
Psychiatric								
Fluoxetine	Level X	Level X	Level X	Level X	Level X	Level X	Level X	Level X
Escitalopram	Level X	Level X	Level X	Level D	Level D	Level X	Level X	Level X
Paroxetine	Level D	Level D	Level D	Level D	Level C	Level D	Level D	Level D
Sertraline	Level D	Level D	Level D	Level C	Level C	Level D	Level D	Level D
Fluvoxamine	Level C	Level A	Level C	Level A	Level C	Level A	Level C	Level A
Wellbutrin	Level A	Level C	Level A	Level C	Level C	Level A	Level A	Level A
Endocrine								
Insulin	Level A	Level A	Level C	Level A	Level A	Level C	Level A	Level A
Metformin	Level A	Level A	Level C	Level A	Level A	Level A	Level C	Level A
Levothyroxine	Level A	Level A	Level A	Level A	Level A	Level A	Level A	Level C
Neurologic								
Pregabalin	Level A	Level A	Level A	Level A	Level A	Level A	Level A	Level A
Gabapentin	Level A	Level A	Level A	Level A	Level A	Level A	Level A	Level A
Lisdexamfetamine	Level A	Level A	Level A	Level A	Level A	Level A	Level A	Level A
Opioid analgesics	Level C	Level A	Level C	Level A	Level A	Level A	Level A	Level A

Key:

Level A: No known drug interaction.

Level B: No action needed; the agents may interact but there is little to no evidence of clinical concern.

Level C: Monitor therapy; appropriate monitoring therapy should be implemented; possible dose adjustment.

Level D: Consider therapy modification; aggressive monitoring, possible dose change, or choose alternative agents.

Level X: Avoid combination.

Mayo Clin Proc. 2018;93(3):373-380

OVERVIEW

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  - adverse effects
  - drug interactions and considerations in anesthesia
- **Anticoagulants**
  - stroke prevention
  - Direct Oral AntiCoagulants (DOACS)
  - regional anesthesia
- Conclusions

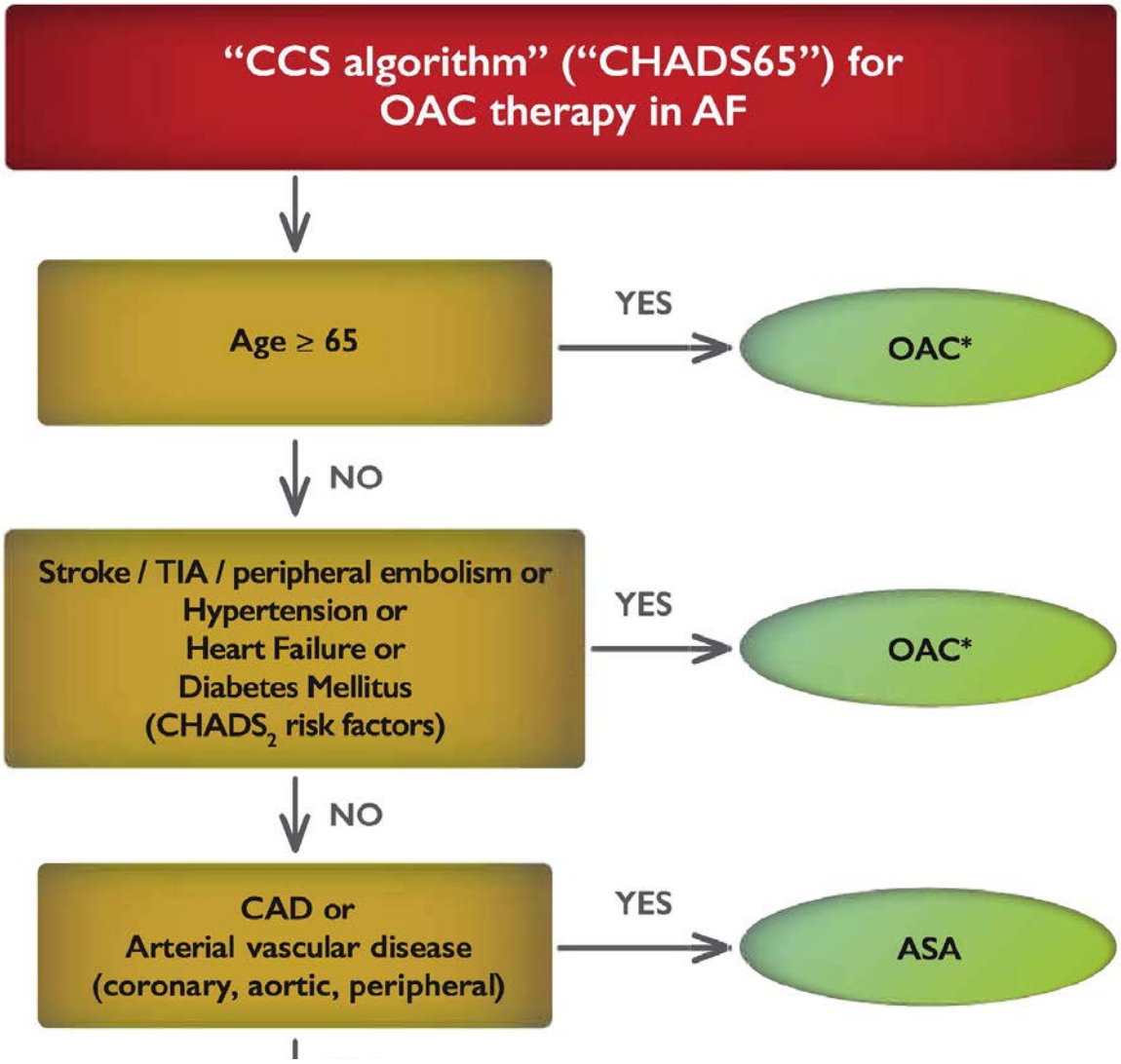
Table 2. Clinical Indications Approved by the US Food and Drug Administration for the Use of Non-Vitamin K Oral Anticoagulants

Indication		Reduction in Risk of Stroke and Systemic Embolism in Patients With Nonvalvular AF	Treatment of DVT or PE	Reduction in Risk of Recurrent DVT or PE	Prophylactic Therapy for DVT or PE After Hip or Knee Surgery	Prophylactic Therapy for VTE During Hospitalization for an Acute Medical Illness
Direct thrombin inhibitor	Dabigatran etexilate	Approved	Approved	Approved	Approved	NA
Activated factor X inhibitor	Apixaban	Approved	Approved	Approved	Approved	NA
	Edoxaban tosylate	Approved	Approved	NA	Approved	NA
	Rivaroxaban	Approved	Approved	Approved	Approved	NA
	Betrixaban	NA	NA	NA	NA	Approved

Abbreviations: AF, atrial fibrillation; DVT, deep vein thrombosis; NA, not applicable; PE, pulmonary embolism; VTE, venous thromboembolism.

