Cremona, 2 marzo 2012

Gestione pratica dei nuovi anticoagulanti

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Quali pazienti dovrebbero essere fin da subito trattati con nuovi farmaci anticoagulanti orali (NAO)

- Tutti i pazienti con caratteristiche simili a quelli arruolati negli studi clinici di Fase III (Grado A)
- I pazienti con pregressa emorragia intracranica (Grado A)
- Pazienti ad alto rischio di ictus (Grado A)
- Pazienti che desiderano ricevere il nuovo farmaco .
- Pazienti con problemi logistici che rendono difficile il monitoraggio laboratoristico, come quelli allettati per altre patologie.

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In quali pazienti i NAO dovrebbero rimpiazzare i farmaci VKA ?

- Pazienti trattati con AVK che presentano un TTR (time spent in therapeutic range) inferiore al 50-55%. (Grado A)
- Pazienti con importanti problemi logistici o lavorativi.
- Pazienti con pregressa emorragia cerebrale (Grado A).
- Pazienti che utilizzano farmaci che interferiscono con gli VKA , provocando continue oscillazioni dell'INR.
- Pazienti che preferiscono i nuovi farmaci anticoagulanti o che non vogliono più fare i prelievi di controllo.

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Come passare da warfarin ai NAO?

- Se l'INR è ≤ 2 si possono assumere subito i NAO.
- Se l'INR è compreso tra 2.0 e 3,0, sospendere il warfarin e iniziare i NAO quando INR inferiore a 2, presumibilmente 48 ore dopo l'ultima assunzione di warfarin.
- Se l'INR è >3, sospendere il warfarin e controllare l'INR dopo 48 ore.

Guida FCSA 2012

Come passare da eparina ai NAO?

- Subito prima della dose successiva di LMWH o fondaparinux
- Dopo 90 minuti dalla sospensione della infusione di eparina endovena o quando aPTT è rientrato nella norma

Cosa fare prima del trattamento

- aPTT, PT e un emocromo con conta delle piastrine, funzione epatica e renale (clearance della creatinina).
- Anamnesi farmacologica per farmaci potenzialmente interferenti
- Educazione del paziente
- Portare con sé un documento che certifichi l'uso del farmaco
- Centro Trombosi o medico di riferimento in caso di problemi

Potenziali interazioni farmacologiche dei NAO

	DABIGATRAN	RIVAROXABAN, EDOXABAN, APIXABAN
Inibitori della P-glicoproteina Amiodarone, Fenotiazina, Acido Carbossilico, Antifungini azolici, Verapamil, Antimalarici, Ciclosporinea Tioxanteni.	Si	Si
Induttori della P-glicoproteina Desametasone, Rifampicina, Erba di S.Giovanni.	Si	Si
Inibitori del CYP3A4 Fenotiazina, Acido Carbosslico, Antifungini azolici, , Verapamil, Eritromicina, Telitromicina, Nefazodone, Antimalarici, Ciclosporina, Tioxantenei	No	Si
Induttori del CYP3A4 Carbamazepina, Efavirenz, Nevirapinea Fentoina, Fenobarbitone, Rifabutin, Rifapentina, Rifampicina, Erba di S.Giovanni, Alcohol, Eucaliptolo.	No	Si
FANS Aspirina, Naproxene, Diclofenac.	Si	Si
Agenti antipiastrinici Clopidogrel	Si	Si

