Evento MEDICI RSA/RSD IN FORMAZIONE
24 novembre 2023

Antiaggreganti e anticoagulanti: come utilizzarli ?

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Anticoagulanti: indicazioni cliniche

- TVP e EP
- Fibrillazione atriale
- Profilassi in chirurgia ortopedica
- Sindrome coronarica acuta, BP aortocoronarico
- Emofiltrazione, ECMO, aferesi
- Cateterismo centrale o venoso periferico
- Arteriopatia periferica

L'evoluzione dei farmaci anticoagulanti

1930

Eparina

AT + Xa + IIa (1:1 ratio)

1940

AVK

II, VII, IX, X (Proteina C, S)

1980

EBPM

AT + Xa + IIa (Xa > IIa)

1990

Inibitori diretti della trombina

IIa

2002

Inibitori indiretti del Fattore Xa

AT + Xa

Ximelagatran 2006

2004

Inibitori orali diretti della trombina

IIa

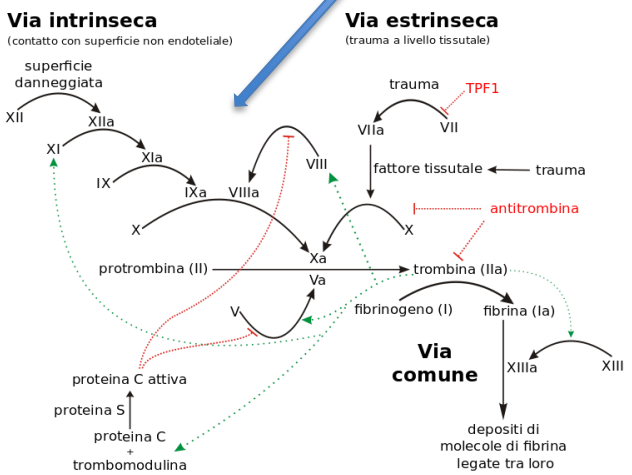
2008

Inibitori orali diretti del Fattore Xa

Xa

2020-21 ?

Inibitori orali diretti del fattore XI



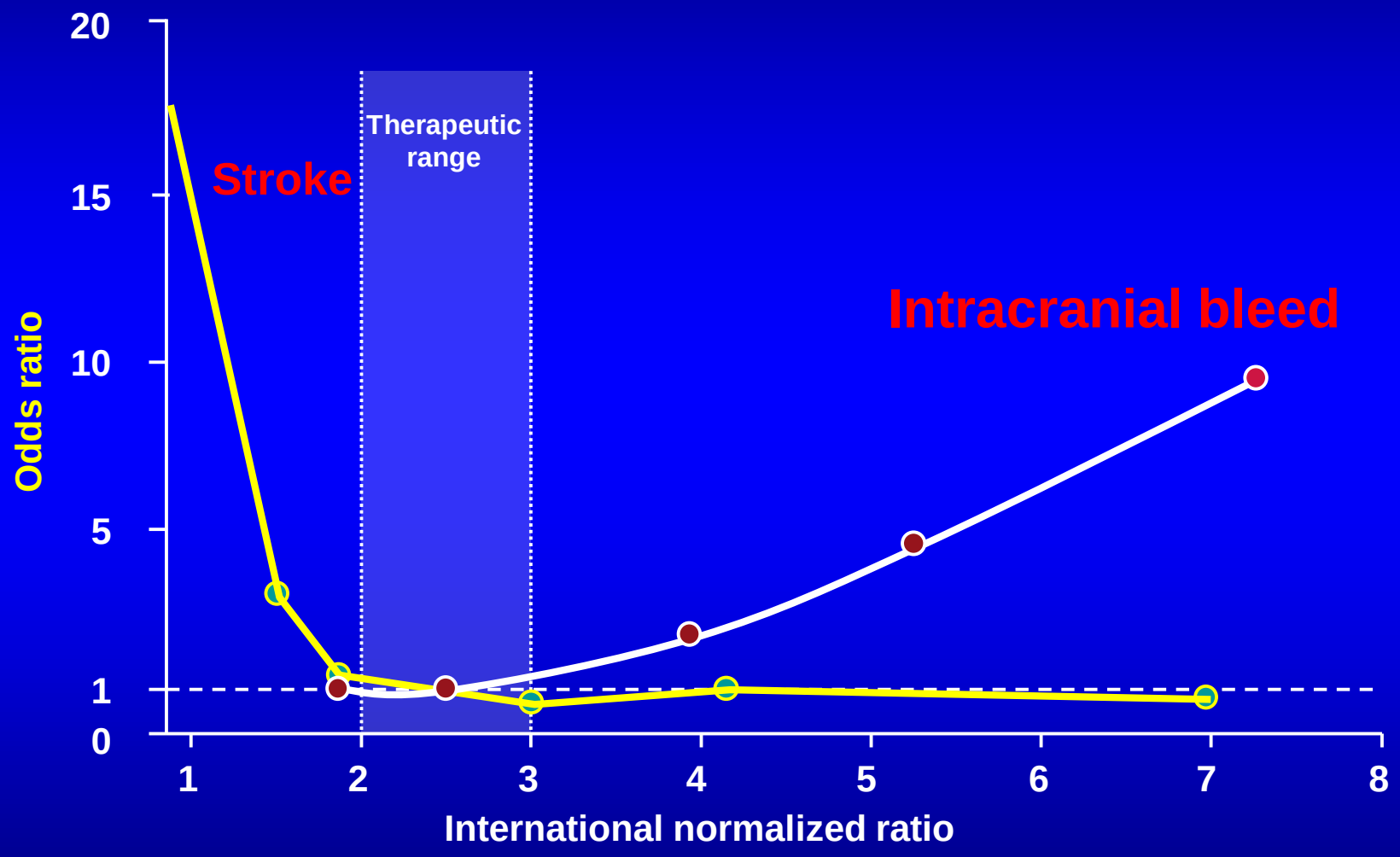
AVK, antagonisti della vitamina K; EBPM, eparina a basso peso molecolare.

Modificata da Perzborn E, et al. *Nat Rev Drug Discov* 2011;10:61-75

Anticoagulanti tradizionali

Limiti

VKAs have a Narrow Therapeutic Window

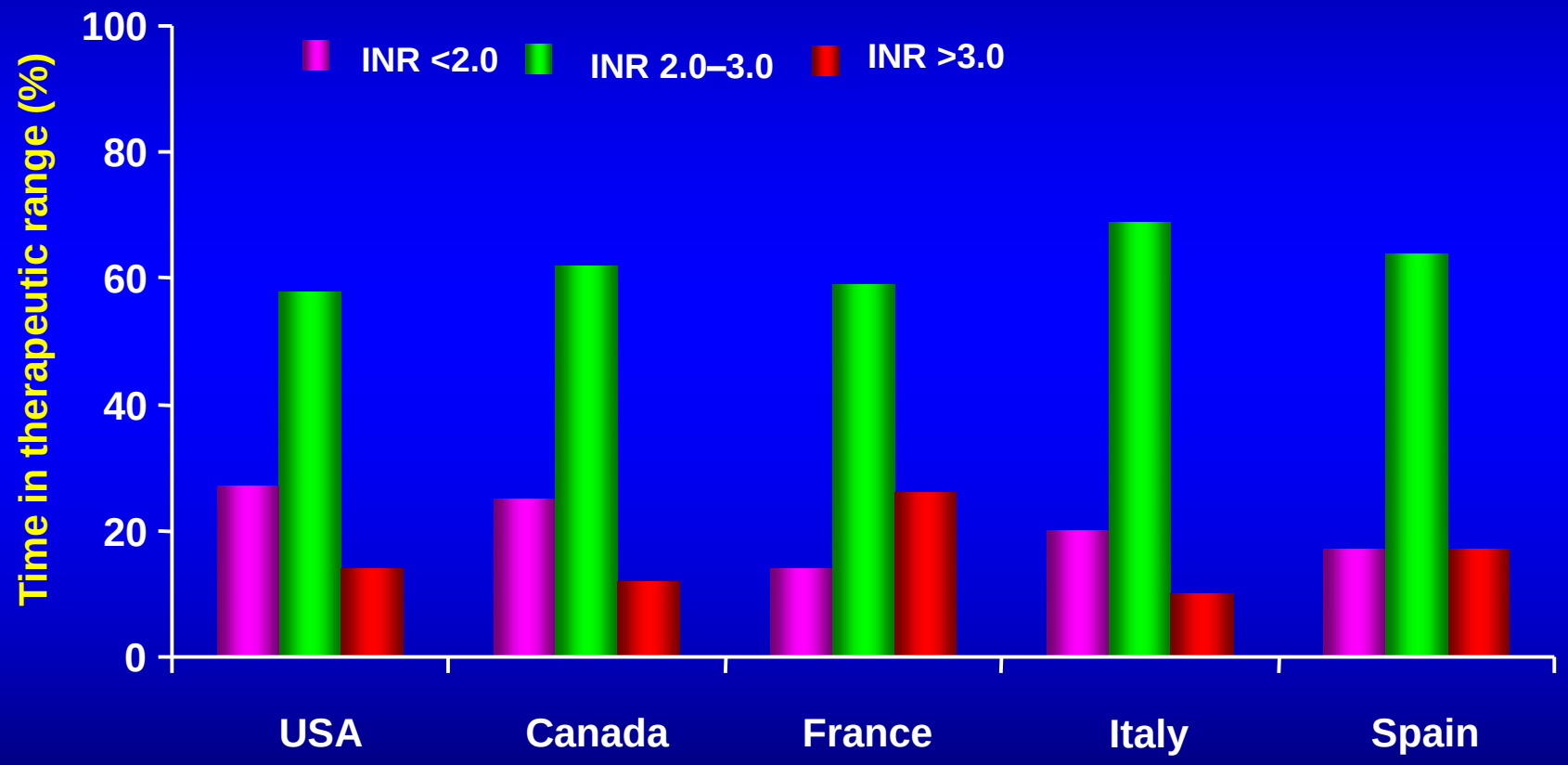


VKAs = vitamin K antagonists

ACC/AHA/ESC guidelines: Fuster V et al. Circulation 2006;114:e257–354& Eur Heart J 2006;27:1979–2030

Graph reproduced with permission: ©2010 American College of Chest Physicians

The INR for VKAs is Often Outside the Therapeutic Range: International Study of Anticoagulation Management



The predominant vitamin K antagonist (VKA) in use was warfarin in the USA, Canada and Italy; acenocoumarol in Spain; and fluindione in France; INR = international normalized ratio

Ansell J et al. J Thromb Thrombolysis 2007;23:83–91

Limitations of warfarin

- Delayed onset/effect
- Multiple food and drug interactions
- Genetic variability in metabolism (VKORK1 and CYP2C9)
- Requires frequent monitoring of INR because of limited therapeutic index

Range terapeutico raccomandato per la terapia anticoagulante orale

Indicazione	INR
Profilassi della trombosi venosa (chirurgia ad alto rischio)	
Trattamento della trombosi venosa	
Trattamento dell'embolia polmonare	
Prevenzione dell'embolia sistemica	
Valvole cardiache tissutali	2.0-30
IMA (per prevenire l'embolia sistemica)*	
Valvulopatia cardiaca	
Fibrillazione atriale	
Protesi valvolari meccaniche (ad alto rischio)	2.5-3.5
Valvola meccanica a doppio disco in posizione aortica	2.0-3.0

*Qualora la terapia anticoagulante orale sia instaurata al fine di prevenire l'infarto miocardico, si raccomanda un INR di 2.5-3.5, secondo le raccomandazioni della Food and Drug Administration.