Canadian Journal of Cardiology
Volume 32 2016

Canadian Cardiovascular Society Algorithm



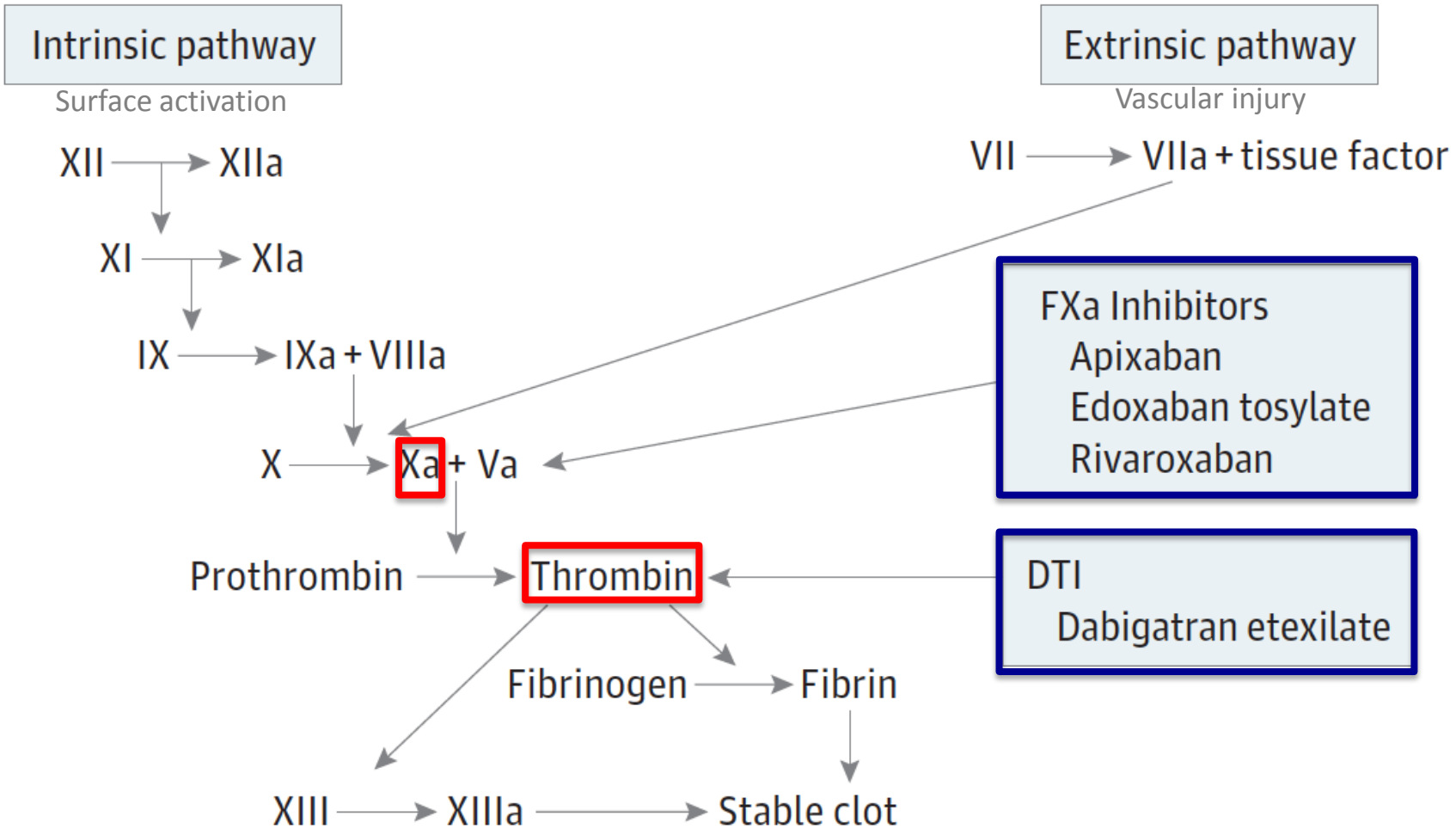
Consider and modify (if possible) all factors influencing risk of bleeding during OAC treatment (hypertension, antiplatelet drugs, NSAIDs, corticosteroids, excessive alcohol, labile INRs) and specifically bleeding risks for NOACs (low creatinine clearance, age ≥ 75, low body weight)†

DOACS

- DOACs are a major step forward for patients with non-valvular AF
    - anti-IIa: dabigatran
    - anti-Xa: rivaroxaban, apixaban, and edoxaban

- Dosage determined mainly by indication, age and/or creatinine clearance, body weight, and the use of concomitant drugs

Figure. Pathways of Activated Factor X (FXa) Inhibitors and Direct Thrombosis Inhibitors (DTIs)



JAMA Surgery Published online April 18, 2018

DOAC prescribing for atrial fibrillation

DOACS	Commercial name	Standard	Renal impairment	Comment
Dabigatran	Pradaxa™	150 mg oral bid	110 mg oral bid if creat. cl. 30-50 ml/min, or age > 80 or at risk of bleeding	Avoid below creat. cl. 35 ml/min
Rivaroxaban	Xarelto™	20 mg oral od	15 mg oral od if creat. cl. 15-50 ml/min	Can be prescribed with creat. cl. 15 ml/min or more
Apixaban	Eliquis™	5 mg oral bid	2.5 mg oral bid if 2/3: weight < 60 kg, creat. > 133 µmol/l, age > 80	Can be prescribed with creat. cl. 15 ml/min or more
Edoxaban	Lixiana™	60 mg oral, od	30 mg oral od if creat. cl. < 50 ml/min	Can be prescribed with creat. cl. 15 ml/min or more

od: once daily; bid: twice daily

Hogg et al. *Eur J Emerg Med* 2016

creat. cl.: creatinine clearance

Box. Contraindications to the Use of Non–Vitamin K Oral Anticoagulants

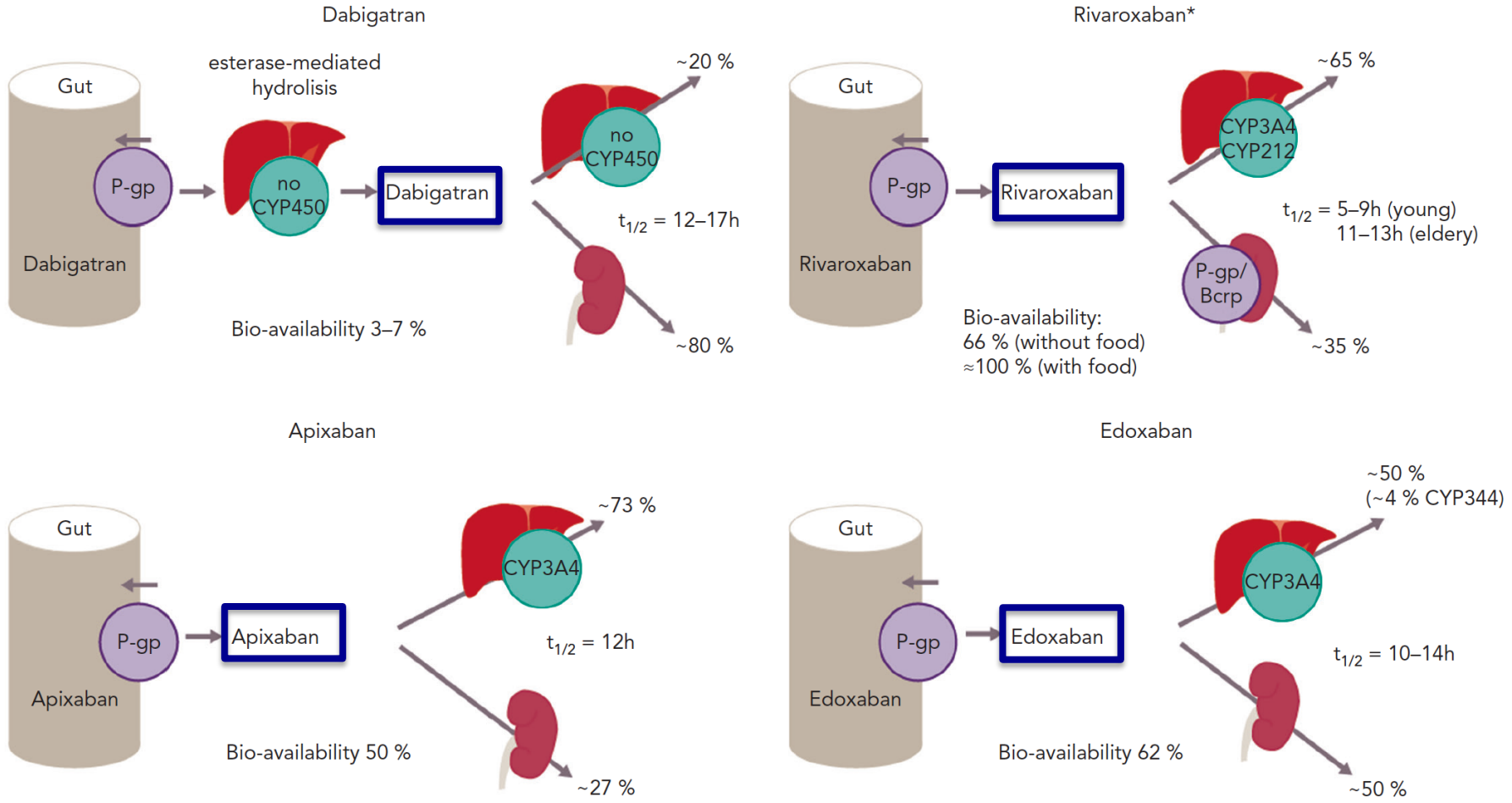
- Valvular atrial fibrillation (prosthetic valve, rheumatic mitral valvular disease, prior mitral valve repair)
- Mechanical prosthetic heart valve
- Severe renal dysfunction with creatinine clearance <15 mL/min or receiving hemodialysis
- Severe liver dysfunction (Child-Pugh C)
- Pregnancy
- Need to take concomitant potent inhibitors of P-glycoprotein (all) and potent inhibitors of cytochrome P450 3A4 (CYP3A4) (apixaban, rivaroxaban)

Verma et al. **JAMA Surgery** Published online April 18, 2018

DOACS - pharmacokinetics

DOACS	Commercial name	Mechanism of action	Time to peak (h)	$T_{1/2}$ (h)
Dabigatran	Pradaxa™	Direct thrombin (IIa) inhibitor	**1.5-3**	**12-17** (28 in RF)
Rivaroxaban	Xarelto™	Factor Xa inhibitor	**3**	**8-10**
Apixaban	Eliquis™	Factor Xa inhibitor	**3-4**	**8-12**
Edoxaban	Lixiana™	Factor Xa inhibitor	**1-3**	**10-14**

Absorption and metabolism of DOACS



* these rivaroxaban figures are valid only for doses exceeding 20 mg.