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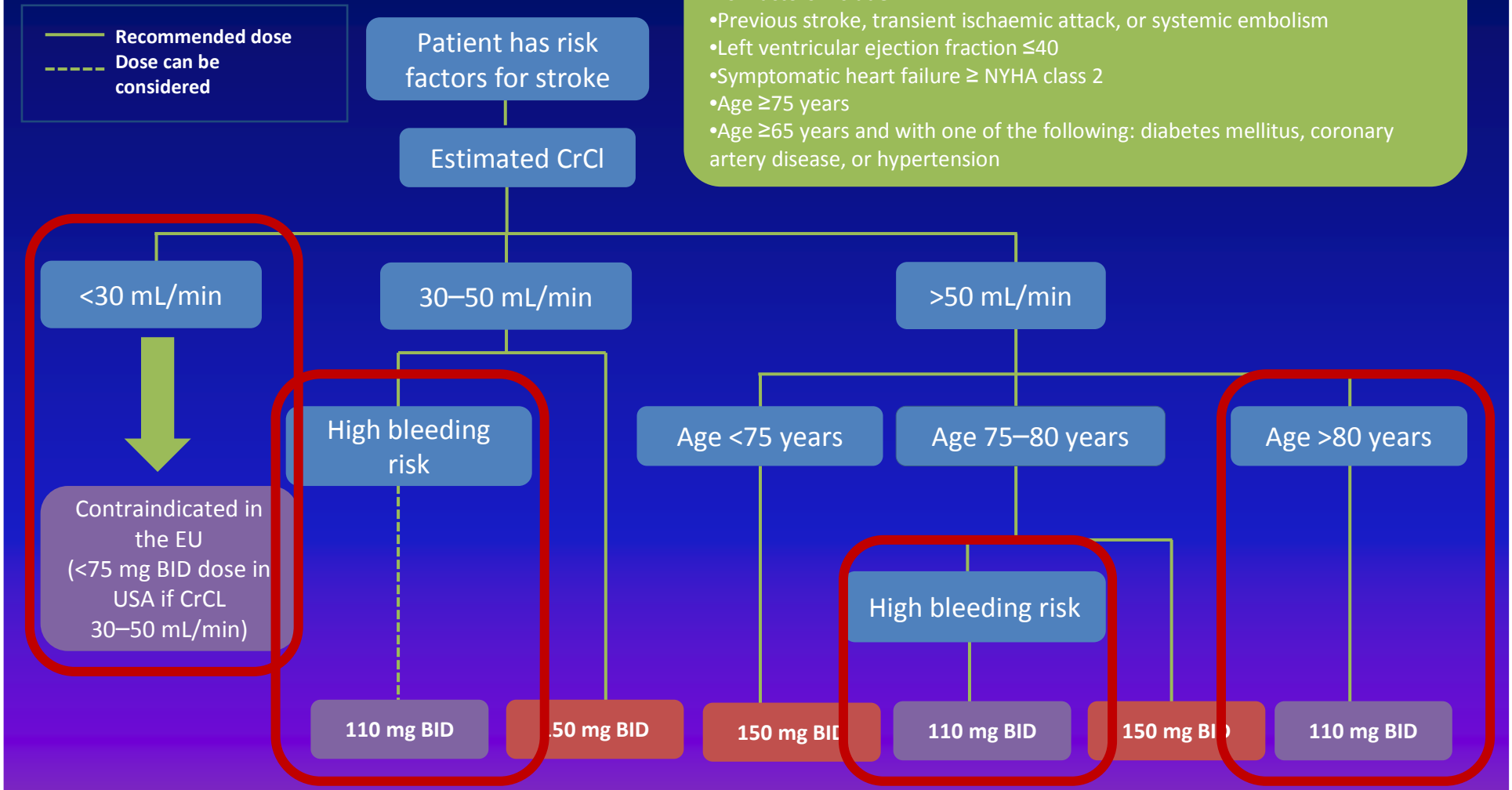
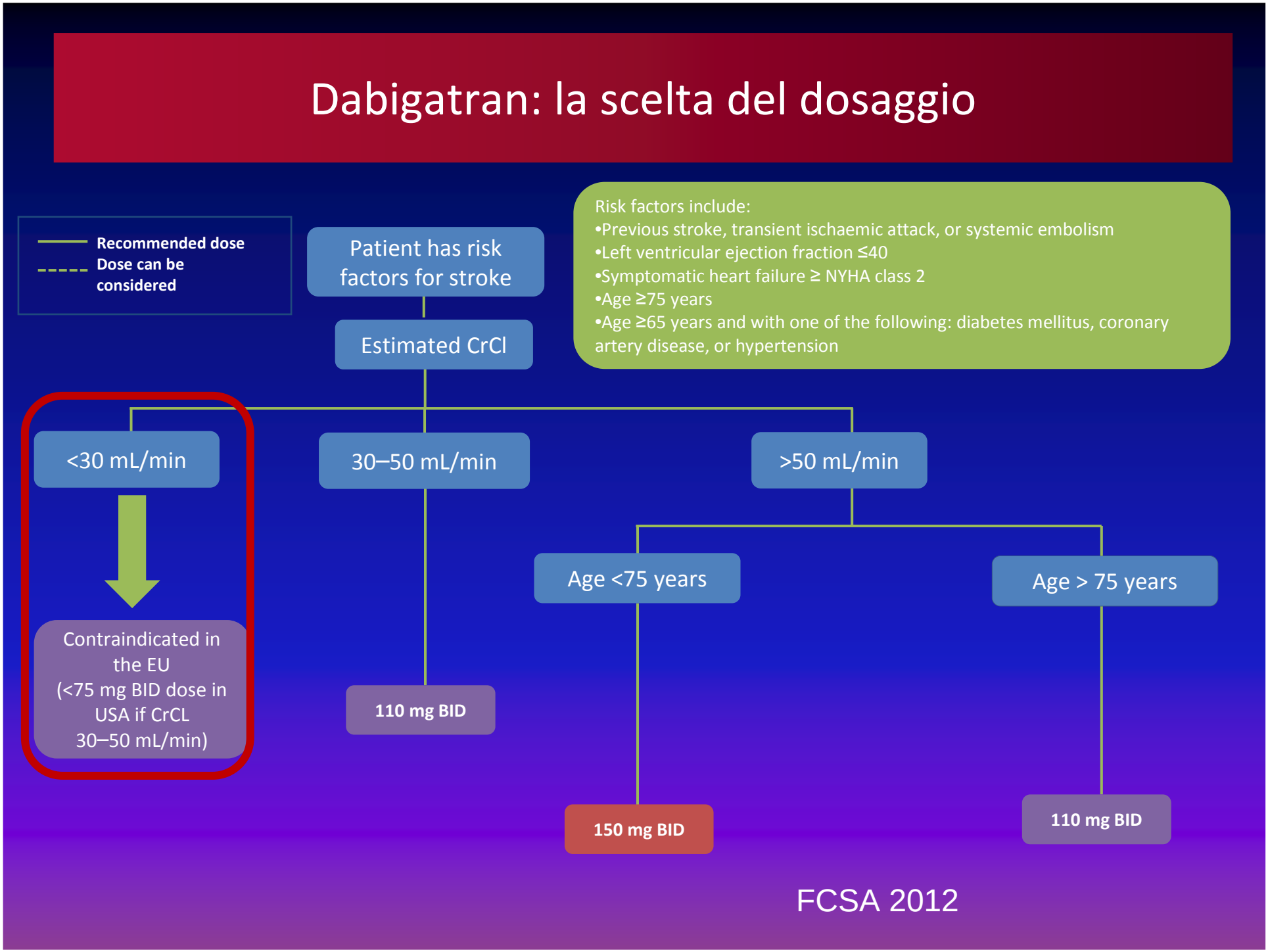
Dabigatran: la scelta del dosaggio