INR	Dose adjustment per week
≤1.5	↑ by 15%/week
1.6–1.9	↑ by 10%/week
2–2.9	Unchanged
3–3.9	↓ by 10%/week
4–4.9	Hold 1 dose, then restart with dose ↓ by 10%/week
≥5	Hold until INR is 2–3, then restart with dose ↓ by 15%/week

Properties of an ideal anticoagulant

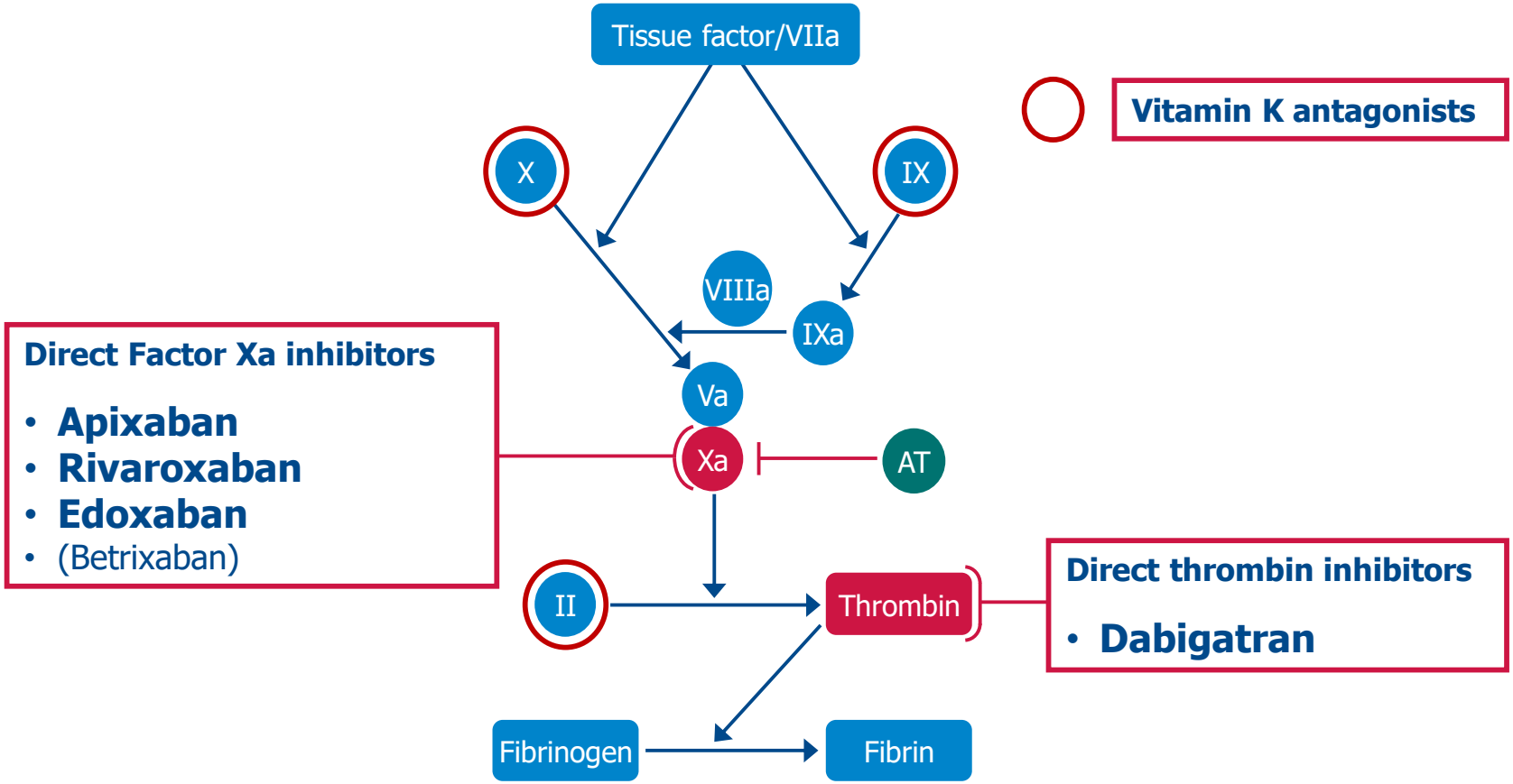
Properties	Benefit
Oral, once-daily dosing	Ease of administration
Rapid onset of action	No need for overlapping parenteral anticoagulant
Minimal food or drug interactions	Simplified dosing
Predictable anticoagulant effect	No coagulation monitoring
Extra renal clearance	Safe in patients with renal disease
Rapid offset in action	Simplifies management in case of bleeding or intervention
Antidote	For emergencies

New oral anticoagulants

Advantage	Clinical Implications
Rapid onset of action	No need for bridging
Predictable anticoagulant effect	No need for routine coagulation monitoring
Specific coagulation enzyme target	Low risk for off-target adverse effects
Low potential for food interactions	No dietary precautions
Low potential for drug interactions	Few drug restrictions

Eikelboom et al, Circulation 2010

Novel agents target specific molecules in the coagulation cascade



Weitz J, Bates S. J Thromb Haemost 2005;3:1843–53; Monroe D, Hoffman M. Arterioscler Thromb Vasc Biol 2006;26:41–8; Crawley J et al. J Thromb Haemost 2007;5 (Suppl 1):95–101

Caratteristiche farmacologiche dei NAO (1)

	Dabigatran	Rivaroxaban	Apixaban	Edoxaban
Meccanismo d'azione	Inibitore diretto trombina	Inibitore diretto FXa	Inibitore diretto FXa	Inibitore diretto FXa
Biodisponibilità	6,5%	80-100% (con cibo)	50%	62%
Frequenza giornaliera	Due volte	Una volta	Due volte	Una volta
Pro-farmaco	Sì	No	No	No
Interazioni alimentari	No	No	No	No
t_{max}	0,5-2 ore	2-4 ore	1-3 ore	1-2 ore
Emivita ($t_{1/2}$)	14-17 ore	5-9 ore nel paziente giovane 11-13 ore nel paziente anziano	10-15 ore	9-11 ore
Clearance renale farmaco attivo	85%	33%	25%	39%
controindicato con CrCl	<30 ml/min	<15 ml/min	<15 ml/min	<30 ml/min
dosaggio per CKD	Non studiato nel RE-LY	15 mg	5 o 2,5* mg	15-30 mg
Avvertenze	• assorbimento pH-dipendente • non aprire la capsula	• assumere con cibo	–	-

*In presenza di almeno 2 dei seguenti criteri: ≥80 anni, ≤60 kg, creatininemia 1,5 mg/dl.
CrCl, clearance della creatinina; CKD, malattia renale cronica.

	Dabigatran[158,182]	Apixaban[183]	Edoxaban[184]	Rivaroxaban[185,186]
Bioavailability	3–7%	50%	62%	15 mg/20 mg: 66% without food, 80–100% with food
Prodrug	Yes	No	No	No
Clearance non-renal/renal of absorbed dose	20%/80%	73%/27%	50%/50%	65%/35%
Plasma protein binding	35%	87%	55%	95%
Dialysability	50–60% (in part dialysable)	14% (in part dialysable)	n.a. (in part dialysable)	n.a. (in part dialysable)
Liver metabolism: CYP3A4 involved	No	Yes [elimination, moderate contribution (≈25%)[a]]	Minimal (<4% of elimination)	Yes (hepatic elimination ≈18%)[131]
Absorption with food	No effect	No effect	6-22% more; minimal effect on exposure	+39% more (see above)
Absorption with H2B/PPI	-12% to 30% (not clinically relevant)	No effect	No effect	No effect
Asian ethnicity	+25%[166]	No effect	No effect	No effect
Elimination half-life	12–17 h	12 h	10–14 h	5–9 h (young)
				11–13 h (elderly)
Other	Dyspepsia (5–10%)			Intake of 15 mg/20 mg with food mandatory

[a]Hepatic metabolism in total of ≈25%, mostly via CYP3A4, with minor contributions of CYP1A2, 2J2, 2C8, 2C9, and 2C19.

	Rivaroxaban	Dabigatran	Apixaban	Edoxaban
Prevenzione TEV in ortopedia (anca e ginocchio)	✓	✓	✓	
Ictus/embolia in FANV	✓	✓	✓	✓
Trattamento di TVP ed EP	✓	✓	✓	✓
Malattia coronarica o malattia sintomatica delle arterie periferiche ad alto rischio di eventi ischemici e anche dopo sindrome coronarica acuta	✓			

EP, embolia polmonare; FANV, fibrillazione atriale non valvolare;; TEV, tromboembolismo venoso; TVP, trombosi venosa profonda.

Condition	Eligibility for NOAC therapy
Mechanical prosthetic valve	Contraindicated
Moderate to severe mitral stenosis (usually of rheumatic origin)	Contraindicated
Mild to moderate other native valvular disease (e.g., mild-moderate aortic stenosis or regurgitation, degenerative mitral regurgitation etc.)	Included in NOAC trials
Severe aortic stenosis	Limited data (excluded in RE-LY) Most will undergo intervention
Bioprosthetic valve (after > 3 months post operatively)	Not advised if for rheumatic mitral stenosis
	Acceptable if for degenerative mitral regurgitation or in the aortic position
Mitral valve repair (after > 3 months post operatively)	Some patients included in some NOAC trials
PTAV and TAVI	No prospective data yet May require combination with single or dual antiplatelet therapy
Hypertrophic cardiomyopathy	Few data, but patients may be eligible for NOACs

NOACs
Important Comparative Features

Dabigatran
- Oral direct thrombin inhibitor
- Twice-daily dosing
- Renal clearance 80%

Rivaroxaban
- Direct factor Xa inhibitor
- Once daily
- Renal clearance 33%

Apixaban
- Direct factor Xa inhibitor
- Twice-daily dosing
- Renal clearance 25%

Edoxaban
- Direct factor Xa inhibitor
- Once-daily dosing
- Renal clearance 35%

Eikelboom JW, Weitz JI. *Circulation*. 2010;121:1523-1532.[8]

Atrial Fibrillation

CHADS2 - CHADSVASC

Stroke risk scoring in atrial fibrillation patients

	CHADS2	CHA2DS2-VASc
Heart failure	1 point	1 point
Hypertension	1 point	1 point
Age 75 years or older	1 point	2 points
Diabetes	1 point	1 point
Stroke history	2 points	2 points
Vascular disease		1 point
Age 65-74 years		1 point
Sex category (female)		1 point

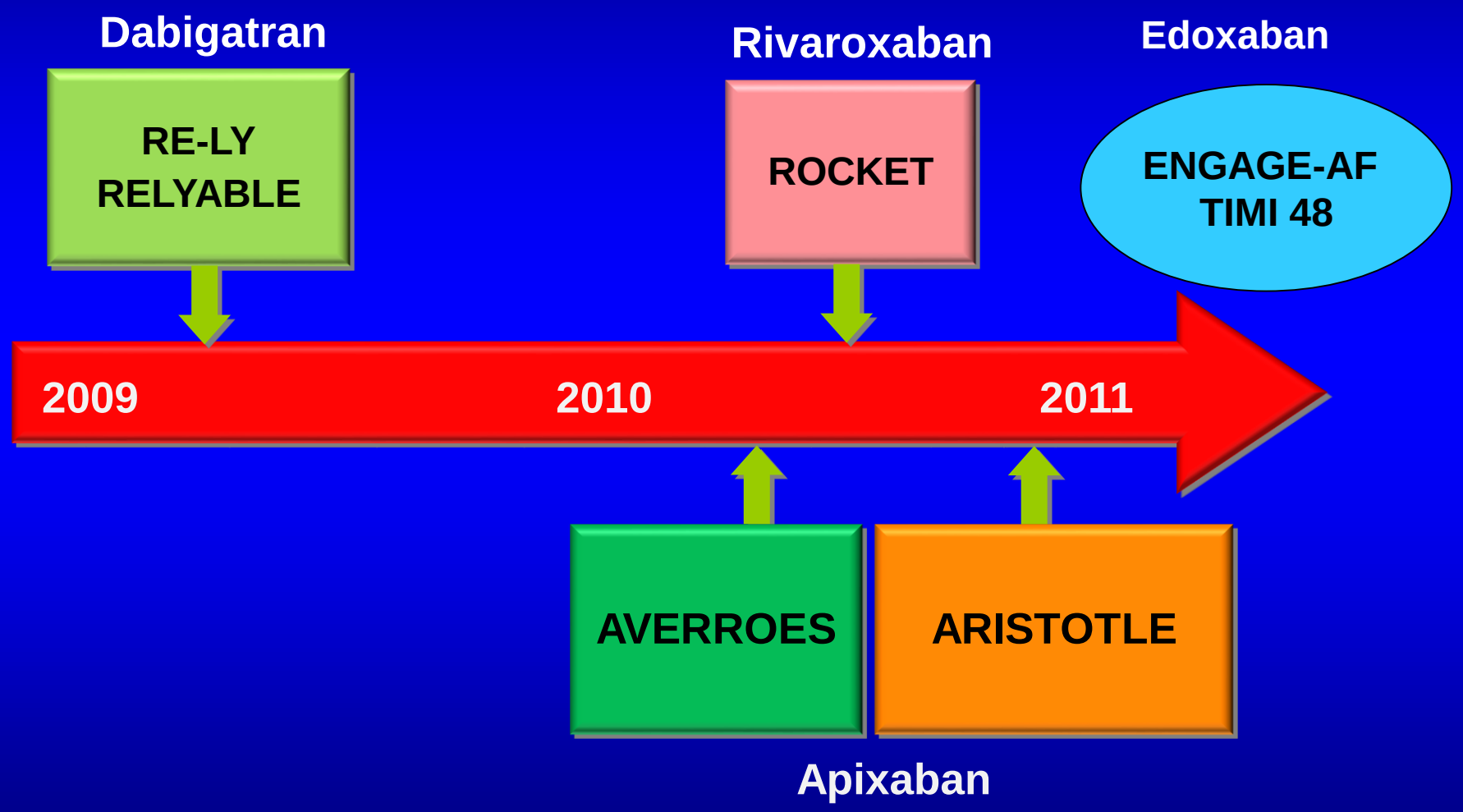
CHADS2: Maximum possible score of 6. Use anticoagulation in patients with a score of 2; consider anticoagulation for a score of 1.