Adapted from: Heidbuchel, et al., 2015.[24]

Vranckx et al. *Drugs & Devices* 2018

Drug interactions

- An important interaction mechanism for all DOACS consists of significant gastrointestinal re-secretion over a P-glycoprotein (P-gp) transporter after absorption in the gut
  - Competitive inhibition of this pathway increased plasma levels
  - Many drugs used in AF patients are P-gp inhibitors (e.g. verapamil, dronedarone, amiodarone, and quinidine)
- Strong CYP3A4 inhibition (verapamil, diltiazem, erythromycin, ketoconazole, ritonavir) may increase plasma concentrations
- Conversely, strong inducers of P-gp and/or CYP3A4 (such as rifampicin, carbamazepine, phenytoin) will markedly reduce DOAC plasma levels

Steffel et al. *Eur Heart J* 2018

Drug interactions (2)

- DOAC dose reduction should be considered for all DOACS when amiodarone, dronedarone or other P-gp competitors is a concomitant medication
  - association between dronedarone and dabigatran or rivaroxaban is not recommended
  - for dronedarone and edoxaban, a 50% reduction dose is recommended
- For dabigatran and edoxaban, dose reduction is recommended when taken simultaneously with verapamil

Gheorghe et al. *Europace* 2018

Table 3 Effect of drug–drug interactions and clinical factors on NOAC plasma levels ('area under the curve')

	Via	Dabigatran etexilate	Apixaban	Edoxaban	Rivaroxaban
P-gp substrate		Yes	Yes	Yes	Yes
CYP3A4 substrate		No	Yes (≈25%)	No (<4%)	Yes (≈18%)[131]
Antiarrhythmic drugs					
Amiodarone	moderate P-gp competition	+12 to 60%[SmPC]	No PK data[a]	+40%[132–134]	Minor effect[a]
Digoxin	P-gp competition	No effect[SmPC]	No effect[135]	No effect	No effect[SmPC]
Diltiazem	P-gp competition and weak CYP3A4 inhibition	No effect[SmPC]	+40%[136]	No data yet	No effect
Dronedarone	P-gp competition and CYP3A4 inhibition	+70 to 100% (US: 2 × 75 mg if CrCl 30–50 mL/min)	No PK or PD data: caution	+85%[b]	Moderate effect, should be avoided
Quinidine	P-gp competition	+53%[SMPC]	No data yet	+77%[137] (no dose reduction required by label)	Extent of increase unknown
Verapamil	P-gp competition (and weak CYP3A4 inhibition)	+12 to 180%[SmPC] (if taken simultaneously)	No PK data	+53% (SR)[137,142] (no dose reduction required by label)	No effect

Steffel et al. *Eur Heart J* 2018

Drug interactions in patients on antiarrhythmics - MCQ

- *75 yrs old female with AF on dronedarone. You want to add a DOAC. Which one do you choose?*
  1. Dabigatran
  2. Rivaroxaban
  3. Apixaban
  4. Edoxaban
  5. None. They are all contraindicated

Drug interactions in patients on antiarrhythmics - MCQ

- *75 yrs old female with AF on dronedarone. You want to add a DOAC. Which one do you choose?*
  1. **Dabigatran is contraindicated**
  2. **Rivaroxaban (try to avoid)**
  3. **Apixaban (no data)**
  4. **Edoxaban dose should be reduced by 50%**
  5. None. They are all contraindicated

Coagulation tests to measure the anticoagulant effects of the DOACs

Test	Dabigatran	Rivaroxaban	Apixaban	Edoxaban
aPTT (intrinsic and common pathways)				
PT / INR (extrinsic and common pathways)				
TT (time to conversion of fibrinogen to fibrin)	↑↑↑↑	-	-	-
Diluted thrombin time (Hemoclot) – to reduce sensitivity	To quantify plasma conc.	-	-	-
Ecarin clotting time (converts prothrombin to meizothrombin)	To quantify plasma conc.	-	-	-
Chromogenic anti-Xa assay	-	To quantify plasma conc.	To quantify plasma conc.	To quantify plasma conc.

Normal value does NOT exclude anticoagulant effect

Thrombosis Canada

Thrombose Canada

Peri-operative management of patients on DOAC

Administration of DOACs influenced by:

- Drug elimination half-life
- Effect of renal function on drug elimination
- Bleeding risk associated with the surgery type
- Whether patient is to receive spinal/epidural anesthesia

TABLE 1: BLEEDING RISK FOR VARIOUS INVASIVE/SURGICAL PROCEDURES

Thrombosis Canada
Thrombose Canada

LOW RISK	MODERATE RISK	HIGH RISK
• Dental extractions (1 or 2 teeth), endodontic (root canal) procedure, • Subgingival scaling or other cleaning • Cataract surgery • Dermatologic procedures (e.g. biopsy) • Gastroscopy or colonoscopy without biopsies • Coronary angiography • Permanent pacemaker insertion or internal defibrillator placement (if bridging anticoagulation is not used) • Selected procedures (e.g. thoracentesis, paracentesis, arthrocentesis)	• Other intra-abdominal surgery (e.g. laparoscopic cholecystectomy, hernia repair, colon resection) • Other general surgery (e.g. breast) • Other intrathoracic surgery • Other orthopedic surgery • Other vascular surgery • Non-cataract ophthalmologic surgery • Gastroscopy or colonoscopy with biopsies • Selected procedures (e.g. bone marrow biopsy, lymph node biopsy) • Complex dental procedure (e.g. multiple tooth extractions)	• Any surgery or procedure with neuraxial (spinal or epidural) anesthesia • Neurosurgery (intracranial or spinal) • Cardiac surgery (e.g. CABG, heart valve replacement) • Major intra-abdominal surgery (e.g. intestinal anastomosis) • Major vascular surgery (e.g. aortic aneurysm repair, aortofemoral bypass) • Major orthopedic surgery (e.g. hip or knee replacement) • Lung resection surgery • Urological surgery (e.g. prostatectomy, bladder tumour resection) • Extensive cancer surgery (e.g. pancreas, liver) • Reconstructive plastic surgery • Selected procedures (e.g. kidney biopsy, prostate biopsy, cervical cone biopsy, pericardiocentesis, colonic polypectomy)

Can J Anesth/J Can Anesth (2017) 64:656–672
DOI 10.1007/s12630-017-0868-2

CONTINUING PROFESSIONAL DEVELOPMENT

Managing the perioperative patient on direct oral anticoagulants

Jordan Leitch, MD · Janet van Vlymen, MD, FRCPC

Table 3 Summary of recommendations regarding preoperative stopping interval for DOACs prior to high bleeding risk procedures/surgeries[10,11]

	ASRA Neuraxial Guidelines (days)	ASRA Interventional Spine and Pain Guidelines (days)	Thrombosis Canada* (days)	Canadian Product Monograph (days)
Dabigatran				
Normal	5	4-5	2 or 4	2
Mild Renal Impairment		4-5	2 or 4	3
Moderate Renal Impairment		6	1-2 extra	4
Rivaroxaban	3	3	2	2-4
Apixaban	3	3-5	2	2

* *Editor's note*: These are the latest recommendations at the time of going to press. Note that some these recommendations are purposefully vague, reflecting the uncertainty surrounding early studies. Ongoing trials may allow more definitive recommendations in the near future

