FADOI
Sezione Regionale Calabria

AZIENDA SANITARIA PROVINCIALE REGGIO CALABRIA

IPAVSI
COLLEGIO PROVINCIALE DI REGGIO CALABRIA

Sezione Regionale Calabria

Sezione Regionale Calabria

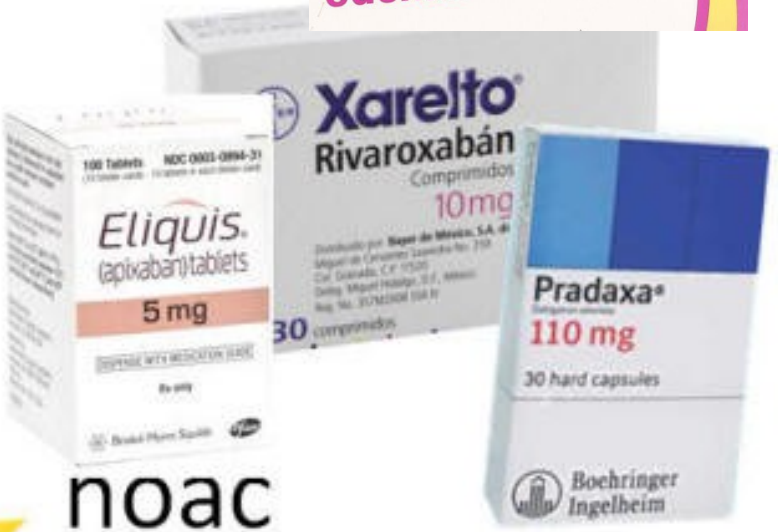
4-7 Aprile 2018

IX^e Giornate di Aggiornamento Medico: Attualità ed opinioni correnti in Medicina Interna

Antiaggreganti e anticoagulanti: gli uni, gli altri, entrambi ?

Dr. Vittorio Emanuele

?



noac

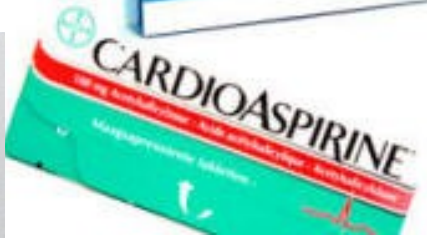
tao

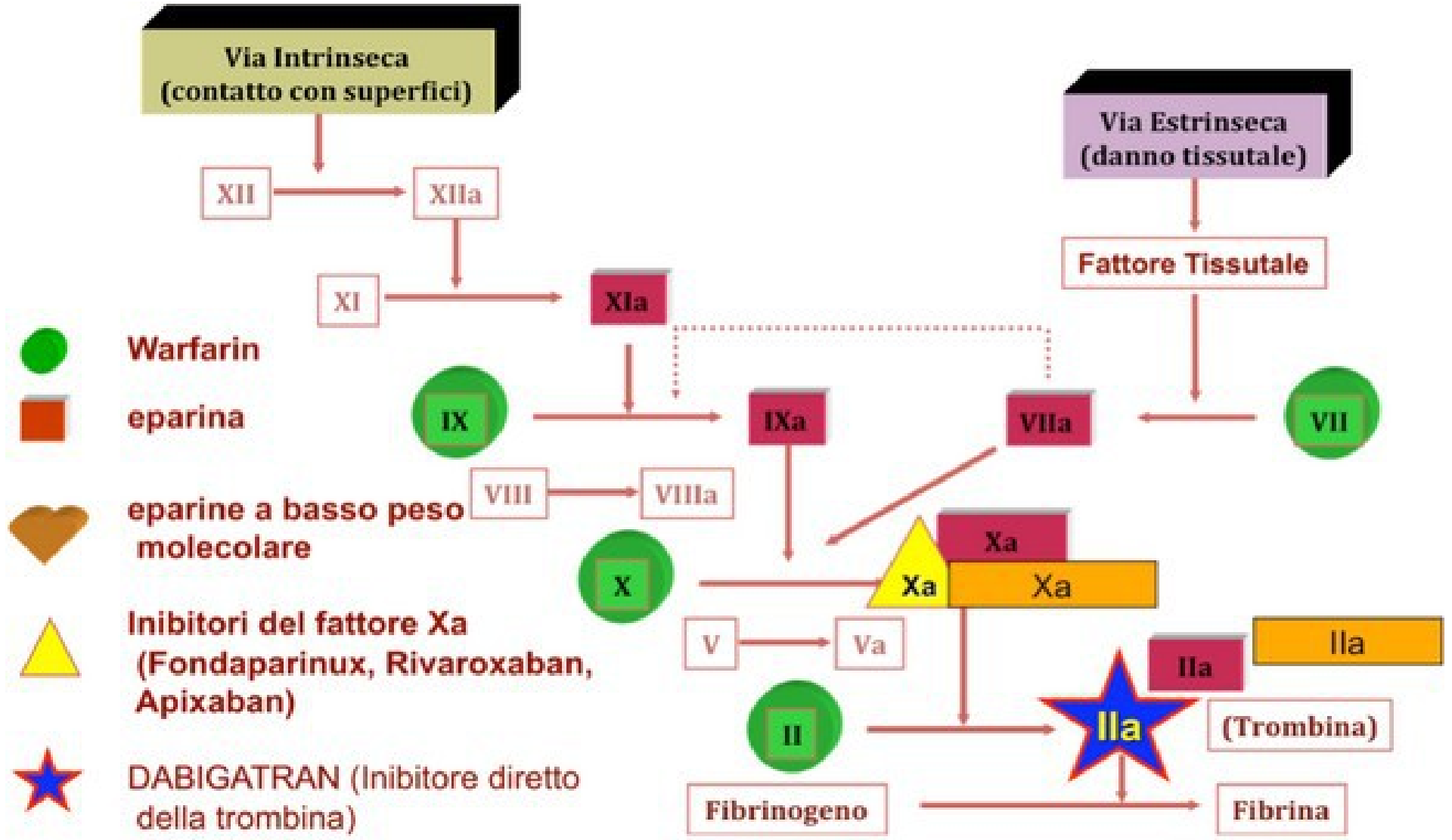
DAPT-SAPT EFIENT, BRILIQUE

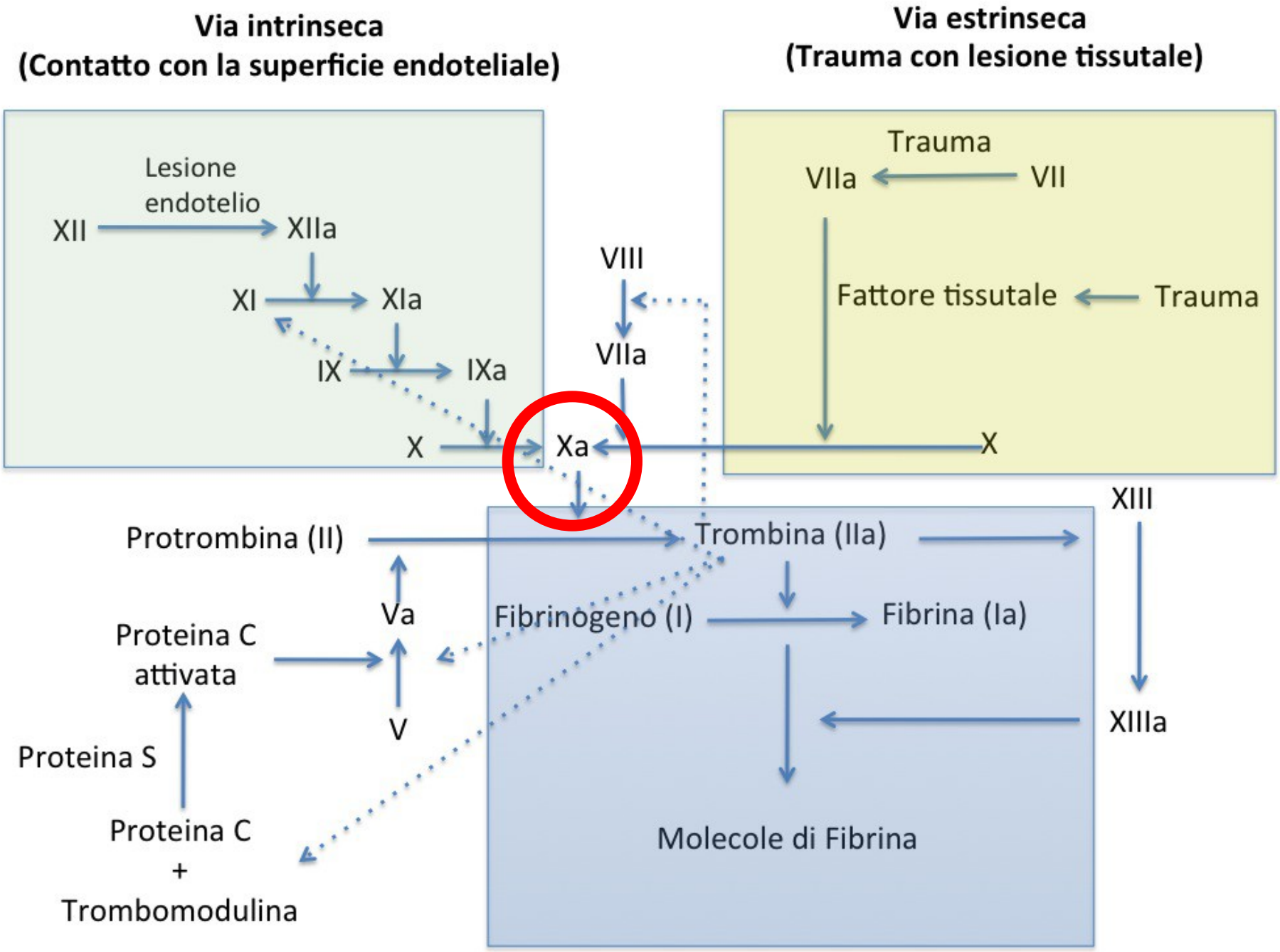
Cardioaspirina.