CHA2DS2-VASc: Maximum possible score of 9. Use anticoagulation in patients with a score of 2; consider anticoagulation for a score of 1.

Source: Dr. Nabauer

IMNG Medical Media

Atrial Fibrillation Phase 3 Study Timelines



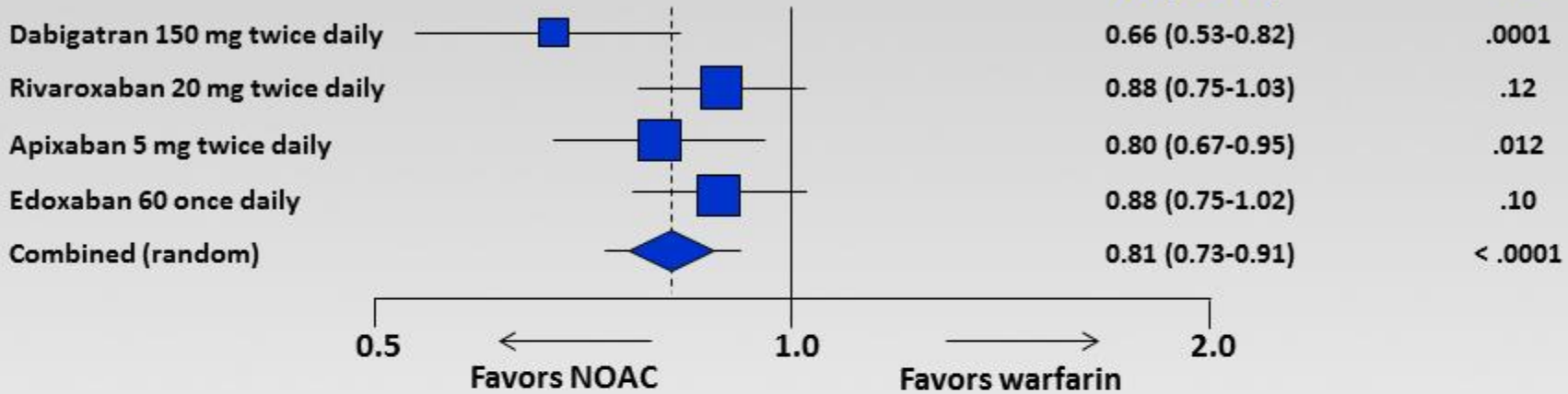
RCTs Comparing Efficacy and Safety of NOACs With Warfarin: Prevention of Stroke/Systolic Embolism in NVAF

RE-LY[a]	ROCKET-AF[b]	ARISTOTLE[c]	ENGAGE AF-TIMI 48[d]
Dabigatran	Rivaroxaban	Apixaban	Edoxaban
Direct thrombin inhibitor	Activated Factor Xa inhibitor	Activated Factor Xa inhibitor	Activated Factor Xa inhibitor
110 & 150 mg twice daily	20 mg once daily	5 mg twice daily	30 & 60 mg once daily
18,113	14,264	18,201	21,105
CHADS2 2.1	CHADS2 3.5	CHADS2 2.1	CHADS2 2.8

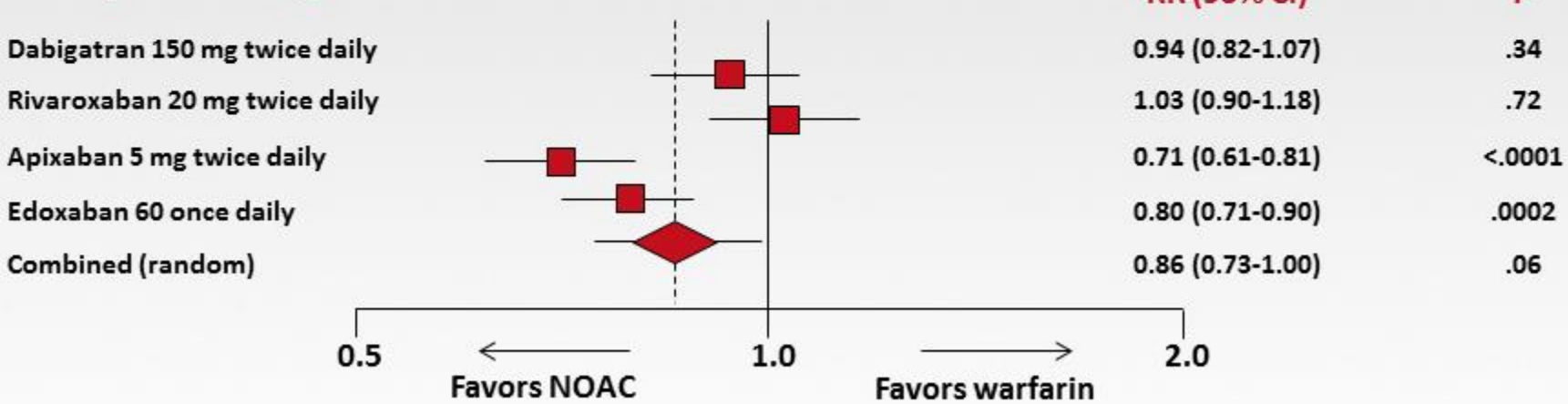
a. Connolly SJ, et al. *N Engl J Med.* 2009;361(12):1139-1151.
b. Patel MR, et al. *N Engl J Med.* 2011; 365(10):883-891.
c. Granger CB, et al. *N Engl J Med.* 2011;365(11):981-992.
d. Giugliano RP, et al. *N Engl J Med.* 2013; 369(22):2093-2104.

NOACs vs Warfarin: Recent Meta-Analysis of RCTs

Stroke/Systemic Embolism: Overall ~19% Risk Reduction



Major Bleeding: Overall ~14% Risk Reduction

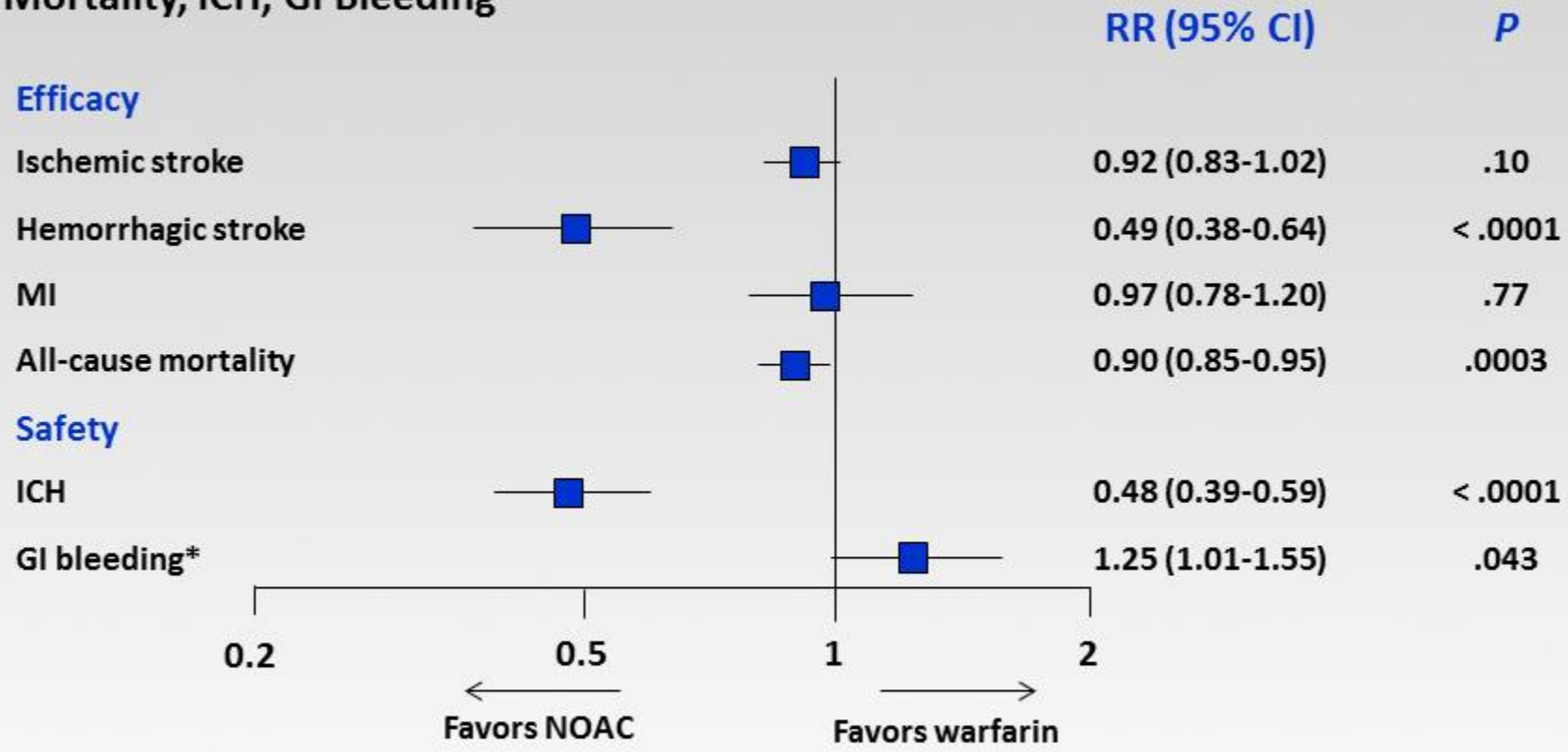


CI = confidence interval; RR = risk ratio

Ruff CT, et al. *Lancet*. 2013 Dec 3. Epub ahead of print.

NOACs vs Warfarin: Recent Meta-Analysis of RCTs (cont)

Overall Risk of Secondary Outcomes: Ischemic Stroke, Hemorrhagic Stroke, MI, Mortality, ICH, GI Bleeding



*Heterogeneity: GI bleeding I/2=74%, *P*=.009

GI = gastrointestinal; ICH = intracranial hemorrhage

Ruff CT, et al. *Lancet*. 2013 Dec 3. Epub ahead of print.