ASRA = American Society of Regional Anesthesia and Pain Medicine

Thrombosis Canada
Thrombose Canada

NOACS/DOACS*: PERI-OPERATIVE MANAGEMENT

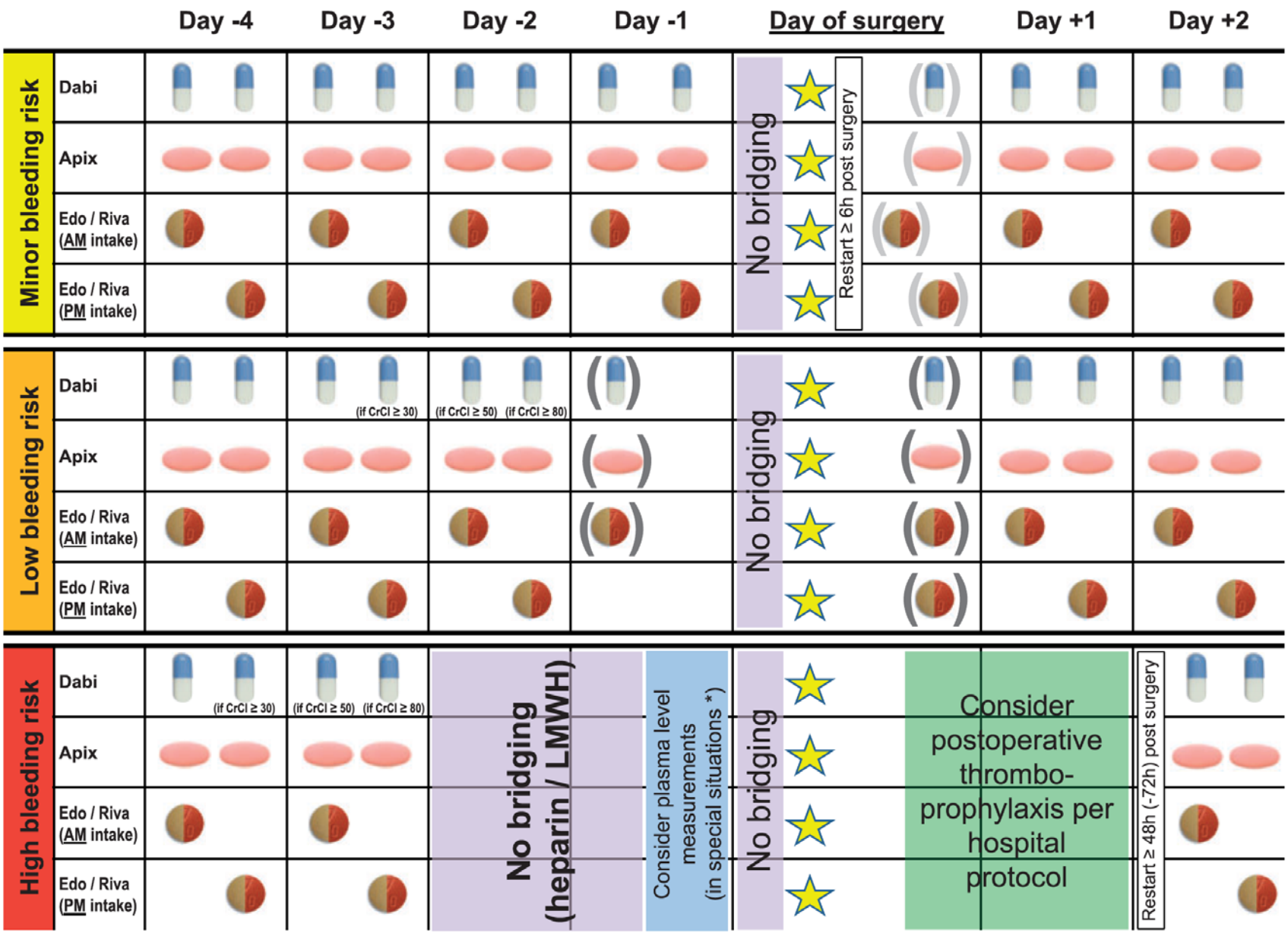
DOAC	Low bleed risk surgery	Moderate bleed risk surgery	High bleed risk surgery
Dabigatran (Creat. cl. ≥ 50)	Safe not to interrupt anticoagulation	last dose **2 days** before surgery	last dose **3 days** before surgery
Dabigatran (Creat. cl. < 50)	Safe not to interrupt anticoagulation	last dose **3 days** before surgery	last dose **5 days** before surgery
Rivaroxaban	Safe not to interrupt anticoagulation	last dose **2 days** before surgery	last dose **3 days** before surgery
Apixaban	Safe not to interrupt anticoagulation	last dose **2 days** before surgery	last dose **3 days** before surgery
Edoxaban	Safe not to interrupt anticoagulation	last dose **2 days** before surgery	last dose **3 days** before surgery

When can I restart DOAC therapy for my patient after surgery?

- The timing of restarting DOAC therapy depends on:
  - the type of surgery performed
  - hemostasis
  - unexpected complications at the time of surgery
  - the condition of the patient
- For patients at low bleeding risk who undergo uncomplicated surgery with good postoperative hemostasis, DOACS can be safely resumed after 24 h
- For patients who undergo surgery with higher bleeding risk, the decision to restart DOACS can be made after 48 to 72 h

Verma et al. **JAMA Surgery** Published online April 18, 2018

2018 EHRA Practical Guide on NOACs in AF



Steffel et al. *Eur Heart J* 2018

ESC European Society of Cardiology

European Heart Journal (2017) **38**, 2431–2439
doi:10.1093/eurheartj/ehx403

CLINICAL RESEARCH
Thrombosis and antithrombotic therapy

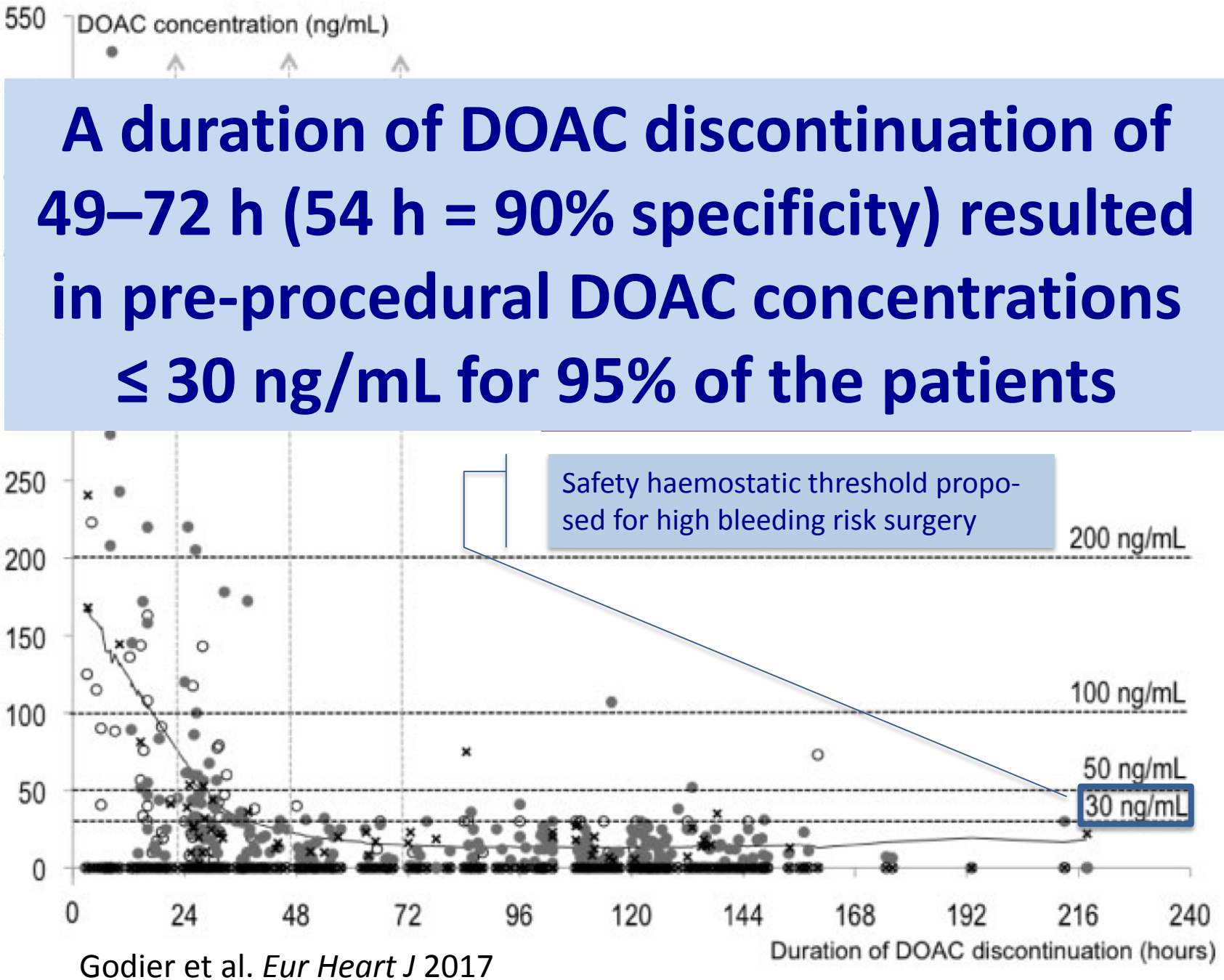
Predictors of pre-procedural concentrations of direct oral anticoagulants: a prospective multicentre study