ticlopidina,

clopidogrel




Via Intrinseca
(contatto con superfici)
XII
XIIa
XI
XIa
Via Estrinseca
(danno tissutale)
Fattore Tissutale
Warfarin
eparina
IX
IXa
VIIa
VII
eparine a basso peso molecolare
VIII
VIIIa
X
Xa
Xa
Xa
Inibitori del fattore Xa
(Fondaparinux, Rivaroxaban, Apixaban)
V
Va
IIa
IIa
(Trombina)
II
IIa
DABIGATRAN (Inibitore diretto della trombina)
Fibrinogeno
Fibrina


Via intrinseca
(Contatto con la superficie endoteliale)
Via estrinseca
(Trauma con lesione tissutale)
Lesione endotelio
XII
XIIa
XI
XIa
IX
IXa
X
Xa
VIII
VIIa
Trauma
VIIa
VII
Fattore tissutale
Trauma
X
XIII
Protrombina (II)
Trombina (IIa)
Fibrinogeno (I)
Fibrina (Ia)
Va
V
Proteina C attivata
Proteina S
Proteina C + Trombomodulina
XIIIa
Molecole di Fibrina

Europace Advance Access published August 31, 2015

Europace
doi:10.1093/europace/euv309

EHRA PRACTICAL GUIDE

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

Table 2 Non-VKA oral anticoagulant drugs, approved for prevention of systemic embolism or stroke in patients with non-valvular AF

	Dabigatran	Apixaban	Edoxaban	Rivaroxaban
Action	Direct thrombin inhibitor	Activated factor Xa inhibitor	Activated factor Xa inhibitor	Activated factor Xa inhibitor
Dose	150 mg BID 110 mg BID[a,b] (75 mg BID)[b]	5 mg BID 2.5 mg BID[a]	60 mg OD[c] 30 mg OD[a]	20 mg OD 15 mg OD[a]
Phase III clinical trial	RE-LY[25]	ARISTOTLE[26] AVERROES[27]	ENGAGE-AF[28]	ROCKET-AF[29]

BID, twice a day; OD, once daily.
[a]See further tables and text for discussion on dose reduction considerations.
[b]110 mg BID not approved by FDA. 75 mg BID approved in USA only, if CrCl 15–30 mL/min or if CrCl 30–49 mL/min and other 'orange' factor as in *Table 6* (e.g. verapamil).
[c]FDA provided a boxed warning that 'edoxaban should not be used in patients with CrCL > 95 mL/min'. EMA advised that 'edoxaban should only be used in patients with high creatinine clearance after a careful evaluation of the individual thrombo-embolic and bleeding risk'.

How to choose appropriate direct oral anticoagulant for patient with nonvalvular atrial fibrillation

Ann Hematol (2016) 95:437–449
DOI 10.1007/s00277-015-2566-x

Jordan K. Schaefer[1] · Robert D. McBane[2,3] · Waldemar E. Wysokinski[2,3]

REVIEW ARTICLE

Situazione clinica	Prima scelta	Seconda scelta	Da evitare
Rischio TE alto **Rischio EM basso**	Dabigatran 150 mg	Apixaban Edoxaban 60 mg Rivaroxaban Dabigatran 110 mg	Edoxaban 30 mg
Rischio TE basso **Rischio EM alto**	Edoxaban 30 mg Apixaban	Edoxaban 60 mg Dabigatran 110 mg	Dabigatran 150 mg Rivaroxaban
Rischio TE moderato **Rischio EM moderato**	Apidaban Edoxaban 60 mg Dabigatran 110 mg	Dabigatran 150 mg	
Rischio TE elevato **Rischio EM elevato**	Apixaban	Rivaroxaban Edoxaban 60 mg Dabigatran 150 mg	Edoxaban 30 mg
Problemi di compliance	Edoxaban 60 mg Rivaroxaban	Edoxaban 30 mg	Dabigatran Apixaban
Disfunzione renale moderata (clearance 30-44 mL/min)	Apixaban	Rivaroxaban Dabigatran 110 mg Edoxaban 60 o 30 mg	Dabigatran 150 mg

Confronti con il warfarin

Proprietà[35]	*Warfarin*	NAO
Inizio effetto	Lento	Rapido
Posologia	Variabile	Fissa
Effetto dei cibi	Sì	No
Interazioni	Molte	Poche
Monitoraggio	Sì	No
Conclusione effetto	Lungo	Breve

Antidoto **SI** **SO**

IRC (gfr <15/30) **SI** **NO**

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

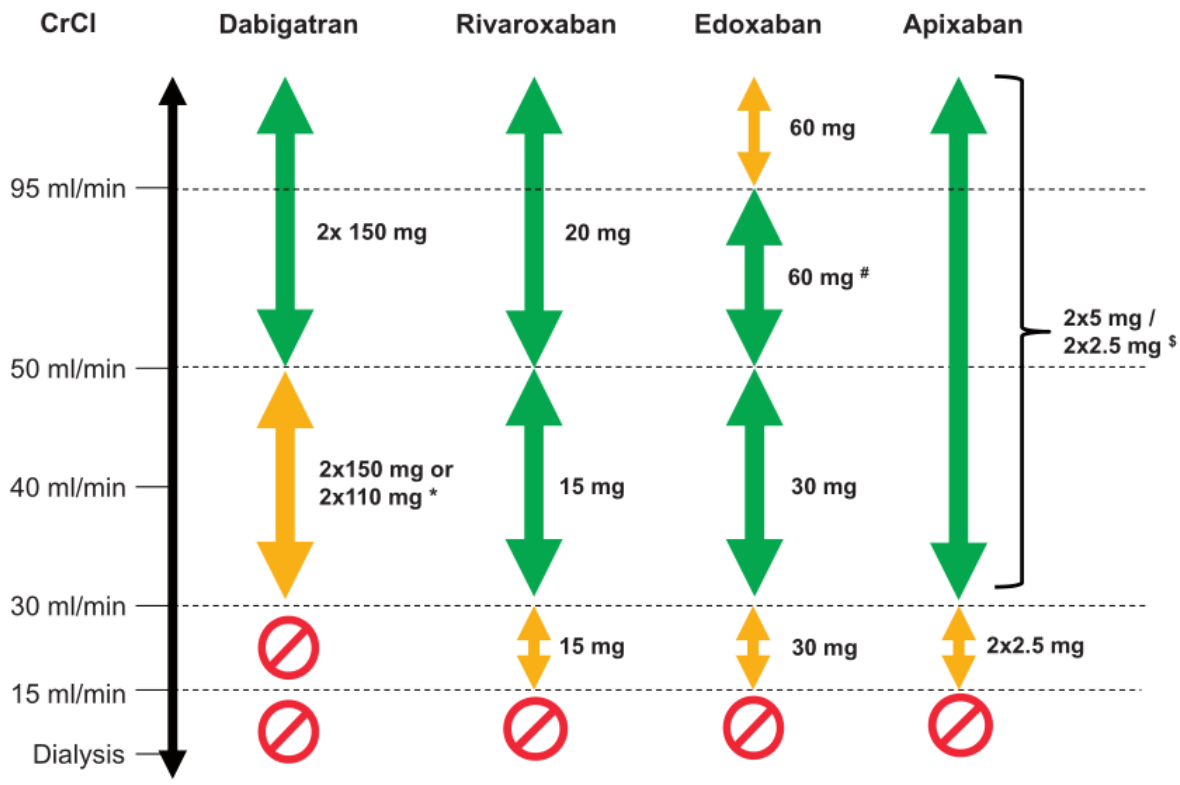
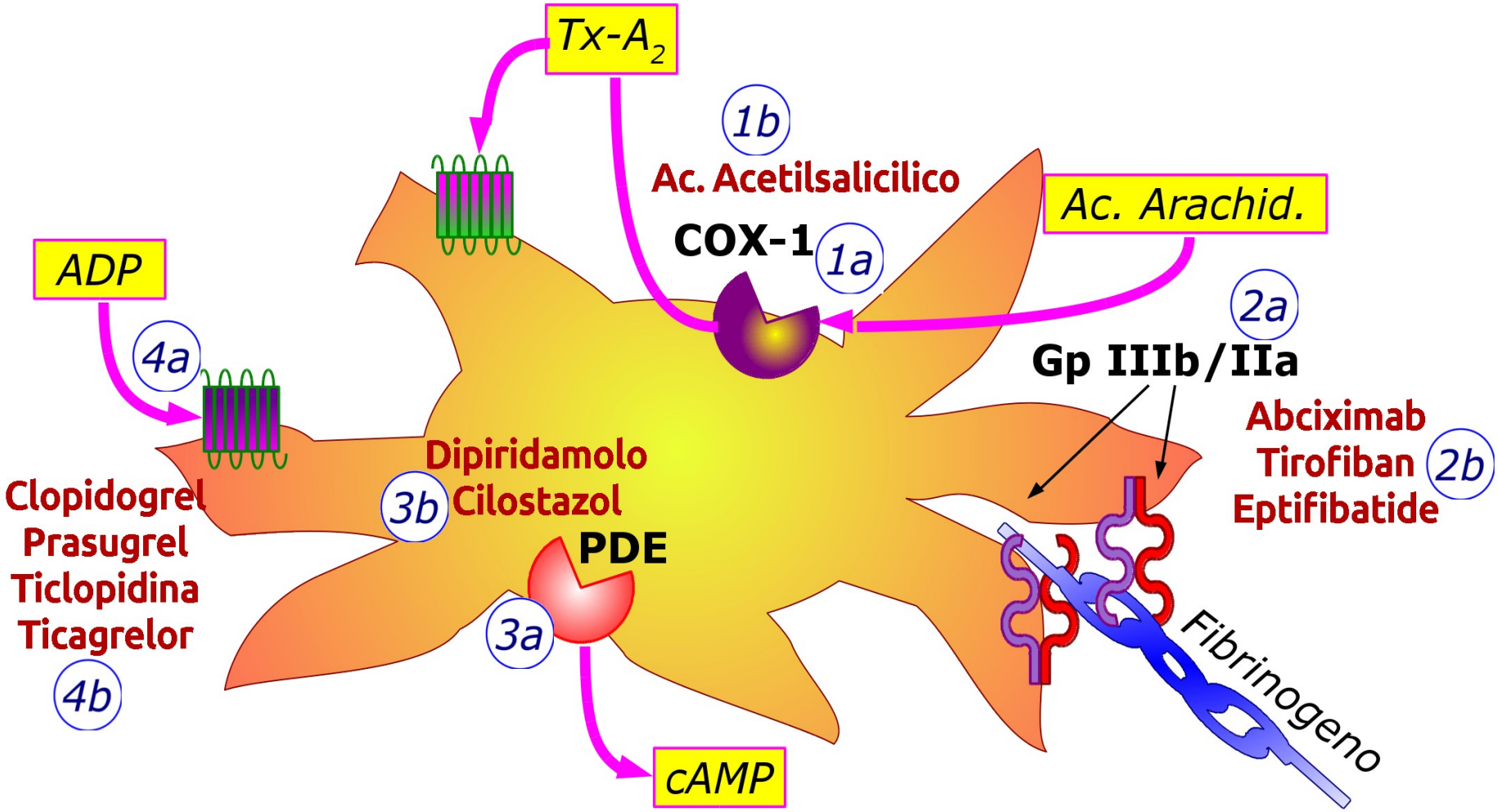