ESC European Society of Cardiology
European Heart Journal (2020) 42, 373–498
doi:10.1093/eurheartj/ehaa612

2020 ESC Guidelines for the diagnosis and management of atrial fibrillation developed in collaboration with the European Association for Cardio-Thoracic Surgery (EACTS)

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

Recommendations for the prevention of thrombo-embolic events in AF

Recommendations	Class[a]	Level[b]
For stroke prevention in AF patients who are eligible for OAC, NOACs are recommended in preference to VKAs (excluding patients with mechanical heart valves or moderate-to-severe mitral stenosis).[423,424]	I	A
For stroke risk assessment, a risk-factor-based approach is recommended, using the CHA_2DS_2-VASc clinical stroke risk score to initially identify patients at 'low stroke risk' (CHA_2DS_2-VASc score = 0 in men, or 1 in women) who should not be offered antithrombotic therapy.[334,388]	I	A
OAC is recommended for stroke prevention in AF patients with CHA_2DS_2-VASc score ≥2 in men or ≥3 in women.[412]	I	A
OAC should be considered for stroke prevention in AF patients with a CHA_2DS_2-VASc score of 1 in men or 2 in women. Treatment should be individualized based on net clinical benefit and consideration of patient values and preferences.[338,378,380]	IIa	B
For bleeding risk assessment, a formal structured risk-score-based bleeding risk assessment is recommended to help identify non-modifiable and address modifiable bleeding risk factors in all AF patients, and to identify patients potentially at high risk of bleeding who should be scheduled for early and more frequent clinical review and follow-up.[388,395,404,406]	I	B

The HAS-BLED bleeding risk score

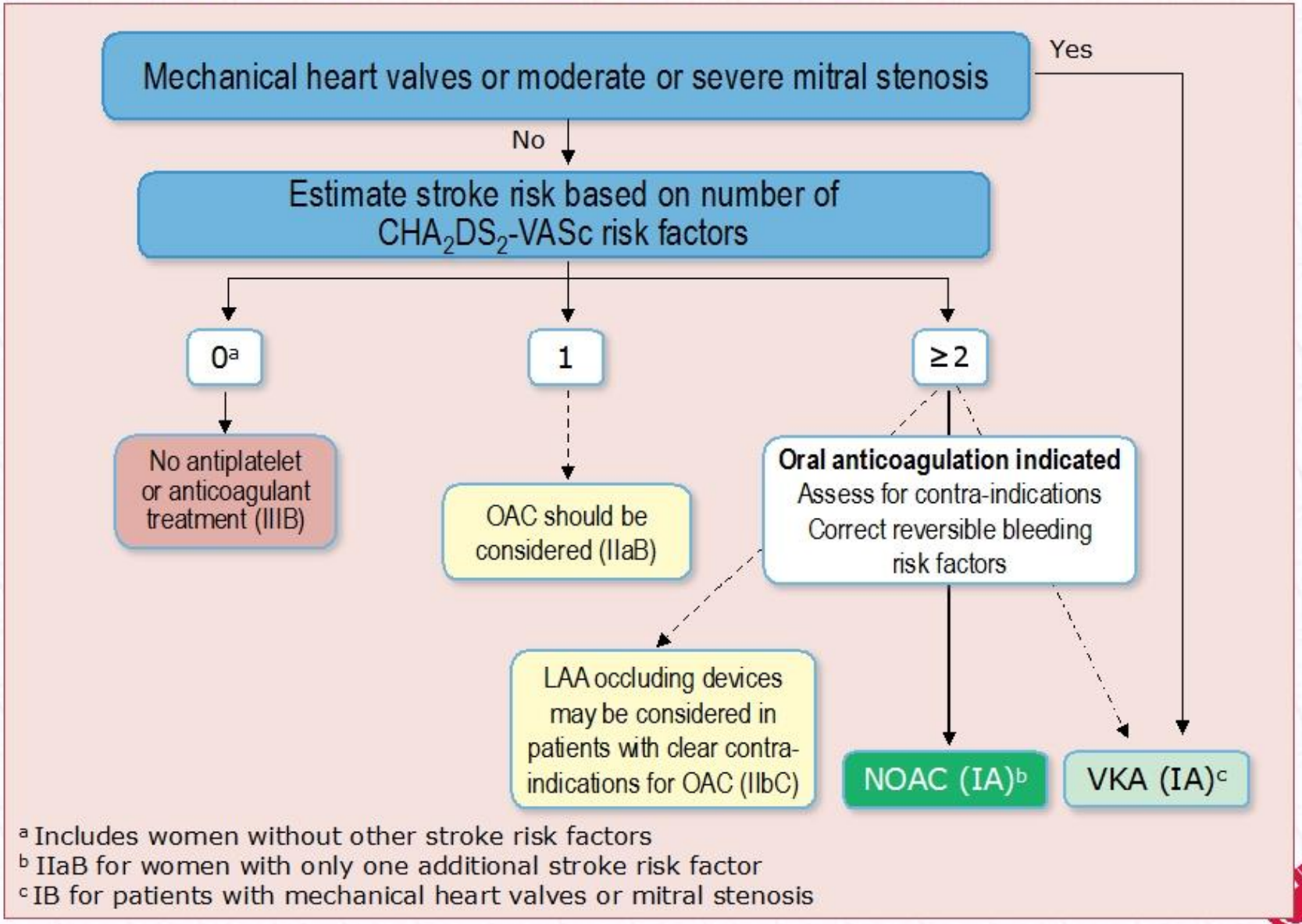
Letter	Clinical characteristic*	Points awarded
H	Hypertension	1
A	Abnormal renal and liver function (1 point each)	1 or 2
S	Stroke	1
B	Bleeding	1
L	Labile INRs	1
E	Elderly (e.g. age > 65 years)	1
D	Drugs or alcohol (1 point each)	1 or 2
		Maximum 9 points

rischio emorragico sostanziale con valori ≥3

*Hypertension is defined as systolic blood pressure > 160 mmHg.

INR = international normalized ratio.

Stroke prevention in atrial fibrillation



European Heart Journal - doi:10.1093/eurheartj/ehw210

EUROPEAN SOCIETY OF CARDIOLOGY®

Recommendations for Selecting an Anticoagulant Regimen—Balancing Risks and Benefits
Referenced studies that support new or modified recommendations are summarized in Online Data Supplements 1 and 2.

COR	LOE	RECOMMENDATIONS
I	A	1. For patients with AF and an elevated CHA_2DS_2-VASc score of 2 or greater in men or 3 or greater in women, oral anticoagulants are recommended. Options include: ▪ Warfarin (LOE: A) (S4.1.1-5-S4.1.1-7) ▪ Dabigatran (LOE: B) (S4.1.1-8) ▪ Rivaroxaban (LOE: B) (S4.1.1-9) ▪ Apixaban (LOE: B) (S4.1.1-10), or ▪ Edoxaban (LOE: B-R) (S4.1.1-11) MODIFIED: This recommendation has been updated in response to the approval of edoxaban, a new factor Xa inhibitor. More precision in the use of CHA_2DS_2-VASc scores is specified in subsequent recommendations. The LOEs for warfarin, dabigatran, rivaroxaban, and apixaban have not been updated for greater granularity as per the new LOE system. (Section 4.1. in the 2014 AF Guideline) The original text can be found in Section 4.1 of the 2014 AF guideline. Additional information about the comparative effectiveness and bleeding risk of NOACs can be found in Section 4.2.2.2.
	B	
	B	
	B	
	B-R	
I	A	2. NOACs (dabigatran, rivaroxaban, apixaban, and edoxaban) are recommended over warfarin in NOAC-eligible patients with AF (except with moderate-to-severe mitral stenosis or a mechanical heart valve) (S4.1.1-8-S4.1.1-11). NEW: Exclusion criteria are now defined as moderate-to-severe mitral stenosis or a mechanical heart valve. When the NOAC trials are considered as a group, the direct thrombin inhibitor and factor Xa inhibitors were at least noninferior and, in some trials, superior to warfarin for preventing stroke and systemic embolism and were associated with lower risks of serious bleeding.

AD PROOF

January C et al J Am Coll Cardiol. 2019 Jan 21. pii: S0735-1097(19)30209-8

Recommendations for acute-phase treatment of intermediate- or low- risk PE (1)

ESC
European Society of Cardiology

Recommendations	Class	Level
Initiation of anticoagulation		
Initiation of anticoagulation is recommended without delay in patients with high or intermediate clinical probability of PE, while diagnostic work-up is in progress.	I	C
If anticoagulation is initiated parenterally, LMWH or fondaparinux is recommended (over UFH) for most patients.	I	A
Oral anticoagulants		
When oral anticoagulation is started in a patient with PE who is eligible for a NOAC (apixaban, dabigatran, edoxaban, or rivaroxaban), a NOAC is recommended in preference to a VKA.	I	A

NOAC = non-vitamin K antagonist oral anticoagulant; LMWH = low molecular weight heparin; VKA = vitamin K antagonist; UFH = unfractionated heparin.

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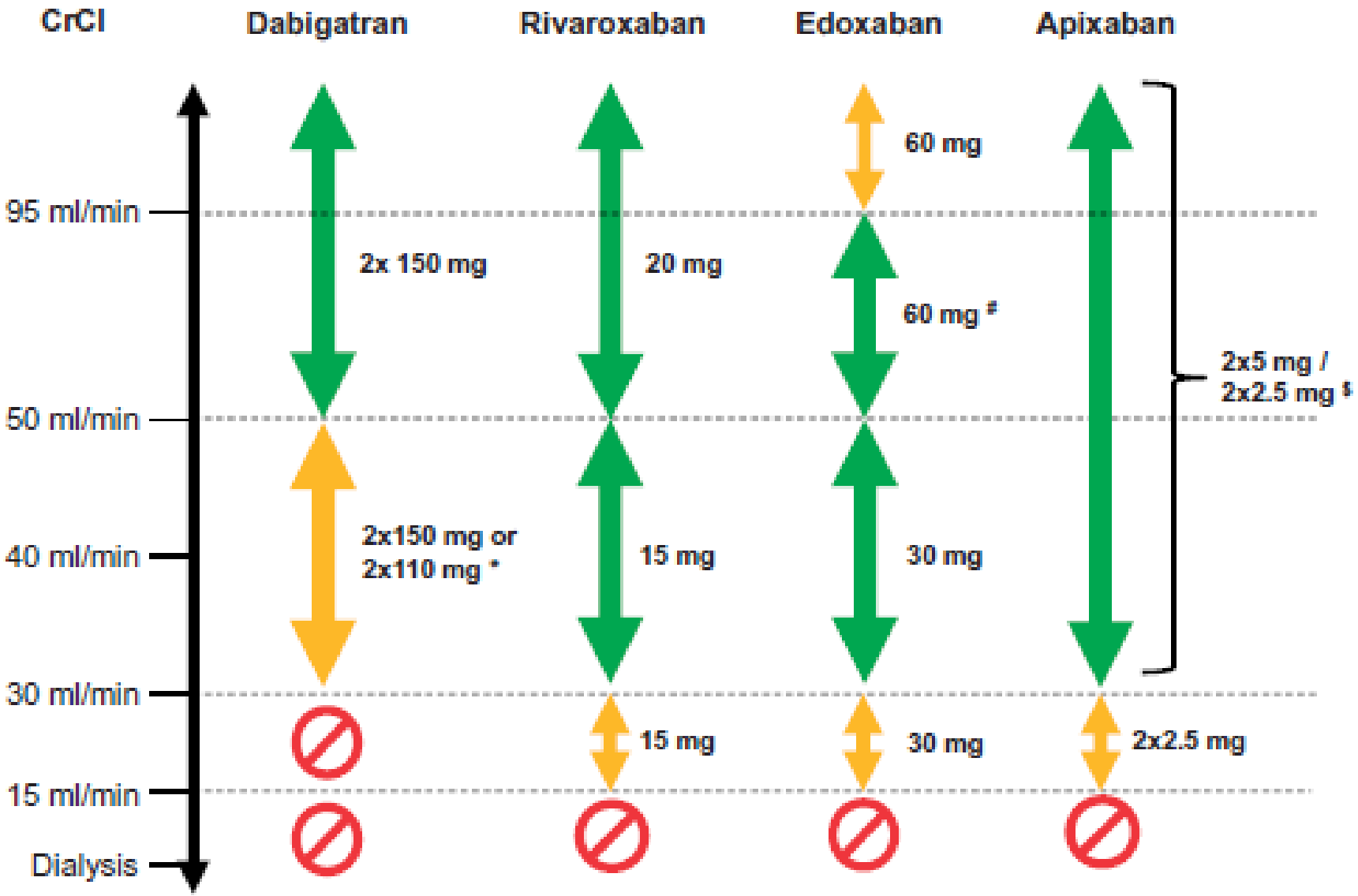
2019 ESC Guidelines on the diagnosis and management of acute pulmonary embolism
(European Heart Journal 2019 - doi/10.1093/eurheartj/ehz405)