Anne Godier[1,2]*, Anne-Sophie Dincq[3], Anne-Céline Martin[2,4], Adrian Radu[5], Isabelle Leblanc[6], Marion Antona[7], Marc Vasse[8,9], Jean-Louis Golmard[10], François Mullier[11], and Isabelle Gouin-Thibault[2,12,13]

[1]Fondation Adolphe de Rothschild, Service d'Anesthésie-Réanimation, 25 rue Manin, 75019, Paris, France; [2]Inserm UMR-S1140, Faculté de Pharmacie, Université Paris Descartes,

- Last DOAC intake **3 days** before surgery resulted in minimal pre-procedural anticoagulant effect for almost all patients

A duration of DOAC discontinuation of 49–72 h (54 h = 90% specificity) resulted in pre-procedural DOAC concentrations ≤ 30 ng/mL for 95% of the patients



Godier et al. *Eur Heart J* 2017

Box 2 | **Managing bleeding or emergency surgery in patients taking NOACs**

Mild bleeding

- Identify and manage bleeding site
- Stop anticoagulant if necessary
- Restart anticoagulant as soon as possible

Moderate-to-severe bleeding

Resuscitation:

- Haemodynamic and haemostatic resuscitation
- Obtain coagulation test results and calculate creatinine clearance

Control source of bleeding:

- Identify source of bleeding and treat if possible

Reversal:

- Consider reversal if there is ongoing bleeding (see below)

Life-threatening bleeding

Reversal of anticoagulant:

- Dabigatran: idarucizumab (5 g by intravenous bolus)
- Apixaban, edoxaban, or rivaroxaban: four-factor prothrombin complex concentrate (PCC; 25–50 units/kg). If there is ongoing bleeding despite PCC, consider activated PCC (50 units/kg) or recombinant coagulation factor VIIa (90 μg/kg)

With massive or uncontrollable haemorrhage:

- Initiate massive transfusion protocol
- Consider tranexamic acid (1 g intravenously)

Emergency surgery

- Measure non-vitamin K antagonist oral anticoagulant drug levels if possible, but do not wait for test results if surgery is urgent
- Reverse dabigatran with idarucizumab
- Consider four-factor PCC for reversal of apixaban, edoxaban, or rivaroxaban either before surgery or during or after surgery if there is excessive bleeding

Levy et al.
Nature Rev Cardiol
2018

TABLE 2: DOSING OF PROTHROMBOTIC THERAPIES AND PRODUCTS

Product	Bleeding on	Dosing	Notes
Idarucizumab (Praxbind®)	dabigatran	• administered as two 50-mL bolus infusions containing 2.5 g each of idarucizumab (total 5 g) no more than 15 minutes apart	• Complete reversal is expected within minutes and lasts for 24 hrs or more in most patients. • Ongoing bleeding is due to anatomical cause
PCC (Octaplex®)	apixaban dabigatran* edoxaban rivaroxaban	• 50 units/kg, max 3000 units • Mix diluent and PCC following manufacturer instructions • infuse at 1 mL/min followed by maximum 3 mL/min (180 mL/hr) per institution/Blood Bank instructions	• Contraindicated in heparin-induced thrombocytopenia • For life-threatening bleeding (e.g. intracranial hemorrhage) give 2000 units IV STAT if weight not available and cannot delay reversal
PCC (Beriplex®)	apixaban dabigatran* edoxaban rivaroxaban	• 50 units/kg, max 3000 units • Mix diluent and PCC following manufacturer instructions • infuse at 1 mL/min followed by maximum 8 mL/min (480 mL/hr) per institution/Blood Bank instructions	• Contraindicated in heparin-induced thrombocytopenia • For life-threatening bleeding (e.g. intracranial hemorrhage) give 2000 units IV STAT if weight not available and cannot delay reversal
Activated PCC (FEIBA®)	dabigatran*	• 50 units/kg, max 2000 units	• Limited availability through Canadian Blood Services • For life-threatening bleeding (e.g. intracranial hemorrhage) give 2000 units IV STAT if weight not available and cannot delay reversal • Can also use for apixaban and rivaroxaban but PCC preferred
Frozen plasma	Coagulopathy (e.g. dilutional from massive transfusion, hepatic failure, DIC)	• 10-15 mL/kg (3-4 units for adults)	• Should not be used to reverse abnormal lab parameters from DOACs • Caution in patient at risk for volume overload (eg. CHF)
Cryoprecipitate	Coagulopathy (eg. dilutional from massive transfusion, hepatic failure, DIC)	• 10 units IV	• Only consider if fibrinogen level is < 1.0 g/L
Tranexamic Acid (Cyclokapron®)	apixaban dabigatran* edoxaban rivaroxaban	• 1g IV bolus then 1 g over 8 hrs	• May exacerbate prothrombotic effect if given with other prothrombotic products

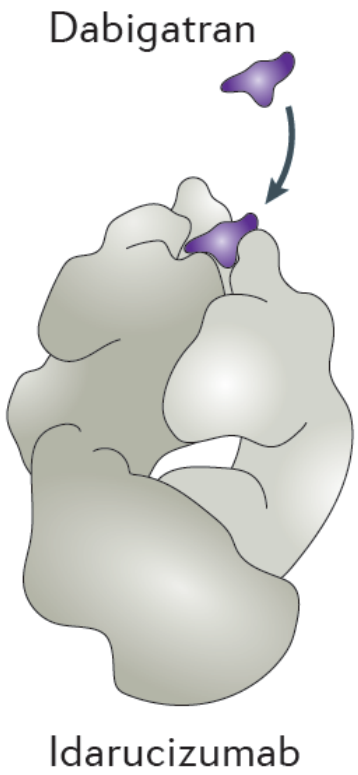
*If idarucizumab unavailable.

Abbreviations: CHF, congestive heart failure; DIC, disseminated intravascular coagulation.