Figure 4 Use of non-vitamin K antagonist oral anticoagulants according to renal function. *2 × 110 mg in patients at high risk of bleeding (per SmPc). #Other dose reduction criteria may apply (weight ≤60 kg, concomitant potent P-Gp inhibitor therapy). $2 × 2.5 mg only if at least two out of three fulfilled: age ≥80 years, body weight ≤60 kg, creatinine ≥1.5 mg/dL (133 µmol/L). Orange arrows indicate cautionary use (dabigatran in moderate renal insufficiency, FXa inhibitors in severe renal insufficiency, edoxaban in 'supranormal' renal function); see text for details.

Antiaggreganti



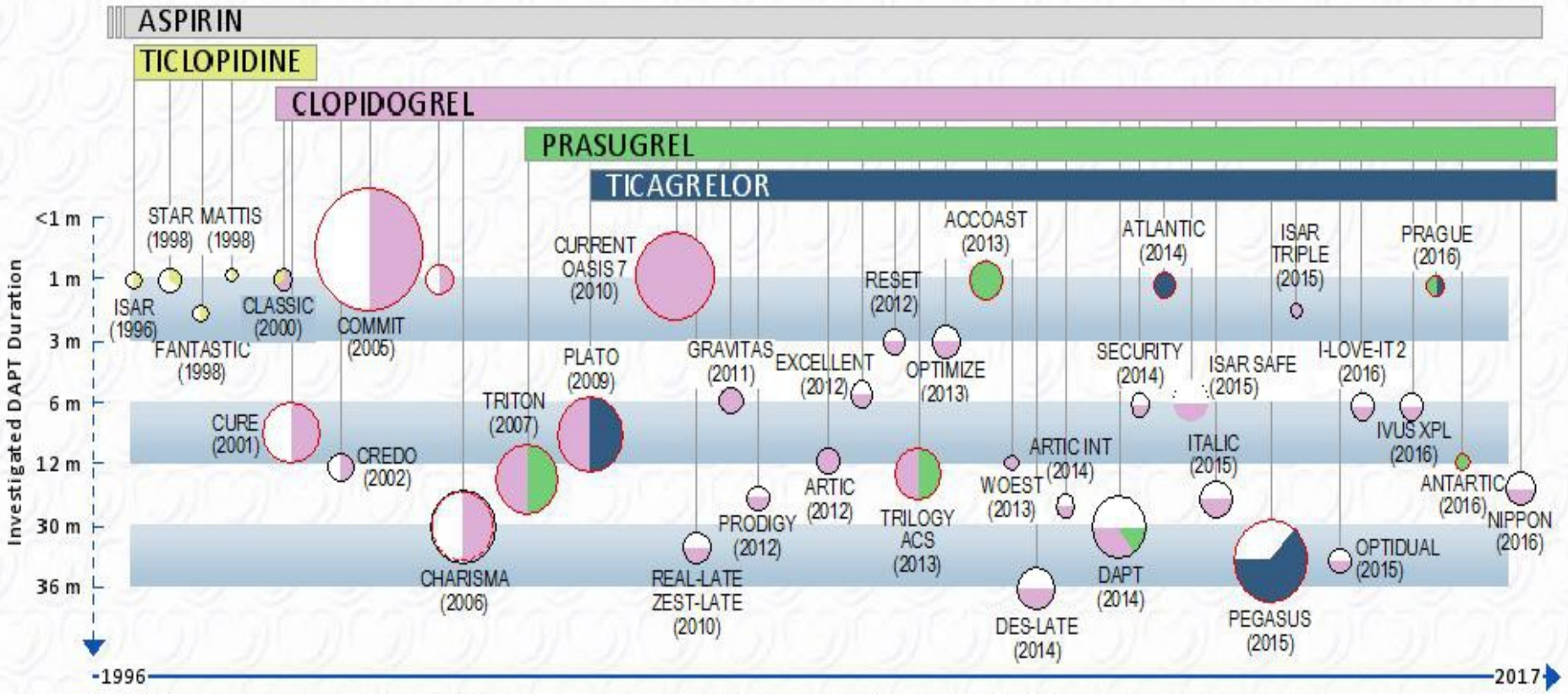
DAPT - SAPT

Farmaco	Via di somministrazione	Profarmaco	Via di eliminazione	Antiaggregazione permanente	Tempo di recupero della funzionalità piastrinica
ASA	Orale	No	Fegato	Sì	30% dopo 48 ore
Clopidogrel	Orale	Sì	Fegato	Sì	40% in 3 giorni
Ticlopidina	Orale	Sì	Fegato	Sì	4-8 giorni
Prasugrel	Orale	Sì	Fegato	Sì	2-3 giorni
Ticagrelor	Orale	No	Fegato	No	57% in 24 ore

ASA: acido acetilsalicilico

History of dual antiplatelet therapy (DAPT) in patients with coronary artery disease

ESC
European Society of Cardiology



Size of the circles denotes sample size

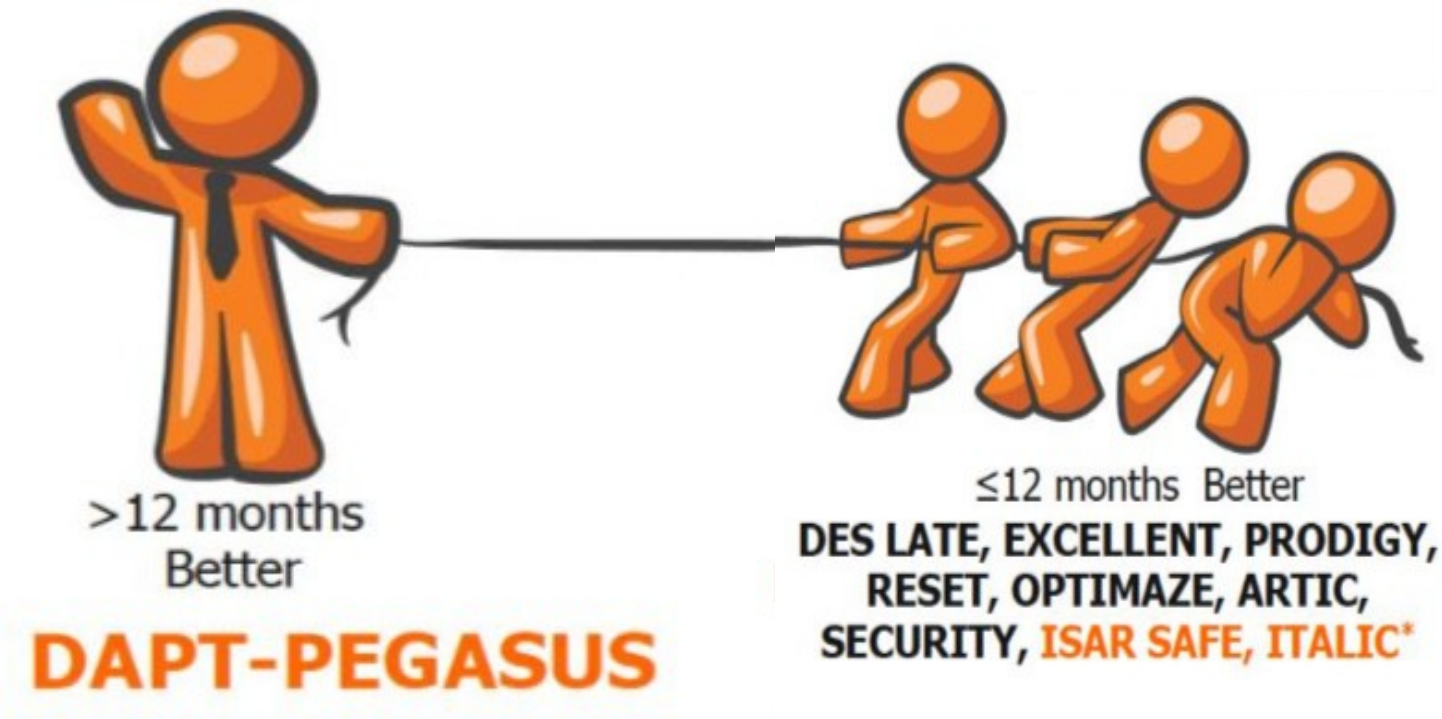
2 5 10 20 K pts

Perimeter of the circles denotes type of investigated population

- Mixed clinical presentation at the time of stent implantation
- Acute coronary syndrome at presentation
- DAPT initiated in patients with prior myocardia infarction
- DAPT for primary prevention

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

DAPT, ma per quanto tempo?