Decreased GFR[a]	GFR <60 mL/min/1.73 m^2		
Markers of kidney damage (≥1)	• Excessive albuminuria (AER ≥30 mg/24 h; ACR ≥30 mg/g or ≥3 mg/mmol) • Urine sediment abnormalities • Electrolyte or other abnormality caused by tubular disorders • Abnormal histology • Structural abnormalities detected by kidney imaging • History of kidney transplantation		
GFR category	CKD stage	GFR[a]	Descriptions
G1	1	≥90	Normal or high
G2	2	60–89	Mildly decreased
G3a	3	45–59	Mildly to moderately decreased
G3b		30–44	Moderately to severely decreased
G4	4	15–29	Severely decreased
G5	5	<15	Kidney failure (requires renal replacement therapy – dialysis or kidney transplantation)

Estimation of renal function in NOAC patients best by Creatinine Clearance (Cockroft–Gault):

$$\text{CrCl [mg/dl]} = \frac{(140 - \text{age}) \times \text{weight (in kg)} \times [0.85 \text{ if female}]}{72 \times \text{serum creatinine (in mg/dL)}]}$$


CrCl
Dabigatran
Rivaroxaban
Edoxaban
Apixaban
95 ml/min
50 ml/min
40 ml/min
30 ml/min
15 ml/min
Dialysis
2x 150 mg
20 mg
60 mg
60 mg #
2x5 mg /
2x2.5 mg $
2x150 mg or
2x110 mg *
15 mg
30 mg
15 mg
30 mg
2x2.5 mg

Recommendations for OAC in CKD

CrCl	Warfarin	Dabigatran		Rivaroxaban	Apixaban
		Europe	USA		
eGFR ≥ 60	Yes	150 mg	150 mg	20 mg	5 mg
eGFR 50-59	Yes	150 mg	150 mg	20 mg	5 mg
eGFR 30-49	Yes	110 mg	150 mg	15 mg	5 mg
eGFR 25-29	Yes	No	75 mg	15 mg	2.5 mg
eGFR 15-24	Yes	No	75 mg	15 mg	2.5 mg
eGFR < 15	?Yes	No		No	No

CrCl = creatinine clearance; eGFR = estimated glomerular filtration rate

Hart RG, et al. *Can J Cardiol* 2013;29(7 Suppl):S71-S78.
Heidbuchel H, et al. *Europace*. 2013;15(5):625-651.

Table 8 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 μmol/L	34–50 μmol/L	>50 μmol/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

Table 9 **Plasma levels and coagulation assays in patients treated with non-vitamin K antagonist 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 *at peak* for standard dose (ng/mL)[a]	64–443	69–321	91–321	184–343
Expected range of plasma levels *at trough* 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	↑↑↑↑	—	—	—

Caratteristiche farmacologiche dei NAO (2)

	Dabigatran	Rivaroxaban	Apixaban
Interazioni farmacologiche	Inibitori/induttori P-gp	Inibitori/induttori CYP3A4 Inibitori P-gp	
Utilizzo con cautela	Inibitori/induttori P-gp: • claritromicina • amiodarone • chinidina • verapamil	Inibitori/induttori di CYP o P-gp: • claritromicina • eritromicina • rifampicina • carbamazepina • fenobarbital • iperico	
Controindicati	Forte inibitore/induttore P-gp: • ketoconazolo • itraconazolo • posaconazolo • ciclosporina • carbamazepina • iperico • fenitoina • ritonavir	Forte inibitore CYP3A4 e P-gp: • ketoconazolo • itraconazolo • voriconazolo • posaconazolo • ritonavir	

Effect on NOAC Plasma Levels From Drug-Drug Interactions, and Recommendations

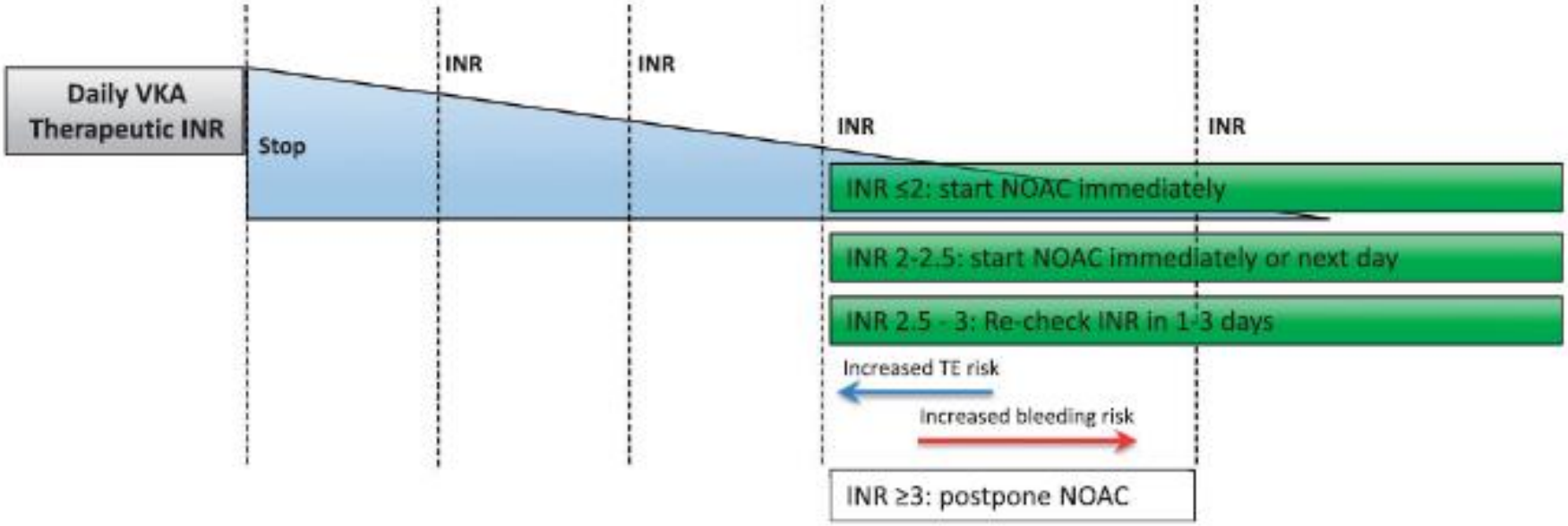
Not recommended/contraindicated
Reduce dose if 2 factors or more
Reduce dose
No data yet

	via	Dabigatran	Apixaban	Edoxaban*	Rivaroxaban
Atorvastatin	P-gp weak CYP3A4	+18%	No data	No effect	No effect
Digoxin	P-gp	No effect	No data	No effect	No effect
Verapamil	P-gp weak CYP3A4	+12%-180% reduce dose, take together	No data	+53% (SR) Reduce dose	Minor effect Use with caution if CrCl: 15-50 mL/min
Diltiazem	P-gp weak CYP3A4	No effect	+40%	No data	Minor effect Use with caution if CrCl: 15-50 mL/min
Quinidine	P-gp	+50%	No data	+80% Reduce dose	+50%
Amiodarone	P-gp	+12%-60%	No data	No effect	Minor effect Use with caution if CrCl: 15-50 mL/min
Dronedarone	P-gp weak CYP3A4	+70%-100%	No data	+88% Reduce dose	No data

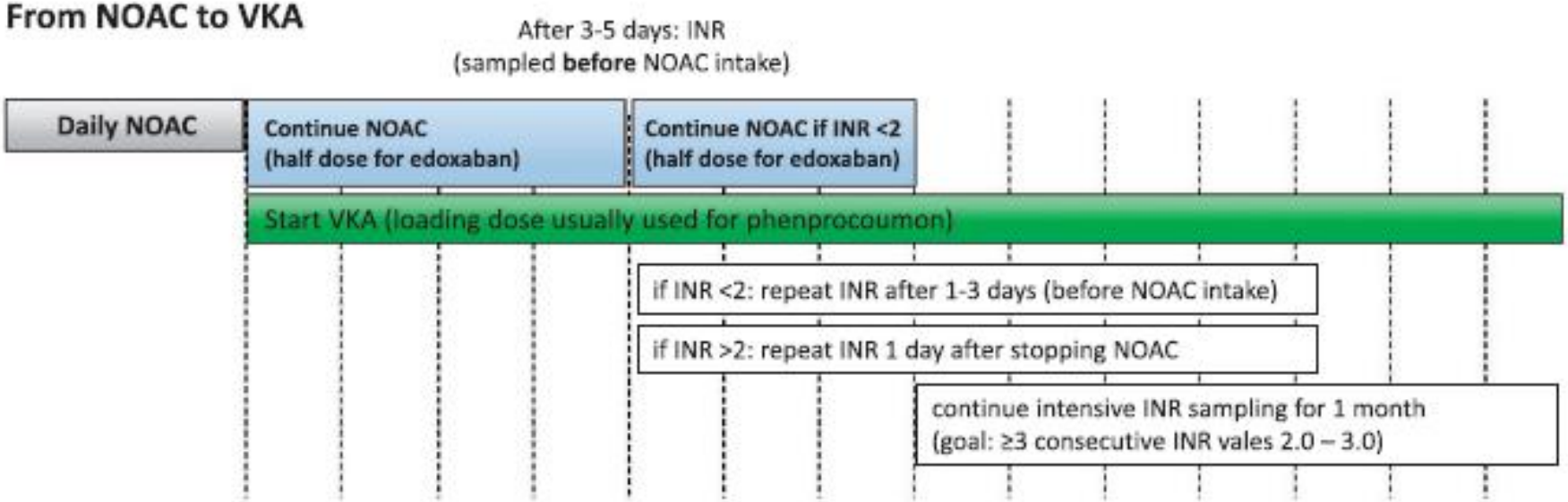
*Not approved for clinical use

Heidbuchel H, et al. *Europace*. 2013;15(5):625-651.

From VKA to NOAC



From NOAC to VKA



Last Intake of NOAC Before Elective Surgical Intervention

	Dabigatran		Apixaban		Edoxaban*		Rivaroxaban	
	No important bleeding risk and/or adequate local hemostasis possible: perform at trough level (ie, ≥ 12h or 24h after last intake)							
	Low risk	High risk	Low risk	High risk	Low risk	High risk	Low risk	High risk
CrCl ≥ 80 mL/min	≥ 24h	≥ 48h	≥ 24h	≥ 48h	No data	No data	≥ 24h	≥ 48h
CrCl 50-80 mL/min	≥ 36h	≥ 72h	≥ 24h	≥ 48h	No data	No data	≥ 24h	≥ 48h
CrCl 30-50 mL/min	≥ 48h	≥ 96h	≥ 24h	≥ 48h	No data	No data	≥ 24h	≥ 48h
CrCl 15-30 mL/min	Not indicated	Not indicated	≥ 36h	≥ 48h	No data	No data	≥ 36h	≥ 48h
CrCl <15 mL/min	No official indication for use							

*Not approved for clinical use

Heidbuchel H, et al. *Europace*. 2013;15(5):625-651.

Periprocedural Management of NOACs: EHRA Practical Guide

Procedure	Anticoagulation Management
Dental interventions - Extraction of 1-3 teeth - Periodontal surgery, incision of abscess, implant Ophthalmology - Cataract or glaucoma intervention - Endoscopy without surgery - Superficial surgery (dermatologic excisions)	Very low bleeding risk: Discontinuation of OAC not usually required (perform procedure at concentration)
Endoscopy with biopsy Prostate or bladder biopsy EP study or SVT ablation with transseptal access Angiography PM or ICD implant (uncomplicated)	Low bleeding risk: Discontinue NOAC 24 hours prior to procedure (longer in patients with renal dysfunction)
Complex left-sided ablation (PVI, VT) Spinal or epidural anesthesia, lumbar diagnostic procedures Thoracic and abdominal surgery Liver and kidney biopsy TURP Major orthopedic surgery	High bleeding risk: Discontinue NOAC 48 hours prior to procedure (longer in patients with renal dysfunction)

Heidbuchel H, et al. *Europace*. 2013;15(5):625-651.