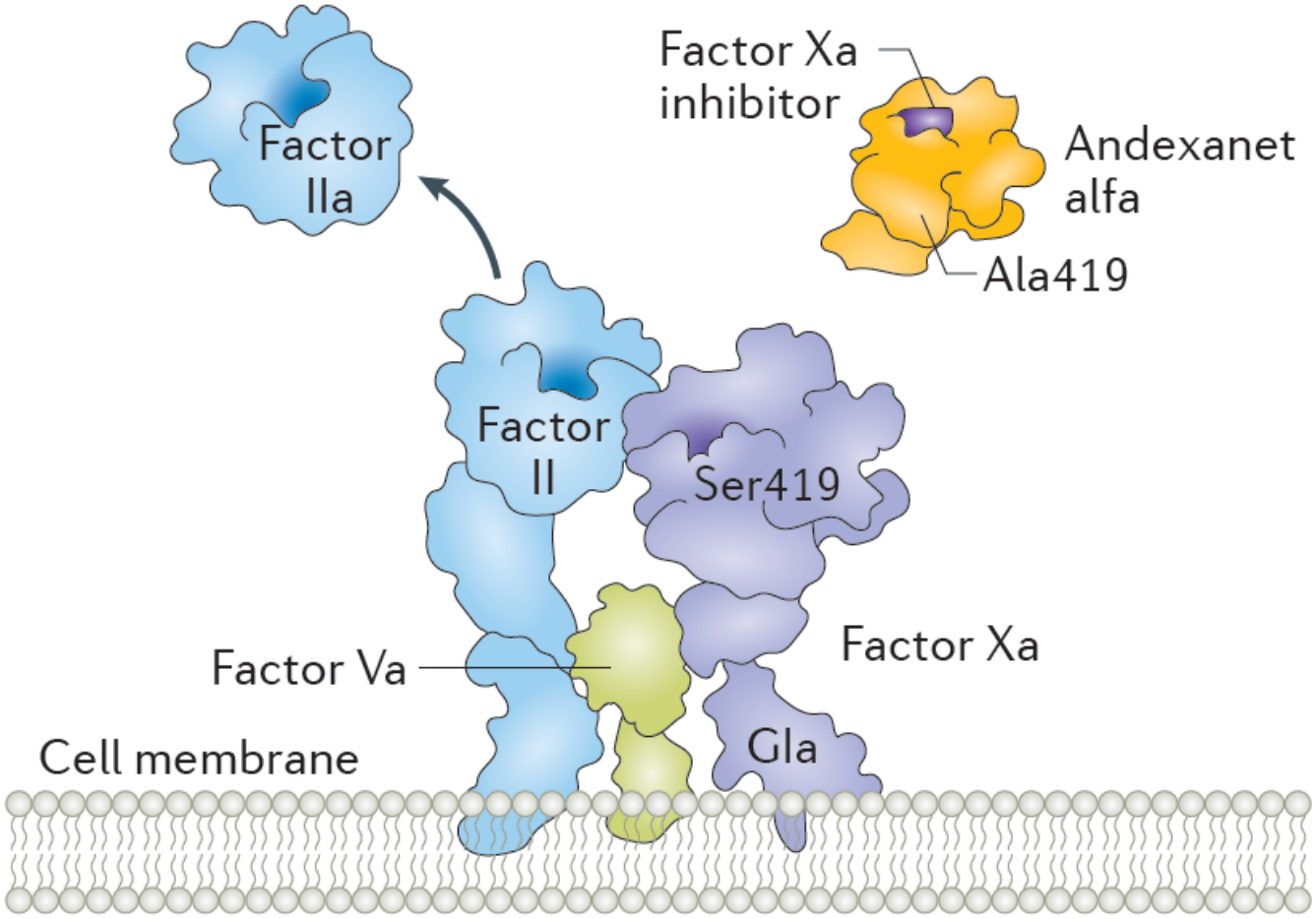
Thrombosis Canada
Thrombose Canada

IDARUCIZUMAB (Praxbind™)

- Humanized mouse monoclonal antibody
- Acts as a non-competitive inhibitor of dabigatran form
- Immediate onset of action (min)
- Lasts 24 h
- Fixed dose of 5 g (50 mL x 2, no more than 15 min apart)
- Approx. $3 000
- REVERSE-AD phase III trial – 503 patients (78 yr.)



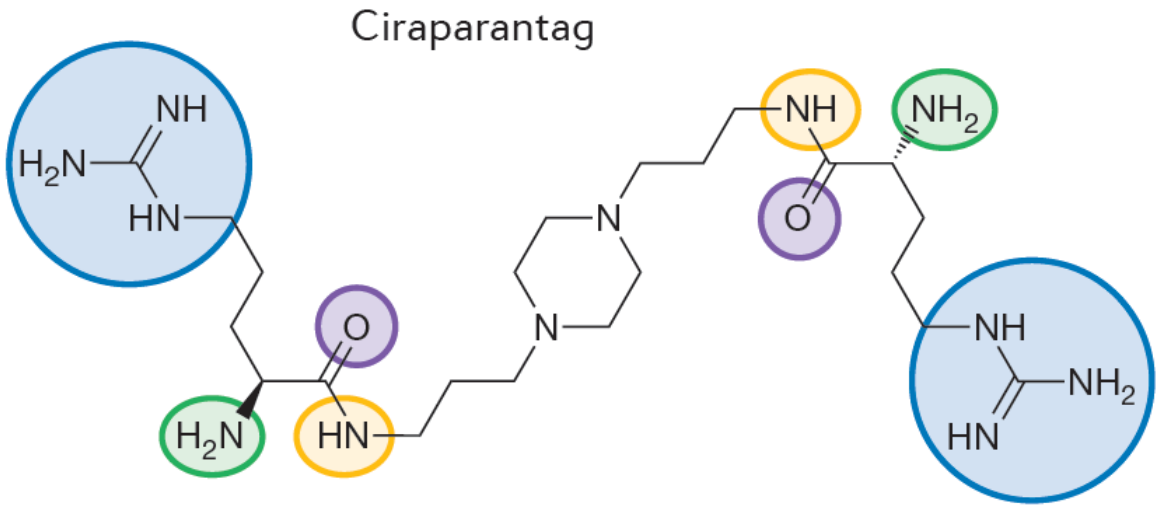
Factor Xa inhibitors antidote: andexanet alfa



CIRAPARANTAG

- **Anticoagulants universal antidote**
- Fast-track designation by FDA
- Broad-spectrum reversal agent fitting to neutralize :
  - DOACs
  - unfractionated heparin (UFH)

Drug	Binding sites
Apixaban	● ●
Dabigatran	● ● ●
Edoxaban	● ●
Fondaparinux	● ● ●
Rivaroxaban	● ● ●
UFH or LMWH	● ● ●



Epidural catheter removal - MCQ

- *68 yrs old man had TKA 48 h ago – normal renal function – epidural inserted for pain relief. Apixaban 2.5 mg bid (8am – 8pm) - last dose this morning at 8am.*

- **When do you remove the epidural catheter?**

- **When do you give the next dose of apixaban?**

From Dr A. Godier 2017 with permission

Epidural catheter removal - MCQ

- *68 yrs old man had TKA 48 h ago – normal renal function – epidural inserted for pain relief. Apixaban 2.5 mg bid (8am – 8pm) - last dose this morning at 8am*
- **When do you remove the epidural catheter?**

  1. Two hours before the next dose of apixaban
  2. No medication tonight and removal tomorrow morning at 8am
  3. At 8pm tonight
  4. No medication neither tonight nor tomorrow morning and removal at 8pm tomorrow
  5. 6 hours after last apixaban intake

From Dr A. Godier 2017 with permission

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  1. 12 hours after catheter removal
  2. 8 hours after catheter removal
  3. 5 hours after catheter removal
  4. 2 hours before the 8pm dose, i.e., at 6pm
  5. The next day at 8am

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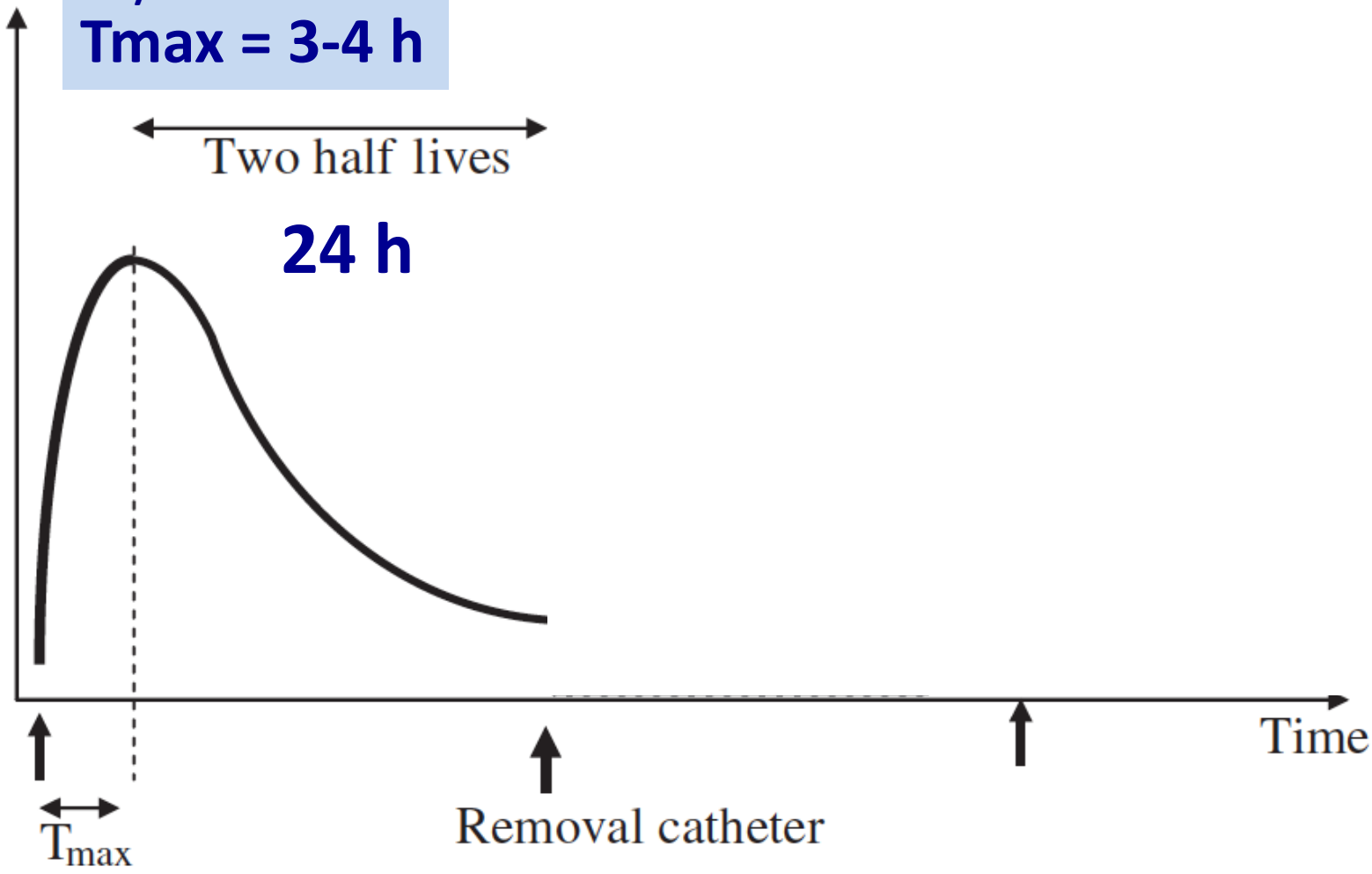
  5. The next day at 8am