2017 ESC Focused Update on Dual Antiplatelet Therapy in Coronary Artery Disease developed in collaboration with EACTS

Risk scores validated for dual antiplatelet therapy duration decision-making

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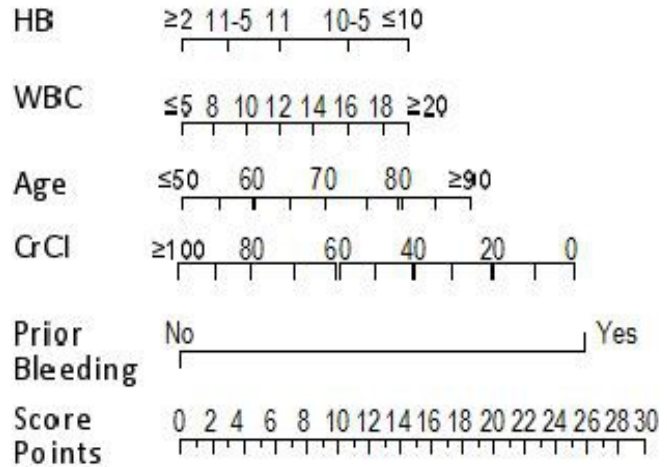
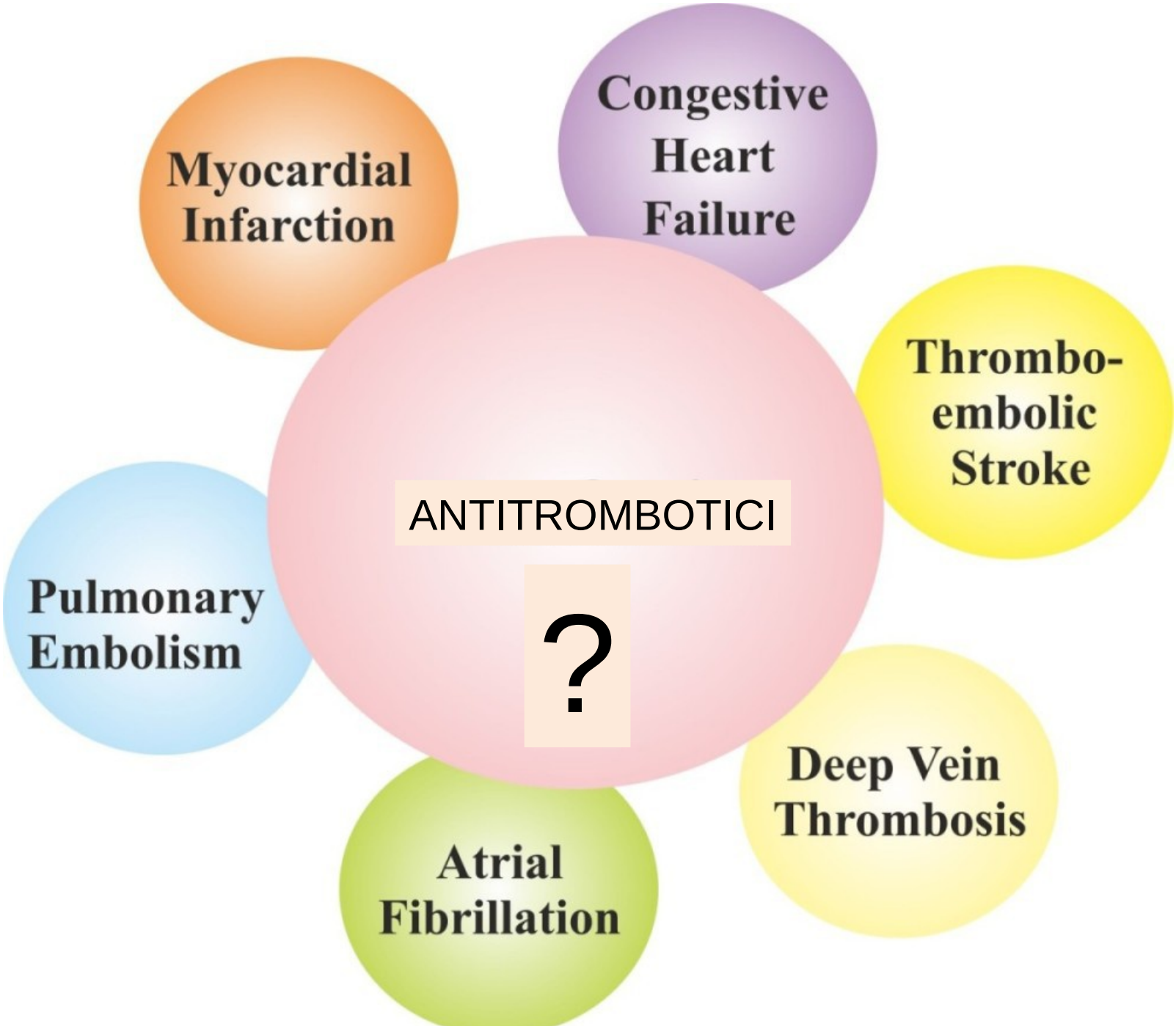
European Society of Cardiology

	PRECISE-DAPT score	DAPT score	
Time of use	At the time of coronary stenting	After 12 months of uneventful DAPT	
DAPT duration strategies assessed	Short DAPT (3–6 months) vs. Standard/long DAPT (12–24 months)	Standard DAPT (12 months) vs. Long DAPT (30 months)	
Score calculation		Age ≥75 65 to <75 <65 Cigarette smoking Diabetes mellitus MI at presentation Prior PCI or prior MI Paclitaxel-eluting stent Stent diameter <3 mm CHF or LVEF <30% Vein graft stent	 −2 pt −1 pt 0 pt +1 pt +1 pt +1 pt +1 pt +1 pt +1 pt +2 pt +2 pt
Score range	0 to 100 points	−2 to 10 points	
Decision making cut-off suggested	Score ≥25 → Short DAPT Score <25 → Standard/long DAPT	Score ≥2 → Long DAPT Score <2 → Standard DAPT	
Calculator	www.precisedaptscore.com	www.daptstudy.org	


Myocardial Infarction
Congestive Heart Failure
Thrombo-embolic Stroke
ANTITROMBOTICI
?
Pulmonary Embolism
Deep Vein Thrombosis
Atrial Fibrillation

CHI e QUANDO ?

DAPT o SAPT: ok
TAO O NAO: ok
…….3PLICE ?

2017 ESC Focused Update on Dual Antiplatelet Therapy in Coronary Artery Disease developed in collaboration with EACTS

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The Task Force for the Management of Dual Antiplatelet Therapy in Coronary Artery Disease of the European Society of Cardiology (ESC) and of the European Association for Cardio-Thoracic Surgery (EACTS)

ESC Chairperson: Marco Valgimigli (Switzerland).

Authors/Task Force Members: Héctor Bueno (Spain), Robert Byrne (Germany), Jean-Philippe Collet (France), Francesco Costa (Italy), Anders Jeppsson (Sweden), Peter Jüni (Canada), Adnan Kastrati (Germany), Philippe Kolh (Belgium), Laura Mauri (USA), Gilles Montalescot (France), Franz-Josef Neumann (Germany), Mate Petricevic (Croatia), Marco Roffi (Switzerland), Philippe Gabriel Steg (France), Stephan Windecker (Switzerland), Jose Luis Zamorano (Spain).

Additional Contributor: Glenn Levine (USA).

Table 4 **Strategies to avoid bleeding complications in patients treated with oral anticoagulant**

• 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.
• 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.[a]
• Clopidogrel is the $P2Y_{12}$ inhibitor of choice.
• Use low-dose (≤ 100 mg daily) aspirin.
• Routine use of PPIs.

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Table 5 High-risk features of stent-driven recurrent ischaemic events

• 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

©ESC 2017

https://academic.oup.com/DocumentLibrary/EHJ/SupplementaryData/ehx419web.pdf

Table 6 **Unfavourable patient profile for a combination of oral anticoagulant and antiplatelet therapy**

• 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

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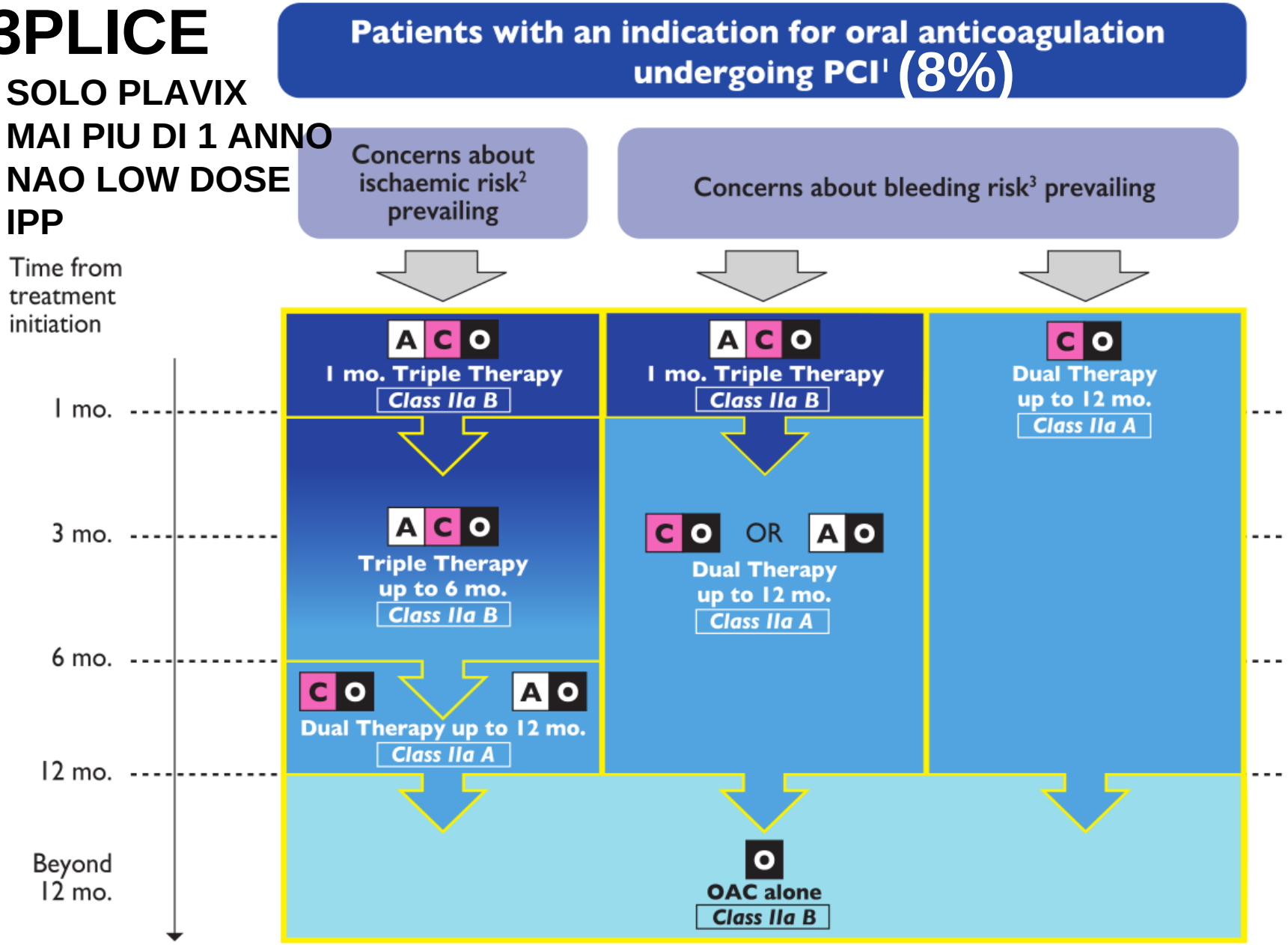
3PLICE