RACCOMANDAZIONI

Range terapeutico < INR < 5 in assenza di sanguinamento clinicamente significativo	Omissione della dose successiva e riduzione del dosaggio quotidiano
5 < INR < 9 in assenza di sanguinamento clinicamente significativo	Omissione di una o più dosi successive, monitoraggio INR e, quando INR rientri nel range, ripristino terapia ad un dosaggio inferiore.
INR > 9 in assenza di sanguinamento clinicamente significativo	Somministrazione di vitamina K_1 per via orale (3-5 mg) e monitoraggio INR nelle 24-48 ore successive (se non vi sia una riduzione sostanziale, ripetere vit. K_1.
Presenza di sanguinamento grave o sovraddosaggio di warfarin (INR > 20)	Somministrazione di K_1 10 mg in infusione e.v. lenta, trasfusione di plasma fresco o complesso concentrato di protrombina (sec. gravità). Ev. somm. K_1 ogni 12 h.
Presenza di sanguinamento potenzialmente letale o grave sovraddosaggio di warfarin	Somministrazione di complesso concentrato di protrombina con 10 mg di vit. K_1 in infusione e.v. lenta; il trattamento può essere ripetuto in base a INR
Necessità di proseguire a terapia con warfarin dopo somm. Di vit. K_1	Somministrazione di eparina fino a che non siano corretti gli effetti della vit. K_1 ed il pz torni a rispondere alla terapia con warfarin.

Idarucizumab

ISTITUTO CLINICO
CITTÀ DI BRESCIA

Brescia, 9 maggio 2016
Prot. 151/PA/sm

Alla cortese attenzione

Signori Medici Responsabili
Loro UU.OO. e/o Servizi
Coordinatori Infermieristici
Loro UU.OO. e/o Servizi

E p.c. **Sig. Sebastian Dumbrava**
Resp.le Magazzino Farmacia

SEDE

Oggetto: **Inserimento del farmaco PRAXBIND nel Prontuario Terapeutico Ospedaliero (PTO).**

Si comunica che è stato inserito nel PTO dell'Istituto il farmaco Praxbind (idarucizumab) inattivatore specifico per dabigatran (Pradaxa).
Praxbind è indicato **nei pazienti adulti** in trattamento con Pradaxa in situazioni in cui è necessaria l'inattivazione rapida dei suoi effetti anticoagulanti:

- **Negli interventi chirurgici di emergenza/nelle procedure urgenti**
- **Nel sanguinamento potenzialmente fatale o non controllato**

In caso di necessità Praxbind (**da conservare a temperatura 2-8°C**) è reperibile presso il Pronto Soccorso dell'Istituto, previa richiesta scritta da parte del medico richiedente riportante i dati del paziente.
Con l'invito a dare ampia diffusione ai propri collaboratori della nota in allegato si inviano cordiali saluti.

ISTITUTO CLINICO
CITTÀ DI BRESCIA
Direttore Sanitario
Dr.ssa Piera Antonelli

La gestione dei sanguinamenti maggiori in corso di terapia con gli anticoagulanti orali diretti è complessa e può includere diverse opzioni terapeutiche. **Andexanet alfa** è un **antidoto** per i farmaci anticoagulanti **inibitori del fattore Xa** che “sequestra” le molecole anticoagulanti all’interno dello spazio vascolare e ne neutralizza l’effetto. Andexanet è stato approvato dall’agenzia regolatoria statunitense nel maggio 2018 per pazienti in terapia con apixaban o rivaroxaban e sanguinamenti incontrollati o potenzialmente fatali.
Sono stati recentemente pubblicati i risultati finali dello studio **ANNEXA-4** che ha arruolato 352 pazienti con emorragia maggiore entro 18 ore dalla somministrazione di anticoagulanti inibitori del fattore Xa (apixaban, rivaroxaban, edoxaban, enoxaparina).
Nonostante l’assenza di un gruppo di controllo in questo studio, andexanet alfa sembra essere una **molecola promettente**, con elevate percentuali di riduzione dell’attività anti-Xa e soprattutto di emostasi efficace, a discapito tuttavia di un incremento degli eventi trombotici. Una estensione di questo studio è in corso in Germania ed in Giappone e fornirà dati aggiuntivi di efficacia e sicurezza.

Ondexxya

Riassunto delle Caratteristiche del Prodotto
Ondexxya: ultimo aggiornamento pagina: 24/04/2020 (Fonte: A.I.FA.)
01.0 Denominazione del medicinale
Ondexxya 200 mg polvere per soluzione per infusione

02.0 Composizione qualitativa e quantitativa
Ogni flaconcino contiene 200 mg di andexanet alfa*.
Dopo ricostituzione, ogni mL di soluzione contiene 10 mg di andexanet alfa.
*Andexanet alfa è prodotto con la tecnologia del DNA ricombinante in cellule ovariche di criceto cinese (*Chinese Hamster Ovary*, CHO).
Per l'elenco completo degli eccipienti, vedere paragrafo 6.1.

03.0 Forma farmaceutica
Polvere per soluzione per infusione
Polvere liofilizzata di colore da bianco a biancastro.

04.0 INFORMAZIONI CLINICHE
04.1 Indicazioni terapeutiche
Per pazienti adulti trattati con un inibitore diretto del fattore Xa (FXa) (apixaban o rivaroxaban), quando è richiesta l'inversione della terapia anticoagulante a causa di emorragie potenzialmente fatali o incontrollate.

04.2 Posologia e modo di somministrazione
Uso esclusivamente ospedaliero. Posologia
Andexanet alfa viene somministrato sotto forma di bolo endovenoso a una velocità target di circa 30 mg/min in 15 minuti (dose bassa) o 30 minuti (dose elevata), seguito da un'infusione continua di 4 mg/min (dose bassa) o 8 mg/min (dose elevata) per 120 minuti.

Comparison of features of new Anticoagulants with Those of Warfarin

Features	Warfarin	New Agents
Onset	Slow	Rapid
Dosing	Variable	Fixed
Food effect	Yes	No
Drug interactions	Many	Few
Monitoring	Yes	No
Half-life	Long	Short
Antidote	Yes	YES

Ok definitivo di Aifa a prescrizione nuovi anticoagulanti orali da parte dei medici di famiglia

Pubblicata in Gazzetta Ufficiale la determina che sancisce l'adozione definitiva della Nota 97 dopo i 120 giorni di sperimentazione. I medici specialisti e i medici di medicina generale potranno continuare a prescrivere i nuovi anticoagulanti orali ad azione diretta (NAO/DOAC: apixaban, dabigatran, edoxaban, rivaroxaban) e gli antagonisti della vitamina K (AVK: warfarin e acenocumarolo) nei pazienti con FANV.

I regime di fornitura dei NAO/DOAC passa quindi definitivamente, solo per l'indicazione FANV, da Ricetta Ripetibile Limitativa (RRL) a Ricetta Ripetibile (RR). La scheda di prescrizione cartacea, che ha sostituito il Piano Terapeutico web AIFA, sarà informatizzata dal 1° dicembre 2020 e, pertanto, a partire da questa data, il monitoraggio attraverso il suddetto Piano Terapeutico non sarà più disponibile.

Considerare sempre nel singolo paziente il rapporto rischio/beneficio della terapia anticoagulante

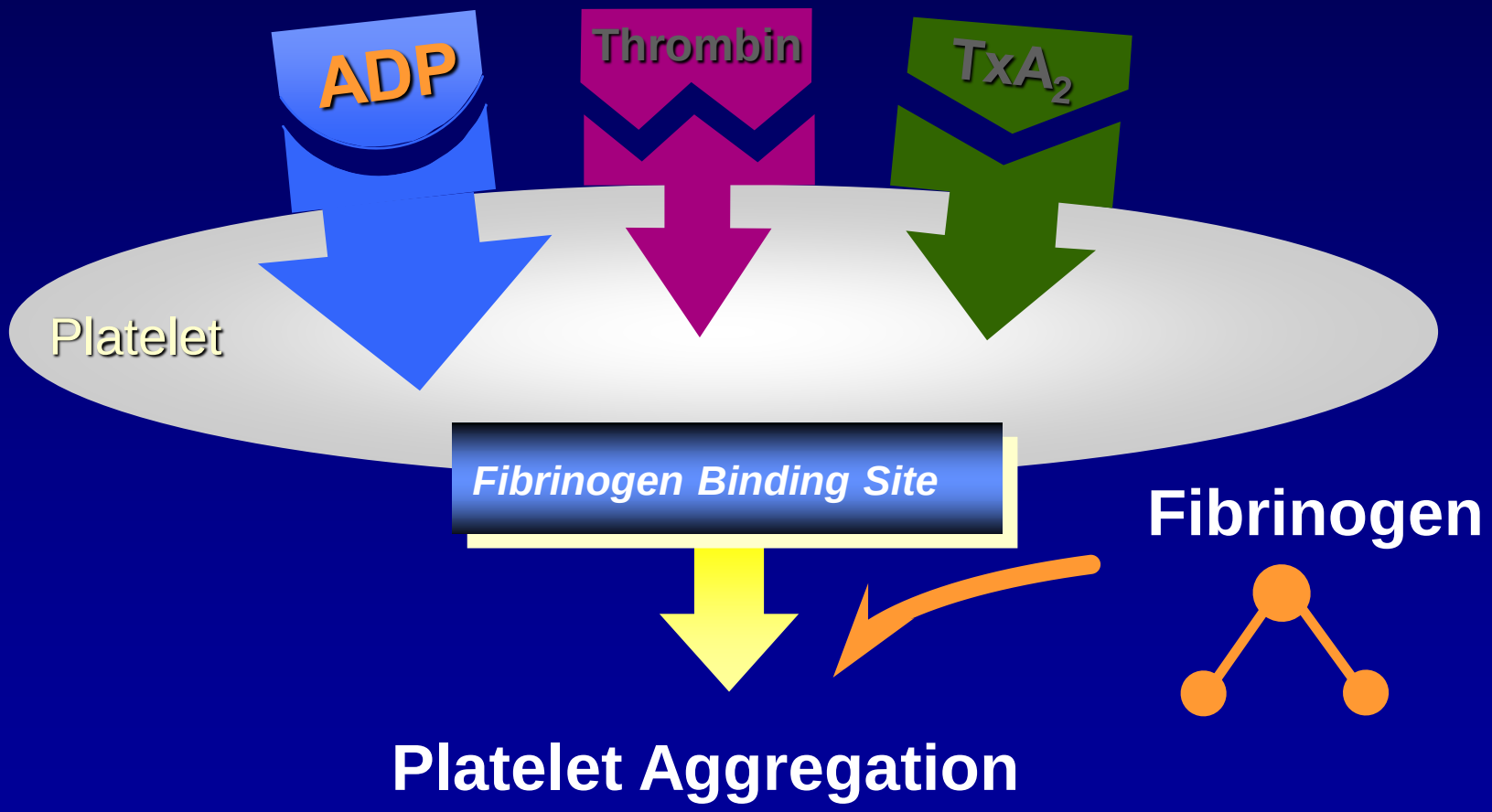
Giustificare per iscritto eventuali decisioni terapeutiche in contrasto con quanto suggerito da linee guida / indicazioni presenti in letteratura

FARMACI ANTIAGGREGANTI PIASTRINICI

Fase piastrinica

1. **Cox inibitori** (FANS: in particolare acido acetilsalicilico e dipiridamolo, Cox2 inibitori: vari coxib)
2. **Antagonisti dei recettori ADP** (Clopidogrel e Ticlopidina)
3. **Inibitori recettori gp IIB/IIIA gp α_{IIB} β_3** (abicximab, eptifibatide, tirofibam, lamifiban)
4. **Inibitori trombina** Ximelagatran: *epatotossicità. Dabigatran*

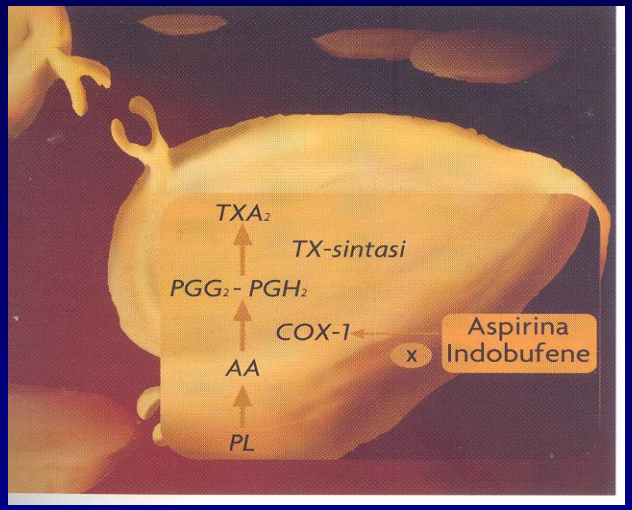
Platelet Activation Pathways



Major Platelet Aggregation Inhibitors

Drug	Mechanism of Action	Efficacy	Safety Profile
Clopidogrel	↓ ADP binding to receptor	+++	++
Aspirin	↓ TxA_2	++	++
Ticlopidine	↓ ADP binding to receptor	+++	+

Farmaci che interagiscono con il metabolismo dell'acido arachidonico



Interferiscono a vari livelli nella via biosintetica che, partendo dall'acido arachidonico liberato dai fosfolipidi di membrana porta alla sintesi di trombossano A2, amplificando i processi di attivazione piastrinica.