Apixaban: catheter removal and next dose

$T_{1/2}$ = 8-12 h
Tmax = 3-4 h



Rosencher et al. *Anaesthesia* 2007

CONCLUSIONS ON DOACS

- Not all procedures require anticoagulants to be held (eg, minor dental and skin procedures, cataract extraction, etc.)
- Bridging anticoagulation is not routinely recommended for DOAC-treated patients during treatment interruption for an elective surgery
- DOACs should be held for 1 to 4 days pre-procedure, with the interruption interval depending on the DOAC, patient renal function, and surgery/procedure bleeding risk
- Postoperative resumption of DOACs can be approximately 24 hours after low-bleed-risk and 48 to 72 hours after high-bleed-risk procedures

Table 1. Characteristics of Non-Vitamin K Oral Anticoagulants

Agent	Mechanism of Action	Standard Dosing	Modified Dosing[a]	Last Dose Before Surgery		Reversal Agents
				Low Bleeding Risk	High Bleeding Risk	
Dabigatran etexilate	Direct thrombin inhibitor	Twice-daily 150 mg	Twice-daily 75 or 110 mg	Last dose 2 d before if CrCl >50 mL/min Last dose 3 d before if CrCl 30-50 mL/min Last dose 4-5 d before if CrCl 15-29 mL/min	Last dose 3 d before if CrCl >50 mL/min Last dose 4-5 d before if CrCl 15-50 mL/min	Idarucizumab, PCC (efficacy is not well established),[b] FEIBA[b]
Apixaban	Activated factor X inhibitor	Twice-daily 5 mg	Twice-daily 2.5 mg	Last dose 2 d before if CrCl >30 mL/min Last dose 3 d before if CrCl 15-29 mL/min	Last dose 3 d before if CrCl >30 mL/min Last dose 3-4 d before if CrCl, 15-29 mL/min	Andexanet alfa, PCC,[b] FEIBA[b]
Edoxaban tosylate	Activated factor X inhibitor	Once-daily 60 mg	Once-daily 30 mg	Last dose 2 d before if CrCl >30 mL/min Last dose 3 d before if CrCl 15-29 mL/min	Last dose 3 d before if CrCl >30 mL/min Last dose 3-4 d before if CrCl 15-29 mL/min	Andexanet alfa, PCC,[b] FEIBA[b]
Rivaroxaban	Activated factor X inhibitor	Once-daily 20 mg	Once-daily 15 mg	Last dose 2 d before if CrCl >30 mL/min Last dose 3 d before if CrCl 15-29 mL/min	Last dose 3 d before if CrCl >30 mL/min Last dose 3-4 d before if CrCl 15-29 mL/min	Andexanet alfa, PCC,[b] FEIBA[b]

Abbreviations: CrCl, creatinine clearance; FEIBA, factor VIII inhibitor bypassing activity; PCC, 4-factor prothrombin complex concentrate.

SI conversion factor: To convert creatinine clearance to milliliter per second, multiply by 0.0167.

[a] Modified dosing is recommended for patients with impaired renal function (CrCl, <50 mL/min [See Should All Patients Requiring Oral Anticoagulation Be Treated With NOACs Instead of Warfarin? subsection for explanation of units of measure being used here.]). Apixaban requires meeting 2 of the following 3 criteria: serum creatinine level at least 1.5 mg/dL, body weight less than 60 kg, or age older than 80 years. Edoxaban requires having impaired CrCl (CrCl, ≥30 to <50 mL/min) or concomitant use of a P-glycoprotein inhibitor. Non-vitamin K oral anticoagulants are generally avoided in patients with stage IV chronic kidney disease (CrCl, 15-25 mL/min) and are contraindicated for CrCl less than 15 mL/min.

[b] Not a specific antidote, and reversal properties are based on limited in vitro or healthy human in vivo experiments. The efficacy of PCC has only been discussed in case reports.

Parker & Sanoski *J Pharm Pract* 2016

Table 1. Antiarrhythmic Drug Indications, Dosing, and Adverse Effects.

Antiarrhythmic Drug	Indications	Dose	Adverse Effects
Amiodarone	Prevention of VT; Restoration and maintenance of SR in AF (off-label)	PO: 400 mg PO BID to TID until 10 g total, then 100-400 mg PO daily	Bradycardia, nausea, vomiting, liver function test abnormalities, cough, pulmonary fibrosis, hypothyroidism, hyperthyroidism, tremor, ataxia, paresthesia, corneal microdeposits, optic neuropathy/neuritis, photosensitivity, blue-gray skin discoloration,
Dofetilide	Restoration and maintenance of SR in AF	CrCl > 60 mL/min: 500 mcg PO BID, CrCl 40-60 mL/min: 250 mcg PO BID, CrCl 20-39 mL/min: 125 mcg PO BID, CrCl <20 mL/min: CI	TdP
Dronedarone	Reduction in risk of hospitalization from AF in patients in SR with history of paroxysmal or persistent AF.	400 mg PO BID	Nausea, vomiting, diarrhea, renal impairment, worsening HF, hepatotoxicity, pulmonary fibrosis
Flecainide	Prevention of VT; Restoration and maintenance of SR in AF	50-200 mg PO every 12 hours; LD for AF (pill-in-the-pocket approach): 200 mg (<70 kg) or 300 mg (≥70 kg) × 1	Blurred vision, dizziness, headache, tremor, worsening HF, ventricular arrhythmias
Propafenone	Prevention of VT Restoration and maintenance of SR in AF	IR: 150-300 mg PO every 8 hours; SR: 225-425 mg PO every 12 hours	Dizziness, fatigue, bronchospasm, bradycardia, heart block, worsening HF, ventricular arrhythmias, taste disturbances (metallic taste)
Sotalol	Prevention of VT; Maintenance of SR in AF	*VT:* CrCL > 60 mL/min: 80-320 mg PO BID, CrCl 30-60 mL/min: 80-320 mg PO daily, CrCl 10-29 mL/min: 80-320 mg PO every 36-48 hours, CrCl < 10 mL/min: Individualize dose, *AF:* CrCL > 60 mL/min: 80-160 mg PO BID, CrCl 40 – 60 mL/min: 80-160 mg PO daily, CrCl < 40 mL/min: CI	Dizziness, fatigue, bronchospasm, bradycardia, heart block, worsening HF, TdP

Abbreviations: AF, atrial fibrillation; BID, twice daily; CI, contraindicated; CrCl, creatinine clearance; HF, heart failure; IR, immediate-release; LD, loading dose; PO, orally; SR, sinus rhythm; TdP, torsades de pointes; TID, 3 times daily; VF, ventricular fibrillation; VT, ventricular tachycardia.