1) SOLO PLAVIX
2) MAI PIU DI 1 ANNO
3) NAO LOW DOSE
4) IPP



3PLICE=3Volte R Sanguinamento
CABG o T. Medica NO DAPT SI NOAC

©ESC 2017

I C: ASA+PLAVIX Periproedurale

IIaB: 3Plice Almeno per 1 MESE (Indipendente da tipo Stent, Es PCI Elettiva)

IIaB: 3Plice fino a 6 MESI (se Alto rischio Ischemico es PCI ACS)

IIaA: 2Plice invece di 1 Mese di 3Plice se alto rischio Emor

IIaB: dopo 1 anno SOLO NAO (stop Antiaggreganti)

IIaB: se 3Plice con TAO INR = 2-2.5 (TTR 65-70%)

IIaC: se 3Plice con NAO = Low Dose

III C: se 3Plice SOLO Clopidogrel (NO Prasugrel NO Ticagrelor)

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 OCTOBER 19, 2017 VOL. 377 NO. 16

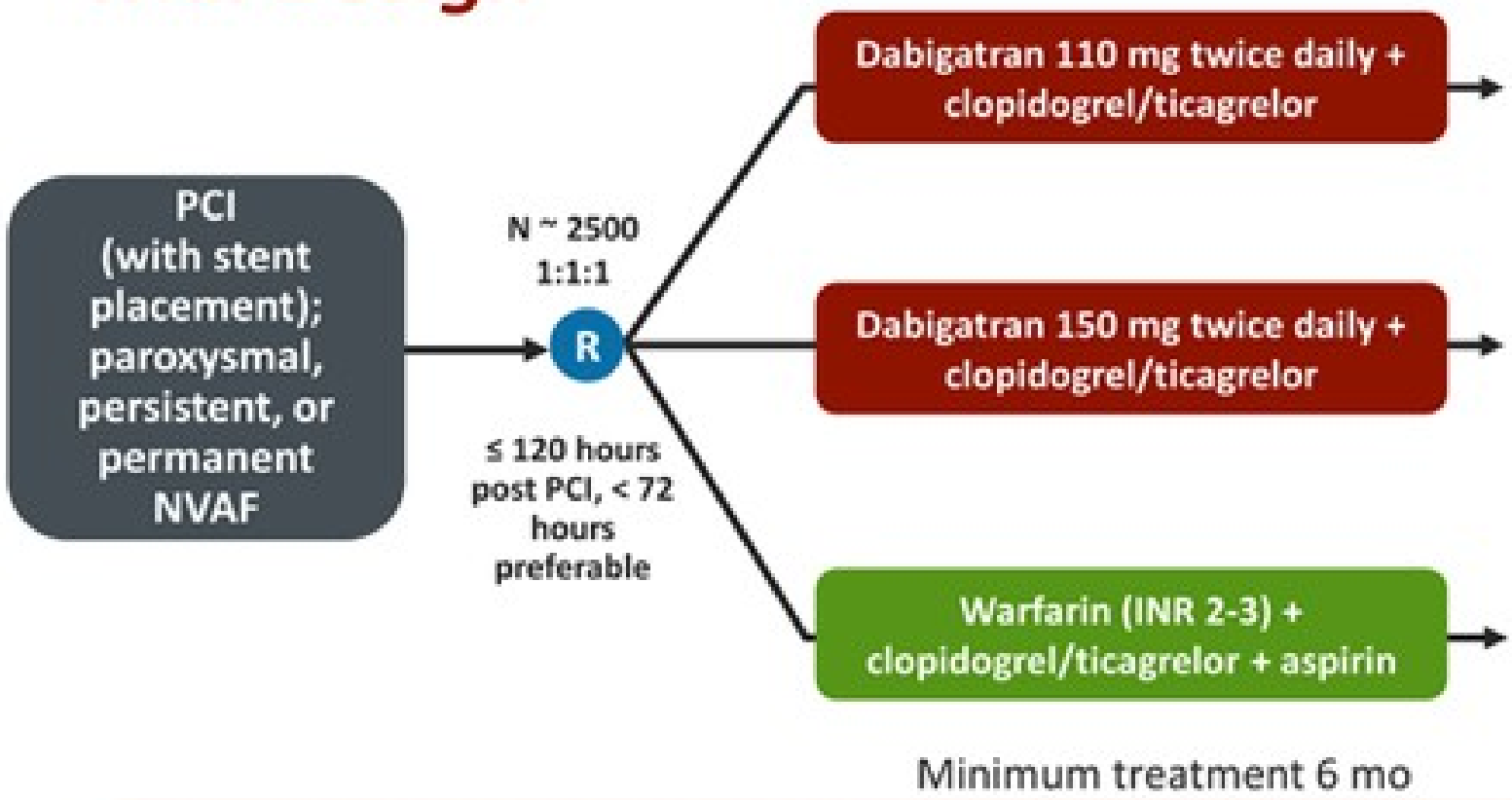
Dual Antithrombotic Therapy with Dabigatran after PCI in Atrial Fibrillation

Christopher P. Cannon, M.D., Deepak L. Bhatt, M.D., M.P.H., Jonas Oldgren, M.D., Ph.D., Gregory Y.H. Lip, M.D., Stephen G. Ellis, M.D., Takeshi Kimura, M.D., Michael Maeng, M.D., Ph.D., Bela Merkely, M.D., Uwe Zeymer, M.D., Savion Gropper, M.D., Ph.D., Matias Nordaby, M.D., Eva Kleine, M.Sc., Ruth Harper, Ph.D., Jenny Manassie, B.Med.Sc., James L. Januzzi, M.D., Jurrien M. ten Berg, M.D., Ph.D., P. Gabriel Steg, M.D., and Stefan H. Hohnloser, M.D., for the RE-DUAL PCI Steering Committee and Investigators*

RE-DUAL PCI™

Study in NVAF patients undergoing PCI

RE-DUAL-PCI
Trial Design



RE-DUAL PCI™
Study in NVAF patients undergoing PCI

Minimum treatment 6 mo

- Primary outcome measure: Time to first ISTH major bleeding or CRNM bleeding event
- Secondary endpoints: Composite of all cause death or thrombotic events (MI, or stroke/SE) and unplanned revascularization

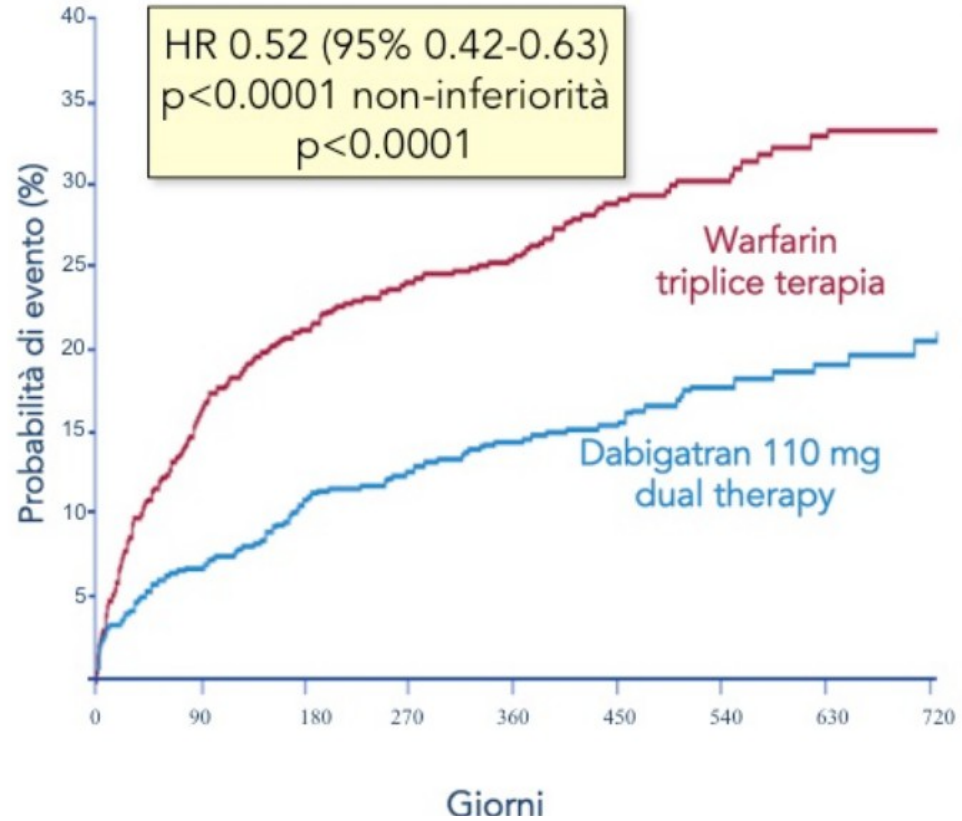
Cannon CP, et al. *Clin Card*. 2016; 39:555-564.