-Inibitori delle ciclo-ossigenasi COX-1 (acido acetilsalicilico)

- Inibitori della trombossano-sintetasi

- Inibitori del recettore del trombossano

- Farmaci ad azione combinata (picotamide)

Le ultime tre categorie: farmaci ancora in fase di sviluppo

Acido acetilsalicilico (ASA)

Acetilazione irreversibile della COX (PGH sintasi) delle piastrine (enzima costitutivo). Nelle piastrine è assente la COX-2 .

L'ASA acetila l' OH di un residuo serinico (Ser 529) posto a 70 aminoacidi dal C-terminale della catena → inattivazione irreversibile dell'enzima (no sintesi proteica nelle piastrine, inibizione persiste fino alla morte della cellula, circa 10 giorni).

Alle dosi comunemente impiegate (100-500 mg/die) l'effetto è selettivo per la COX-1 piastrinicA vs. COX endoteliale (che produce PGI_2 vasodilatante e antiaggregante).

L'ASA inibisce la aggregabilità piastrinica e allunga il tempo di sanguinamento. Non inibisce la adesione piastrinica.

Assorbimento gastrico e nella prima pare del tenue. Picco plasmatico entro 40'. Nella formulazione gastroprotetta → rilascio del principio attivo solo nell'intestino, picco a 3-4 ore. Effetto farmacologico dopo 30 min dall'assunzione, emivita 15-20 min, ma effetto biologico prolungato.

Metabolismo renale. Filtrazione glomerulare e secrezione attiva tubulare, eliminazione favorita a PH urinario basico. Rimuovibile con emodialisi.

Non è necessario alcun monitoraggio della aggregazione piastrinica

Acido acetilsalicilico (ASA)

Controindicazioni: dispepsia, lesioni gastriche (erosioni ulcere, ernia iatale sanguinante), sindromi emorragiche, (emofilia, malattia di Von Willebrand, trombocitopenie e trombocitopatie, gotta, grave insufficienza epatica o renale, bambini sotto i 12 anni (sindrome di Rey: encefalopatia con statosi epatica massiva).

Situazioni cliniche particolari:

- Gravidanza e allattamento: non teratogeno. Profilassi e terapia pre-eclampsia/eclampsia. Controindicato nell'allattamento

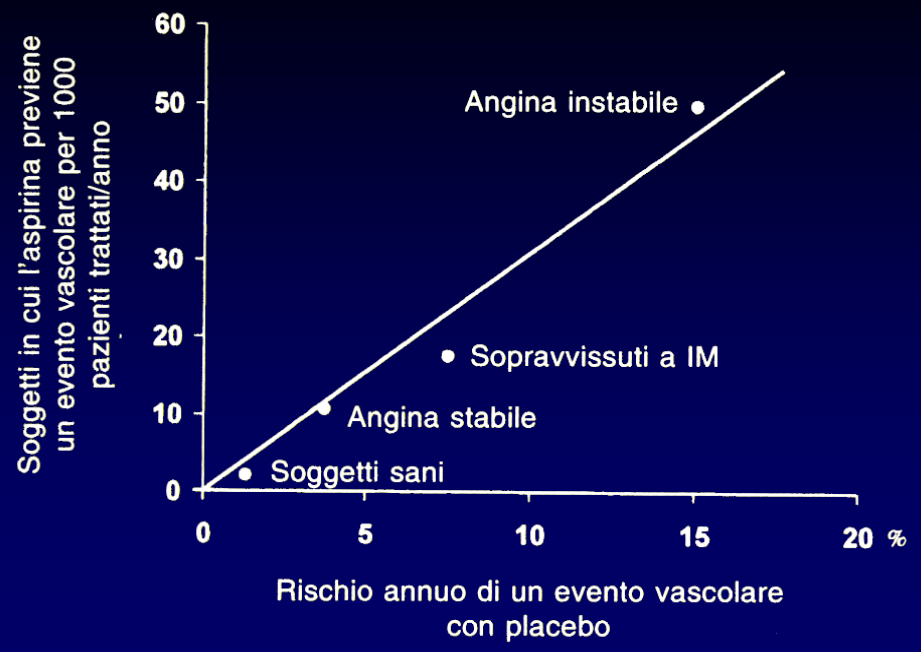
- Chirurgia generale e procedure invasive: Se possibile, la terapia con ASA va sospesa in previsione di un intervento di chirurgia maggiore o procedure invasive (endoscopie, biopsie, procedure odontoiatriche).

- Non sospendere il farmaco nei pazienti ad elevato rischio o nei candidati chirurgia cardiaca o bypass aortocoronarico

Disordini vascolari per cui l'aspirina è apparsa efficace e minima dose efficace

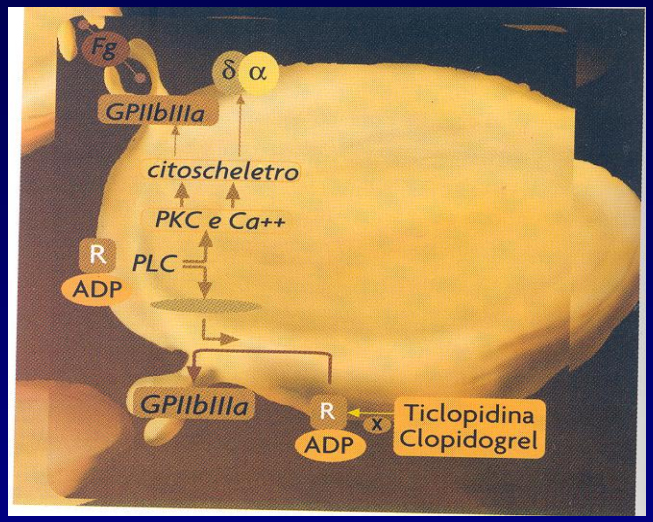
Disordine	Minima dose quotidiana efficace, mg
Ipertensione	75
Angina stabile	75
Angina instabile	75
IM acuto	160
Ischemia cerebrale transitoria e ictus ischemico	50
Ictus ischemico acuto	160

Trial randomizzati ben disegnati hanno evidenziato che l'aspirina è un antiaggregante efficace a dosi variabili tra 50 e 100 mg/die e anche per dosi pari a 30 mg/die. L'aspirina alla dose di 75 mg/die è apparsa efficace nel ridurre il rischio di infarto miocardico acuto (IM) e morte nei pazienti con angina instabile e stabile cronica, nonché quello di ictus e morte nei soggetti con ischemia cerebrale transitoria e nel diminuire il numero di ictus postoperatori dopo endoarteriectomia della carotide.



Il rischio assoluto di complicanze vascolari rappresenta il fattore determinante del beneficio assoluto della profilassi antiaggregante più importante. I dati sono determinati da trial controllati con placebo in diversi contesti clinici. Per ciascuna categoria di pazienti, l'ascissa indica il rischio assoluto di un evento vascolare maggiore come rilevato nel gruppo placebo del trial. Il beneficio assoluto del trattamento antiaggregante viene riportato sull'ordinata come numero di individui in cui si previene un evento vascolare importante (IM non fatale, ictus non fatale o morte vascolare) trattando 1000 soggetti con aspirina per 1 anno.

Inibitori del recettore dell'ADP



Derivati tienopiridinici: ticlopidina e clopidogrel, inattivi *in vitro* ma trasformati in composti farmacologicamente attivi *in vivo*.

Inibiscono al aggregazione piastrinica indotta da ADP agendo come antagonisti non competitivi a livello del recettore purinergico $P2Y_{12}$.

Durata dell'effetto: circa 7 giorni dopo la sospensione del farmaco (legame irreversibile).
Allungamento tempo di sanguinamento. Il clopidogrel è 6 volte più potente della ticlopidina. Assorbiti rapidamente e completamente a livello intestinale. Metabolismo epatico.

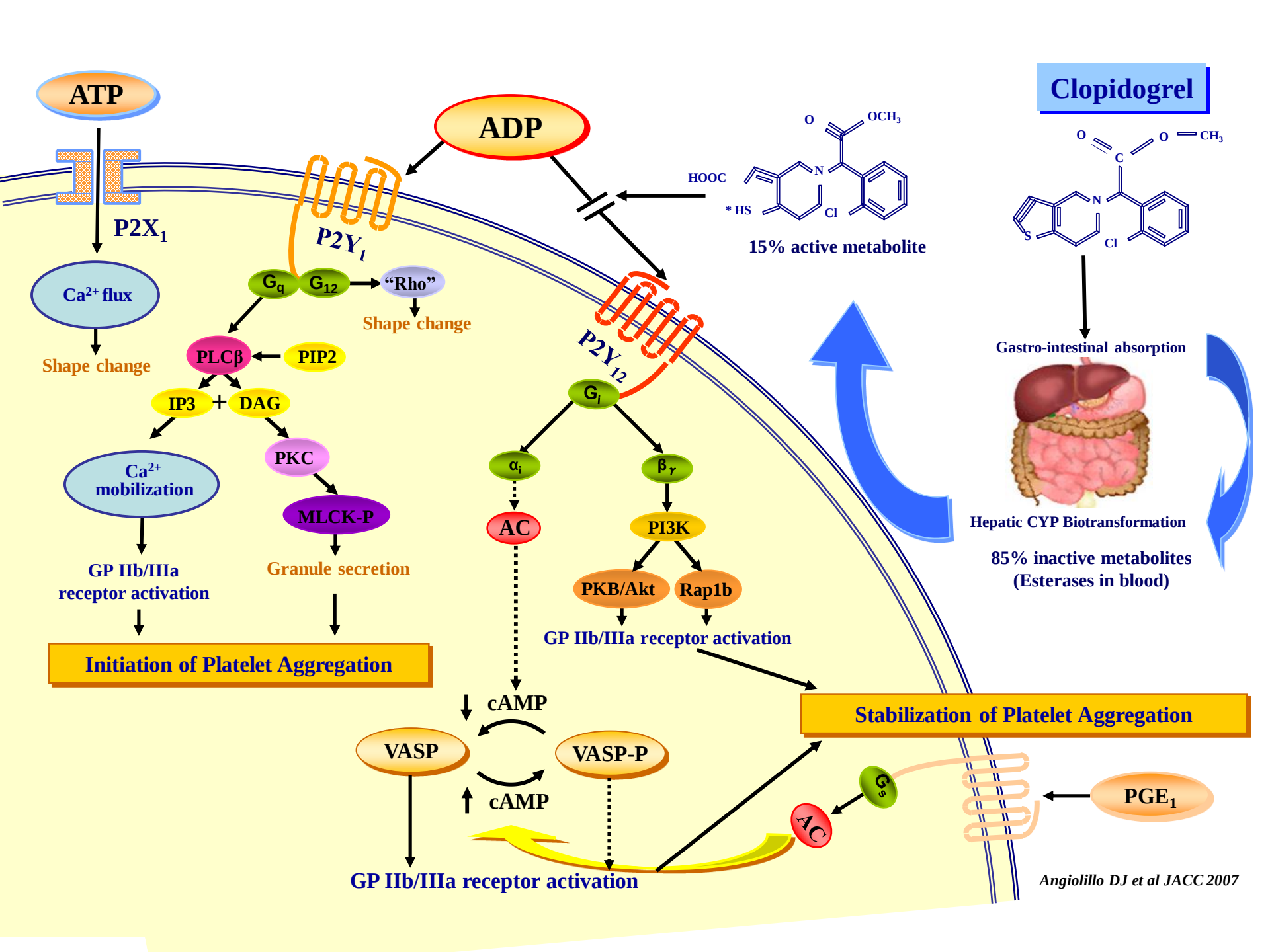
Inibitori del recettore dell'ADP

Dosaggi: ticlopidina 250-500 mg/die, clopidogrel 75 mg/die.