Table 1: The Effect of Drug–Drug Interactions on Direct Oral Anticoagulant Plasma Levels

Vranckx et al. *Drugs & Devices* 2018

	Mechanism	Warfarin*	Dabigatran	Apixaban	Edoxaban	Rivaroxaban
Antiarrhythmic drugs						
Amiodarone (and its metabolite desethylamiodarone)	Inhibitor of CYP3A4, CYP1A2, CYP2C9, CYP2D6 and P-gp	↑	↑	Not known	↑	↑ (minor)
Diltiazem	Inhibitor of CYP3A4	↑	No effect	↑	Not known	↑ (minor)
Dronedarone	Moderate inhibitor of CYP3A4; inhibitor of P-gp	↑	↑	Not known	↑	↑
Propafenone	Inhibitor of CYP3A4	↑	Not known	Not known	Not known	Not known
Propranolol	Inhibitor of CYP1A2	↑	Not known	Not known	Not known	Not known
Quinidine	Inhibitor of CYP3A4 and P-gp	↑	↑	Not known	↑	↑ (minor)
Telmisartan	Inhibitor of CYP3A4	↑				
Verapamil	Weak inhibitor of CYP3A4; P-gp competition	↑	↑	Not known	↑	↑ (minor)
Other cardiovascular drugs						
Statins (atorvastatin, lovastatin, rosuvastatin and simvastatin)	Inhibitor of CYP3A4	↑	↑	Not known	No effect	No effect
Antibiotics						
Clarithromycin and erythromycin	Moderate inhibitor of CYP3A4; P-gp competition	↑	↑	Not known	↑	↑
Isoniazid	Inhibitor of CYP2C9	↑	Not known	Not known	Not known	Not known
Metronidazole	Inhibitor of CYP1A2 and CYP2C9	↑	Not known	Not known	Not known	Not known
Quinolones (e.g. ciprofloxacin)	Strong inhibitor of CYP1A2	↑	Not known	Not known	Not known	Not known
Rifampicin	Inducer of CYP3A4 and CYP2C9	↓	↓	↓	↓	↓
Trimethoprim/sulfametaoxasole	Inhibitor of CYP3A4	↑	Not known	Not known	Not known	Not known
Antiviral drugs						
HIV protease inhibitors (e.g. ritonavir)	Inhibitor of CYP3A4; P-gp/Bcrp competition	↑	Not known	↑	Not known	↑
Fungostatics						
Fluconazole	Moderate inhibitor of CYP3A4, CYP1A2 and CYP2C9	↑	Not known	Not known	Not known	↑

Table 4 CHA_2DS_2-VASC and $CHADS_2$ score

CHA_2DS_2-VASC	Points
Congestive heart failure	1
Hypertension	1
Age	
65–74	1
> 74	2
Diabetes	1
Stroke or TIA	2
Vascular disease	1
Sex	
Female	1

$CHADS_2$	
Congestive heart failure	1
Hypertension	1
Age	
> 74	1
Diabetes	1
Stroke or TIA	2

TIA, transient ischemic attack.

Essential features of vitamin K antagonists and non-vitamin K antagonist oral anticoagulants

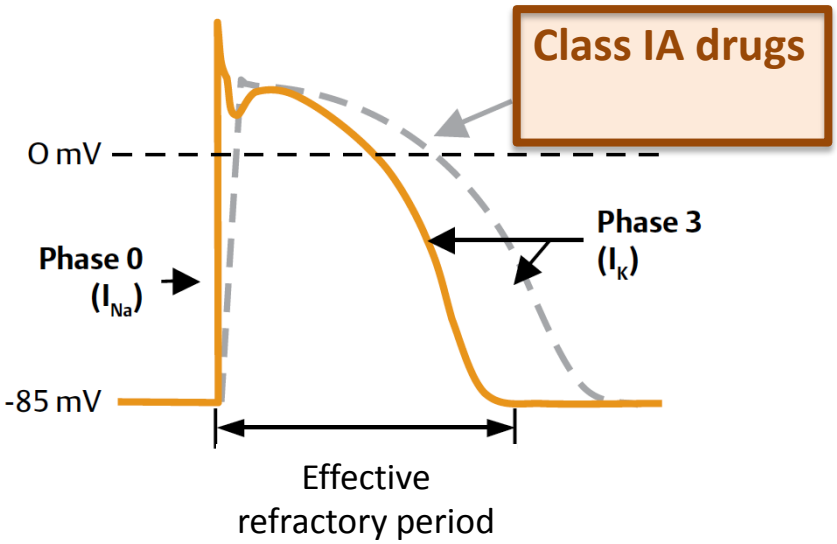
Vitamin K antagonists

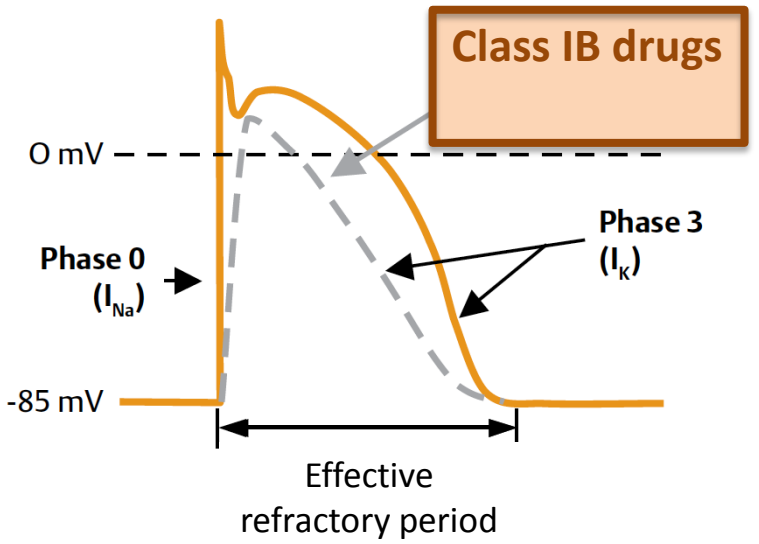
- Slow onset and off set of action, with some thrombophilia during onset and off set
- Narrow therapeutic window (target INR 2.0–3.0)
- Several interactions with food and other drugs
- Variable dose response depending on the individual's genetic background
- Regular INR monitoring and frequent dose adjustments
- TTR of > 65–70% is vital for optimum stroke prevention
- Used in clinical practice for a long time; not expensive

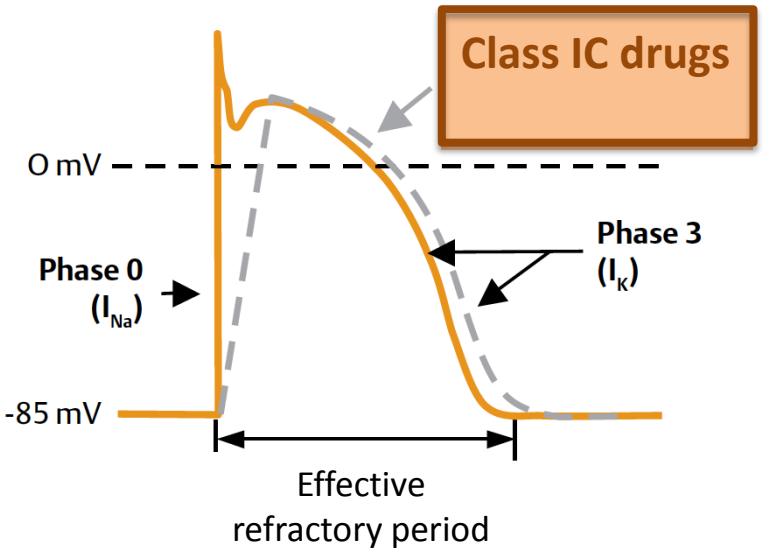
Non-vitamin K antagonist oral anticoagulants

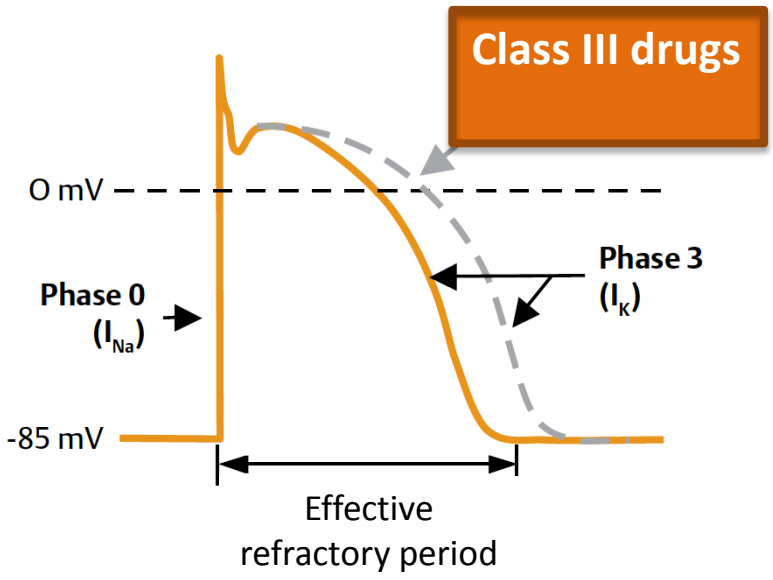
- Fast onset and off set of action; onset faster than off set
- Fixed once or twice daily dosing
- A few clinically relevant interactions with other drugs; no food interaction
- Stable, dose-related anticoagulant effect; no need for regular laboratory monitoring but renal function assessment is mandatory at baseline and during follow-up
- Strict adherence is crucial for optimum efficacy
- Relatively new drugs, expensive, but cost-effective, in comparison with vitamin K antagonists

TTR=time in therapeutic range









Finkel et al. *Pharmacology : Lippincott's Illustrated Reviews* 2009