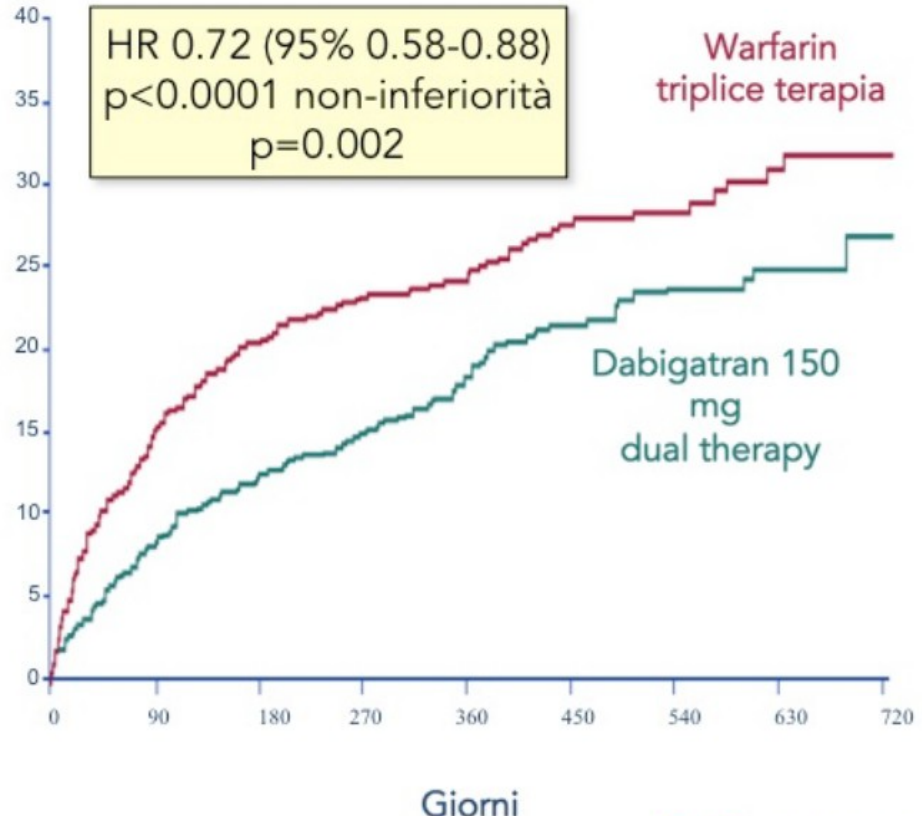
ATBV
Gruppo di studio Aterosclerosi, Trombosi, Biologia Vascolare

RE-DUAL PCI™
Study in NVAF patients undergoing PCI

Andrea Rubboli. 2017

Studio RE-DUAL PCI: sicurezza





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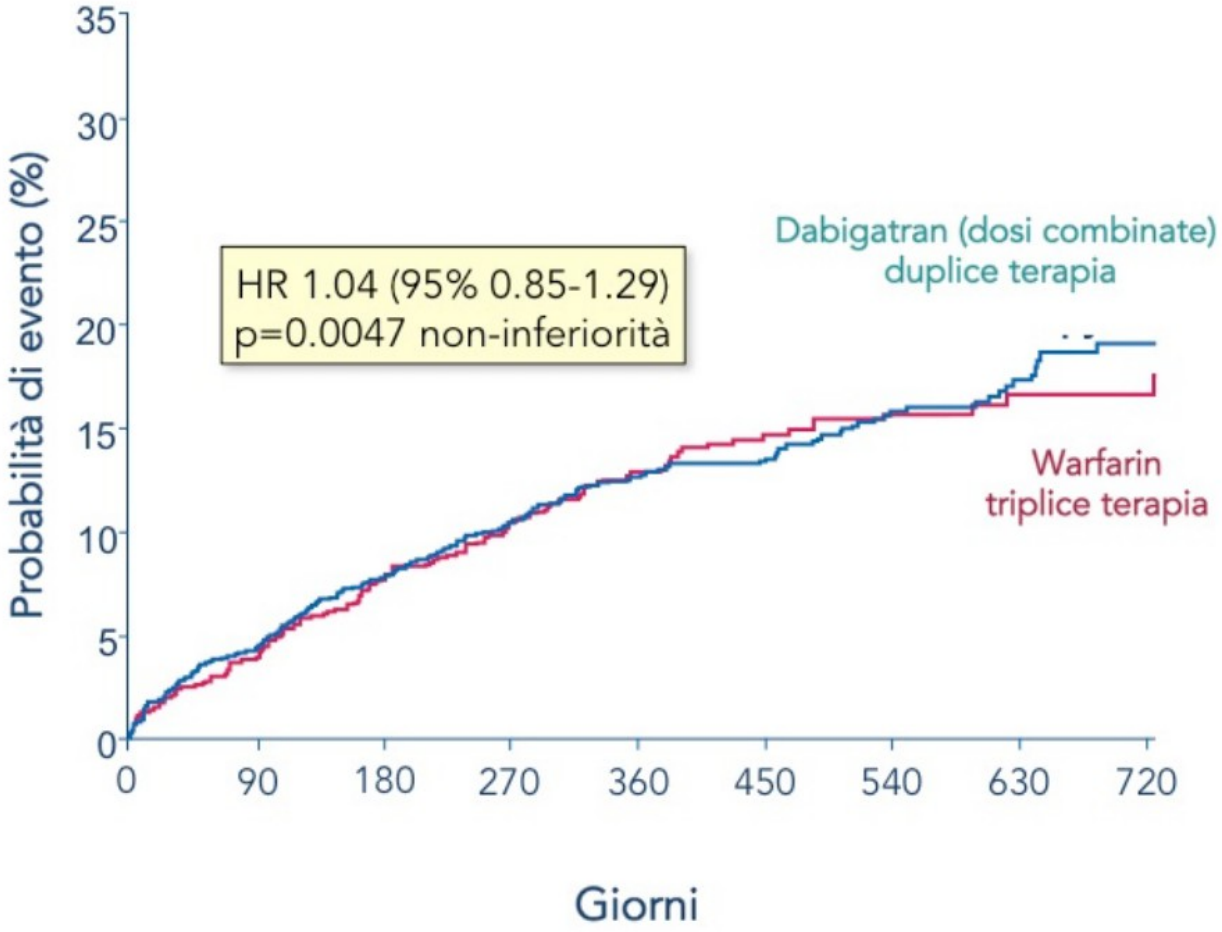
Andrea Rubboli. 2017

RE-DUAL PCI™
Study in NVAF patients undergoing PCI

Studio RE-DUAL PCI: efficacia



…ma

RE-DUAL PCI™

Study in NVAF patients undergoing PCI

….INCIDENZA doppia (p=NS) di trombosi di stent osservata nel braccio trattato con duplice terapia con dabigatran 110 mg BID rispetto al braccio corrispondente di triplice terapia….

?

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 DECEMBER 22, 2016 VOL. 375 NO. 25

Prevention of Bleeding in Patients with Atrial Fibrillation Undergoing PCI

C. Michael Gibson, M.D., Roxana Mehran, M.D., Christoph Bode, M.D., Jonathan Halperin, M.D., Freek W. Verheugt, M.D., Peter Wildgoose, Ph.D., Mary Birmingham, Pharm.D., Juliana Ianus, Ph.D., Paul Burton, M.D., Ph.D., Martin van Eickels, M.D., Serge Korjian, M.D., Yazan Daaboul, M.D., Gregory Y.H. Lip, M.D., Marc Cohen, M.D., Steen Husted, M.D., Eric D. Peterson, M.D., M.P.H., and Keith A. Fox, M.B., Ch.B.

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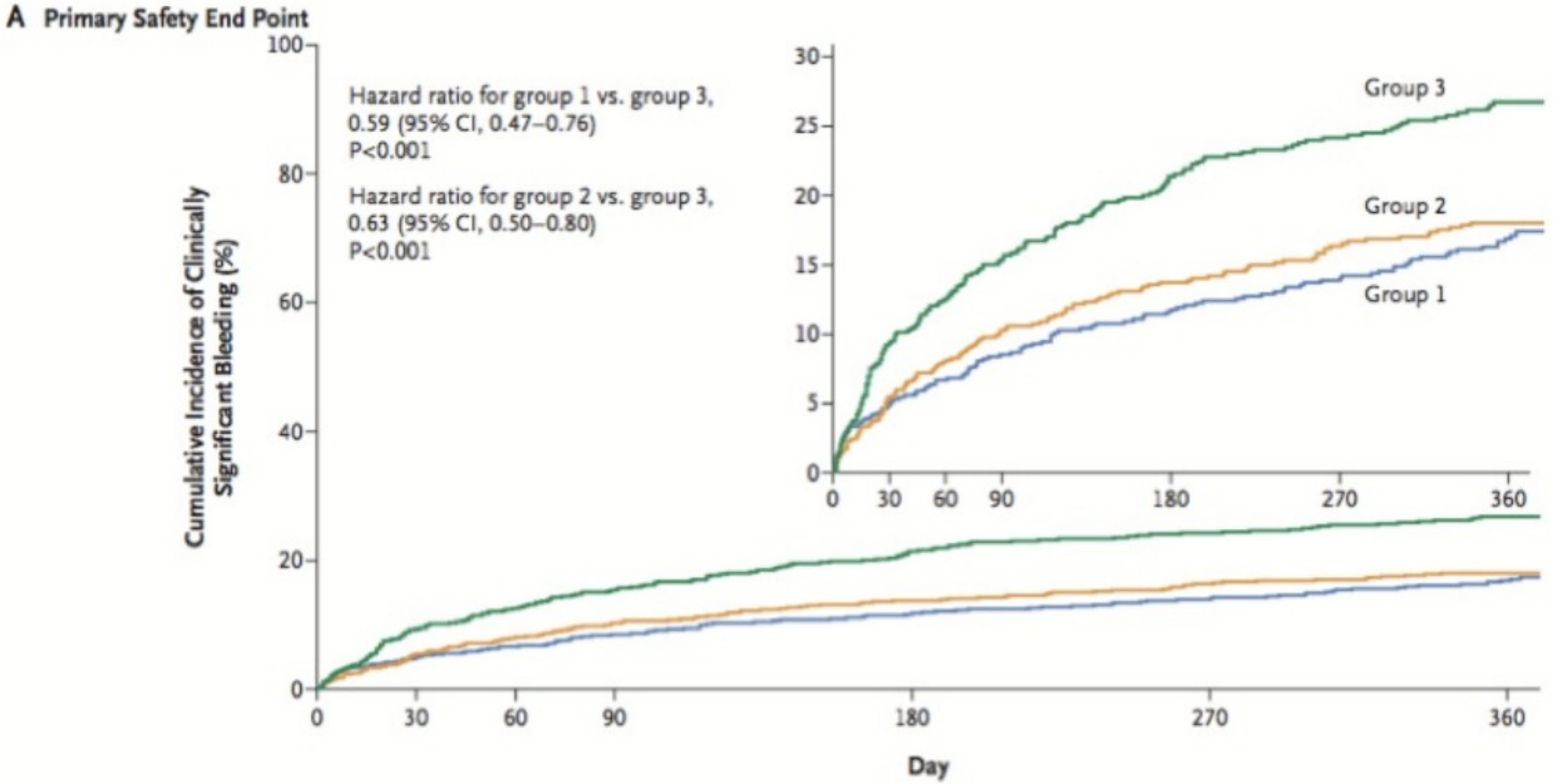
PIONEER AF-PCI