Emivita dei metaboliti attivi del clopidogrel: 8 ore, dei metaboliti della ticlopidina 12.6 ore.
60% della dose escreta per via urinaria, 25% per via fecale.

Cautela se insufficienza epatica. Non indicato alcun monitoraggio attività farmacologica.

Controindicazioni: simili a quelle dell'acido acetilsalicilico.
Controindicati in gravidanza e allattamento.


ATP
ADP
Clopidogrel
P2X1
P2Y1
P2Y12
Ca2+ flux
Shape change
Gq
G12
"Rho"
Shape change
PLCβ
PIP2
IP3
+
DAG
Ca2+ mobilization
PKC
MLCK-P
GP IIb/IIIa receptor activation
Granule secretion
Initiation of Platelet Aggregation
Gi
αi
βγ
AC
PI3K
PKB/Akt
Rap1b
GP IIb/IIIa receptor activation
cAMP
VASP
VASP-P
cAMP
GP IIb/IIIa receptor activation
Stabilization of Platelet Aggregation
Gs
AC
PGE1
HOOC
* HS
15% active metabolite
Gastro-intestinal absorption
Hepatic CYP Biotransformation
85% inactive metabolites
(Esterases in blood)
Angiolillo DJ et al JACC 2007

Definition(s) of “APT Resistance?”

The fact that some patients may experience recurrent vascular events despite the use of APT should be properly defined as “*treatment failure*” rather than “*APT resistance*” (multiple pathways mediate thrombotic events).

APT Resistance/Non-responsiveness = Failure to inhibit the target

APT Resistance/Non-responsiveness ≠ Clinical failure

APT: anti-platelet therapy

Aspirin Resistant Patient Management

- - Educate patient on importance of compliance
- - Eliminate interfering substances (ibuprofen)
- - Increase aspirin dose (?) (.....*increasing the dose of aspirin does not enhance COX-1 inhibition*)
- - Switch to other anti-platelet medications

ESC
European Society of Cardiology
European Heart Journal (2021) **42**, 3227–3337
doi:10.1093/eurheartj/ehab484

ESC GUIDELINES

2021 ESC Guidelines on cardiovascular disease prevention in clinical practice

Developed by the Task Force for cardiovascular disease prevention in clinical practice with representatives of the European Society of Cardiology and 12 medical societies

With the special contribution of the European Association of Preventive Cardiology (EAPC)

4.9. Antithrombotic therapy

Recommendations for antithrombotic therapy

Recommendations	Class[a]	Level[b]
Aspirin 75 - 100 mg daily is recommended for secondary prevention of CVD.[619]	I	A
Clopidogrel 75 mg daily is recommended as an alternative to aspirin in secondary prevention in case of aspirin intolerance.[620]	I	B
Clopidogrel 75 mg daily may be considered in preference to aspirin in patients with established ASCVD.[620,621]	IIb	A
Concomitant use of a proton pump inhibitor is recommended in patients receiving antiplatelet therapy who are at high risk of gastrointestinal bleeding.[622,623]	I	A
In patients with DM at high or very high CVD risk, low-dose aspirin may be considered for primary prevention in the absence of clear contraindications.[5,624,625]	IIb	A
Antiplatelet therapy is not recommended in individuals with low/moderate CV risk due to the increased risk of major bleeding.[624,626–630]	III	A

ASCVD = atherosclerotic cardiovascular disease; CV = cardiovascular; DM = diabetes mellitus.
[a]Class of recommendation.
[b]Level of evidence.

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Recommendations for patients with coronary artery disease

Recommendations	Class[a]	Level[b]
Aspirin 75 - 100 mg daily is recommended for patients with a previous myocardial infarction or revascularization.[619]	I	A
Aspirin 75 - 100 mg daily may be considered in patients without a history of myocardial infarction or revascularization, but with definitive evidence of CAD on imaging.[622]	IIb	C
In ACS, DAPT with a $P2Y_{12}$ inhibitor in addition to aspirin is recommended for 12 months, unless there are contraindications such as excessive risk of bleeding.[681–683]	I	A
In patients with CCS, clopidogrel 75 mg daily is recommended, in addition to aspirin, for 6 months following coronary stenting, irrespective of stent type, unless a shorter duration (1 - 3 months) is indicated due to risk or occurrence of life-threatening bleeding.[622]	I	A
Adding a second antithrombotic drug (a $P2Y_{12}$ inhibitor or low-dose rivaroxaban) to aspirin for long-term secondary prevention should be considered in patients with a high risk of ischaemic events and without high bleeding risk.[83,622,687–689]	IIa	A
Adding a second antithrombotic drug to aspirin for long-term secondary prevention may be considered in patients with a moderate risk of ischaemic events and without a high bleeding risk.[83,622,687–689]	IIb	A
ACE inhibitors (or ARB) are recommended if a patient has other conditions (e.g. HF, hypertension, or DM).[622]	I	A
Beta-blockers are recommended in patients with LV dysfunction or systolic HF.[622]	I	A
In patients with established ASCVD, oral lipid-lowering treatment with an ultimate LDL-C goal of <1.4 mmol/L (55 mg/dL) and a ≥50% reduction in LDL-C vs. baseline is recommended.	I	A

Continued

ACE = angiotensin-converting enzyme; ACS = acute coronary syndromes; ARB = angiotensin receptor blocker; ASCVD = atherosclerotic cardiovascular disease; CAD = coronary artery disease; CCS = chronic coronary syndromes; DAPT = dual antiplatelet therapy; DM = diabetes mellitus; HF = heart failure; LDL-C = low-density lipoprotein cholesterol; LV = left ventricular.

[a]Class of recommendation.

[b]Level of evidence.

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Aspirin and **primary prevention** of colorectal **cancer**: a still evolving story.
McNeil JJ. J Natl Cancer Inst. 2021 Feb 2:djab010. doi: 10.1093/jnci/djab010. Online ahead of print. PMID: 33528017 No abstract available.

Aspirin in the **Prevention** of Cardiovascular Disease and **Cancer**.
Ricciotti E, FitzGerald GA. Annu Rev Med. 2021 Jan 27;72:473-495. doi: 10.1146/annurev-med-051019-102940. PMID: 33502899
Indirect evidence, both preclinical and clinical, suggests that **aspirin** may protect against sporadic colorectal **cancer** and perhaps other **cancers**.

Updates on the molecular mechanisms of **aspirin** in the **prevention** of colorectal **cancer**: Review.
Belayneh YM, Amare GG, Meharie BG. J Oncol Pharm Pract. 2021 Jan 11:107815522098484 6. doi: 10.1177/107815522098484 6. Online ahead of print. PMID: 33427041

Rischio di caduta

When initiating antithrombotic therapy, potential risk for bleeding also needs to be assessed. Non-modifiable and partially modifiable bleeding risks (Table 9) are important drivers of bleeding events in synergy with modifiable factors.

Notably, a history of falls is not an independent predictor of bleeding on OAC (a modelling study estimated that a patient would need to fall 295 times per year for the benefits of ischaemic stroke reduction with OAC to be outweighed by the potential for serious bleeding).

Hindricks G, Potpara T, Dagres N, Arbelo E, Bax JJ, Blomström-Lundqvist C, Boriani G, Castella M, Dan GA, Dilaveris PE, Fauchier L, Filippatos G, Kalman JM, La Meir M, Lane DA, Lebeau JP, Lettino M, Lip GYH, Pinto FJ, Thomas GN, Valgimigli M, Van Gelder IC, Van Putte BP, Watkins CL; ESC Scientific Document Group. 2020 ESC Guidelines for the diagnosis and management of atrial fibrillation developed in collaboration with the European Association for Cardio-Thoracic Surgery (EACTS): The Task Force for the diagnosis and 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. Eur Heart J 2021;42(5):373-498).

Table 9 Risk factors for bleeding with OAC and antiplatelet therapy

Non-modifiable	Potentially modifiable	Modifiable	Biomarkers
Age >65 years Previous major bleeding Severe renal impairment (on dialysis or renal transplant) Severe hepatic dysfunction (cirrhosis) Malignancy Genetic factors (e.g. CYP 2C9 polymorphisms) Previous stroke, small-vessel disease, etc. Diabetes mellitus Cognitive impairment/dementia	Extreme frailty ± excessive risk of falls[a] Anaemia Reduced platelet count or function Renal impairment with CrCl <60 mL/min VKA management strategy[b]	Hypertension/elevated SBP Concomitant antiplatelet/NSAID Excessive alcohol intake Non-adherence to OAC Hazardous hobbies/occupations Bridging therapy with heparin INR control (target 2.0 - 3.0), target TTR >70%[c] Appropriate choice of OAC and correct dosing[d]	GDF-15 Cystatin C/CKD-EPI cTnT-hs von Willebrand factor (+ other coagulation markers)

CKD-EPI= Chronic Kidney Disease Epidemiology Collaboration; CrCl = creatinine clearance; cTnT-hs = high-sensitivity troponin T; CYP = cytochrome P; GDF-15 = growth differentiation factor-15; INR = international normalized ratio; NSAID = non-steroidal anti-inflammatory drug; OAC = oral anticoagulant; SBP = systolic blood pressure; TTR = time in therapeutic range; VKA = vitamin K antagonist.

[a]Walking aids; appropriate footwear; home review to remove trip hazards; neurological assessment where appropriate.

[b]Increased INR monitoring, dedicated OAC clinicals, self-monitoring/self-management, educational/behavioural interventions.

[c]For patients receiving VKA treatment.

[d]Dose adaptation based on patient's age, body weight, and serum creatinine level.

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Hindricks G, Potpara T, Dagres N, Arbelo E, Bax JJ, Blomström-Lundqvist C, Boriani G, Castella M, Dan GA, Dilaveris PE, Fauchier L, Filippatos G, Kalman JM, La Meir M, Lane DA, Lebeau JP, Lettino M, Lip GYH, Pinto FJ, Thomas GN, Valgimigli M, Van Gelder IC, Van Putte BP, Watkins CL; ESC Scientific Document Group. 2020 ESC Guidelines for the diagnosis and management of atrial fibrillation developed in collaboration with the European Association for Cardio-Thoracic Surgery (EACTS): The Task Force for the diagnosis and 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. Eur Heart J 2021;42(5):373-498).

Conclusions

The Beginning of the New Era? YES!!!

- **All new OACs are non-inferior to warfarin in reducing the risk of stroke and systemic embolization**
- **All agents reduce the risk of bleeding and intracranial hemorrhage**

Future Challenges:

- **Accruing experience in post-marketing surveys (real-world patients)**
- **How to measure the anticoagulant effect of the new drugs (rarely, but occasionally this is needed)**
- **How to re-organize the health system around new anticoagulants**

FINE