PIONEER AF-PCI: sicurezza



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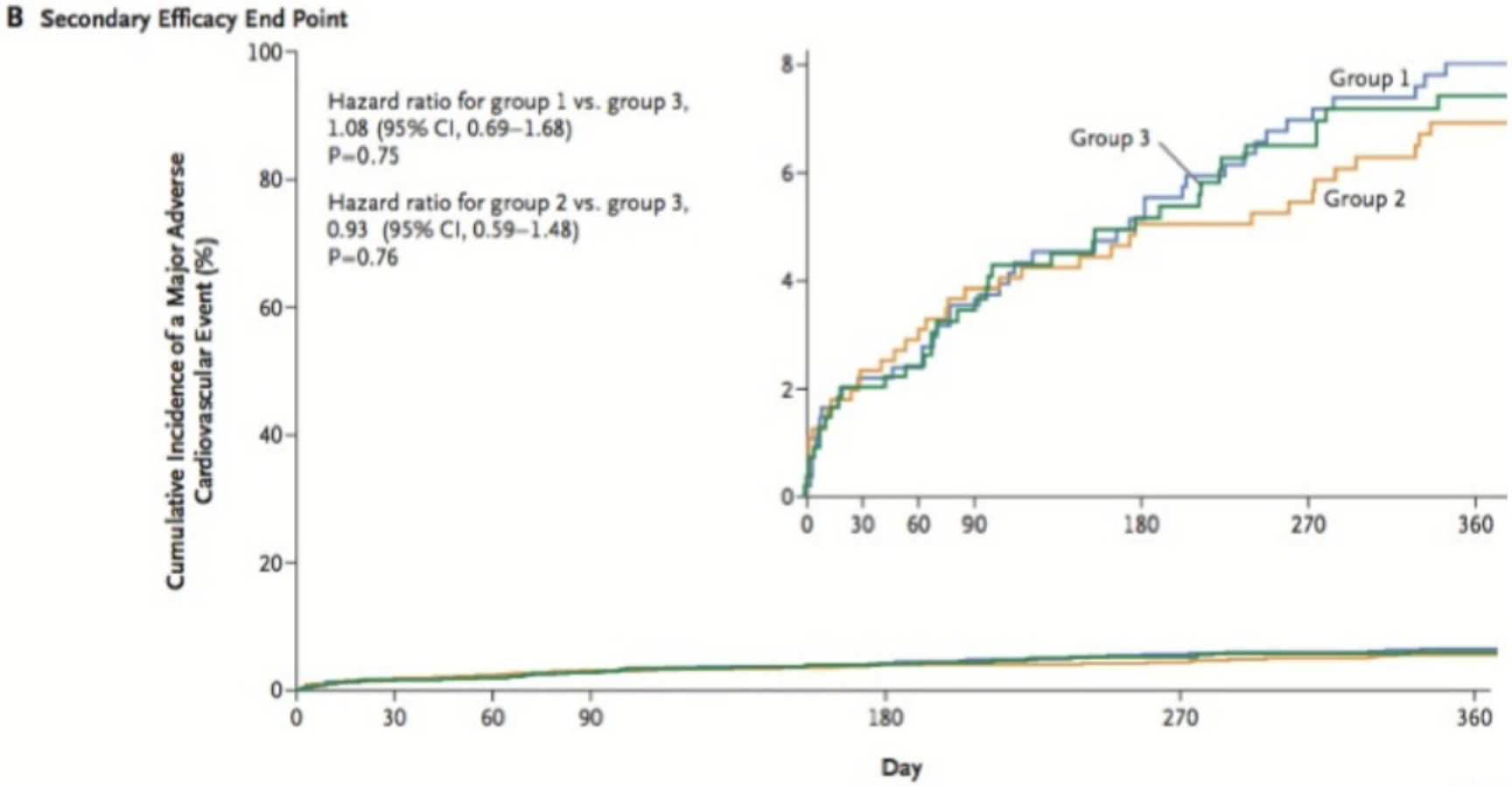
Andrea Rubboli. 2016

PIONEER AF-PCI

PIONEER AF-PCI: efficacia



….ma

…. Le dimensioni della popolazione studiata e dei singoli bracci di trattamento non racchiudeva una potenza statistica sufficiente per essere dirimente in merito *all'efficacia* dei vari regimi antitrombotici. ….

?

….quindi

SICUREZZA = OK

EFFICACIA = ?

ESC European Society of Cardiology

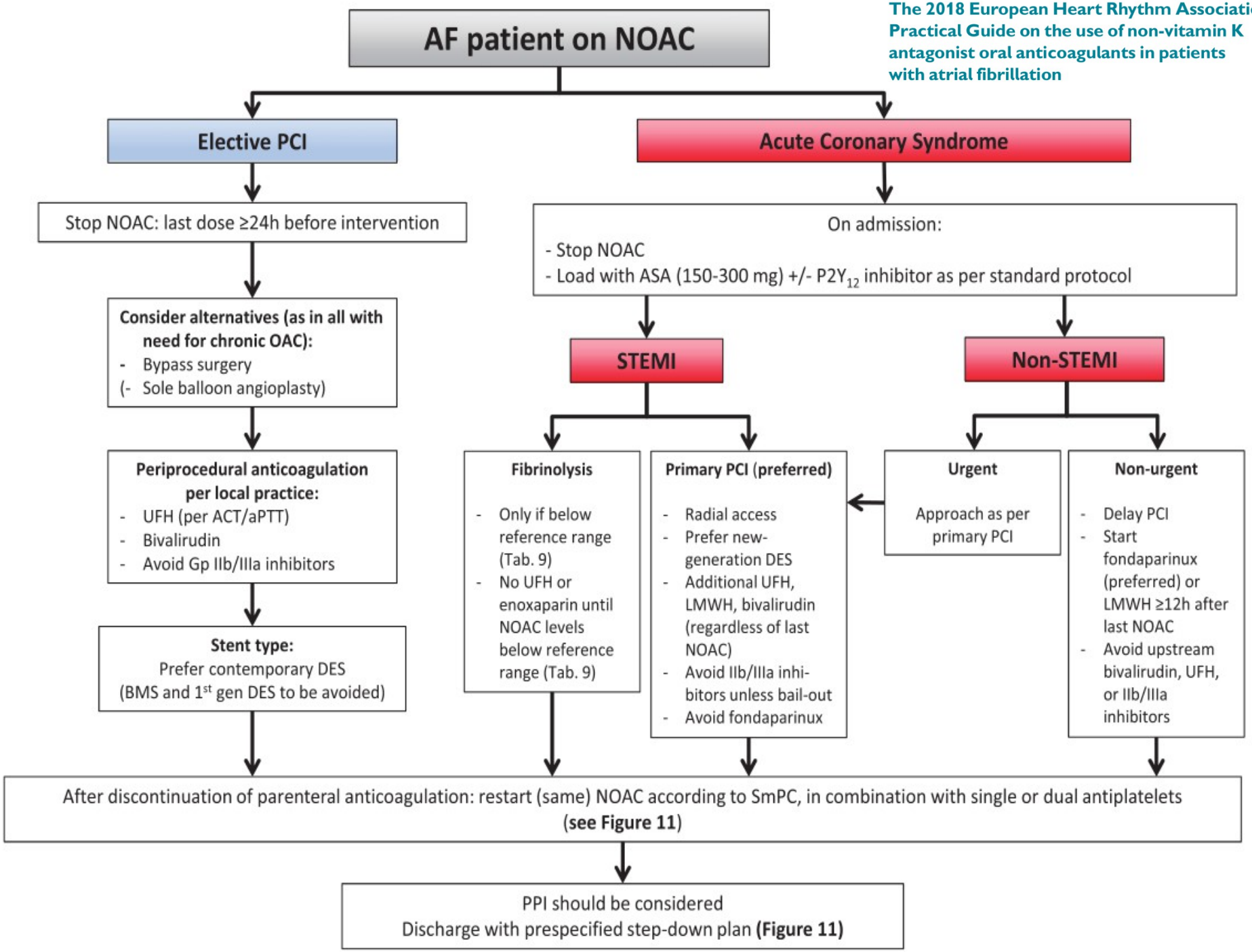
European Heart Journal (2018) **00**, 1–64
doi:10.1093/eurheartj/ehy136

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]

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



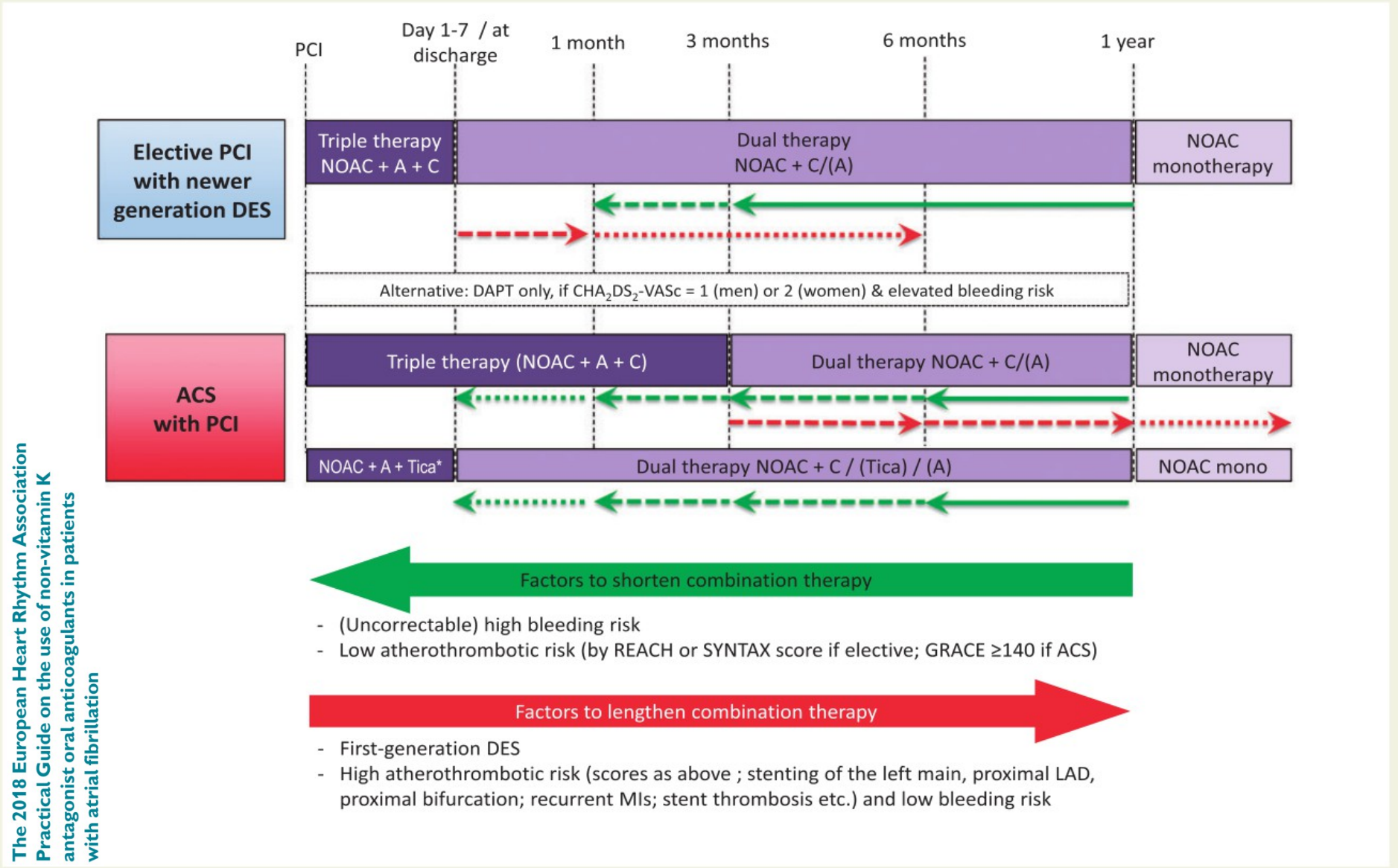


Figure 11 Long-term treatment of patients on non-vitamin K antagonist oral anticoagulant therapy after elective percutaneous coronary intervention or acute coronary syndrome. There are innumerable possible variations on this global theme, as discussed in the text. Patient characteristics and institutional practices should be taken into account to *individualize the approach* to each and every single patient. This figure wants to create a 'backbone' as guidance for such tailored approaches. A: aspirin 75–100 mg OD; C: clopidogrel 75 mg OD; Tica: Ticagrelor 90 mg BID. *If triple therapy needs to be continued after discharge clopidogrel is preferred over ticagrelor (due to lack of data).

What is unknown

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

(1) It is unknown whether the doses of rivaroxaban used in PIONEER AF-PCI (i.e. 2.5 mg BID or 15 mg OD) are sufficient for stroke prevention, at least compared with standard dose-adjusted VKA or compared with the 20 mg OD rivaroxaban dose in patients with a normal renal clearance.[29]

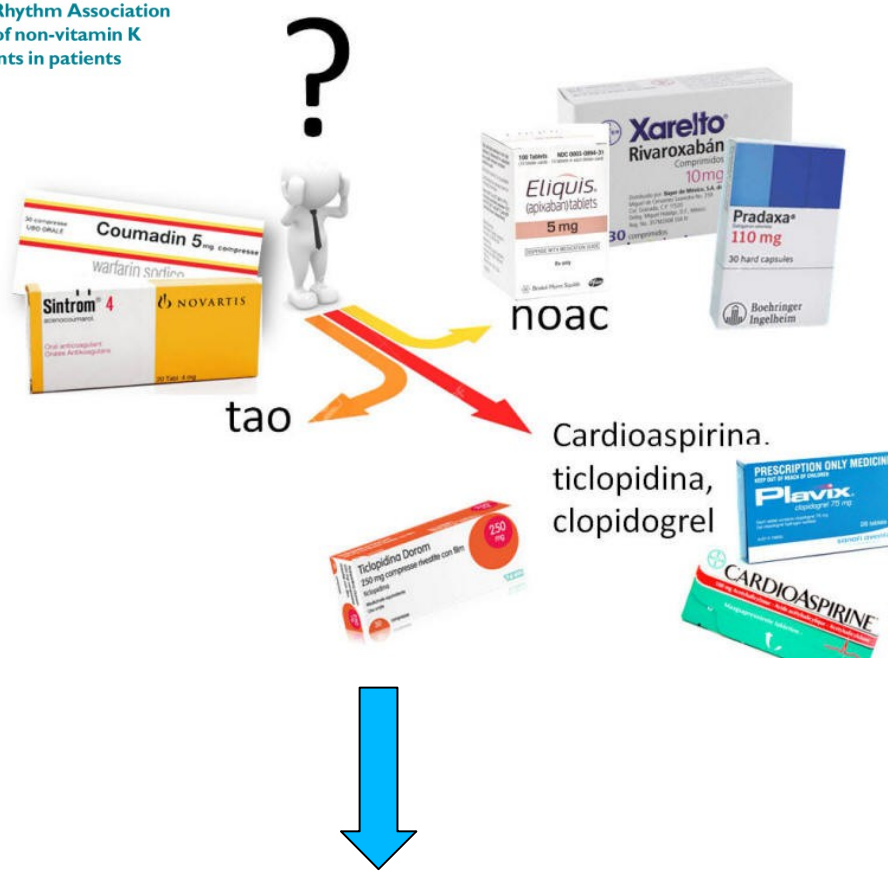
(2) It remains unknown whether dual therapy strategies combining a NOAC with clopidogrel are safer in terms of bleeding risk than a dual therapy with a VKA and clopidogrel. This is currently being addressed in the AUGUSTUS study with apixaban.

(3) It remains unknown whether dual therapy (i.e. rivaroxaban 15 mg OD or dabigatran 110/150 mg BID in combination with a $P2Y_{12}$ inhibitor) sufficiently protects against stent thrombosis or myocardial infarction, due to underpowered clinical trials.[141,308]

(4) It remains unknown whether dual therapy with NOAC and aspirin could be an alternative to NOAC and a $P2Y_{12}$ inhibitor, as there is no randomized study evaluating aspirin vs. a $P2Y_{12}$ inhibitor as part of dual therapy with NOAC or VKA.

(5) There were insufficient numbers of patients on ticagrelor or prasugrel in both PIONEER AF-PCI and RE-DUAL PCI to conclusively assess the safety of combining these more powerful $P2Y_{12}$ inhibitors in dual or triple therapy regimens.

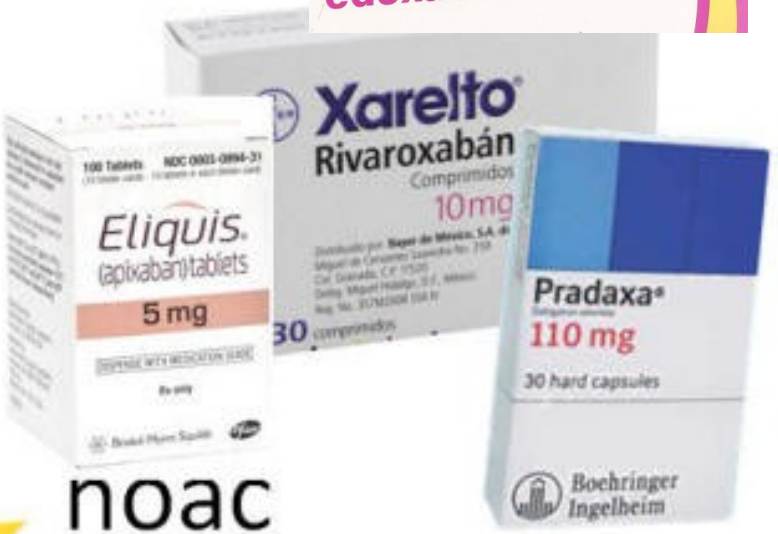
(6) In VKA-treated patients, a PCI seems safe without bridging and without additional periprocedural heparin.[320] It is unknown if this applies also to NOACs, since most clinical studies have suggested interruption of NOAC therapy at PCI. A small pilot study in 50 stable patients undergoing planned PCI and on DAPT suggests that pre-procedural dabigatran provides insufficient anticoagulation during PCI.[321]



AUGUSTUS **Apixaban** Versus Vitamin K Antagonist in Patients With Atrial Fibrillation and Acute Coronary Syndrome and/or Percutaneous Coronary Intervention,

ENTRUST AF-PCI Evaluation of the Safety and Efficacy of an **Edoxaban**-Based Compared to a Vitamin K Antagonist-Based Antithrombotic Regimen in Subjects With Atrial Fibrillation Following Successful Percutaneous Coronary Intervention

?



noac

tao

DAPT-SAPT EFIENT, BRILIQUE

Cardioaspirina.

ticlopidina,

clopidogrel