BID = twice daily; CrCl = creatinine clearance; NYHA = New York Heart Association

Adapted from: Huisman M et al. Thromb Haemost doi:10.1160/TH11-10-0718

Dabigatran: la scelta del dosaggio



Cosa fare durante il trattamento

- Visite a 3, 6, 12 mesi dall'inizio del trattamento e poi annualmente
- Controllare la funzione renale almeno una volta all'anno
- Ogni 6 mesi se la creatinina clearance è tra 30 e 50 ml/min o se il pz ha una età superiore a 75 anni
- Controllare la aderenza al trattamento

Cosa si può fare per aumentare la aderenza/persistenza alla terapia?

- **Visite di follow up sistematiche da parte di:**

i. Medico prescrittore
ii. Medico di Medicina generale
iii. Medico di un Centro Trombosi accreditato
iv. Farmacisti del territorio (annotano la frequenza di approvvigionamento del farmaco)
v. Paramedici sul territorio per i pazienti in ADI

- **Altre misure meno efficaci per aumentare la compliance:**

i. Chiamata telefonica
ii. Registro tenuto dal paziente
iii. Una ampia educazione al momento della prescrizione
iv. Depliant e questionari

Pengo V et al. Thromb Haemost 2011

Quanto tempo dovrebbe passare tra la sospensione dei NAO ed un intervento chirurgico elettivo ?

Dabigatran:

Funzionalità renale (CLCr in ml/min)	Emivita stimata (ore)	Sospensione di dabigatran prima della chirurgia elettiva	
		Elevato rischio di sanguinamento o chirurgia maggiore	Rischio standard
≥80	~13	2 giorni prima	24 ore prima
≥50-<80	~15	2-3 giorni prima	1-2 giorni prima
≥30-<50	~18	4 giorni prima	2-3 giorni prima (>48 ore)

Controllo di laboratorio?

Pradaxa scheda tecnica

Pazienti da sottoporre al test di laboratorio

Nei pazienti in terapia con NAO, il monitoraggio di laboratorio non è generalmente necessario. Fanno tuttavia eccezioni alcune condizioni:

- Necessità di sottoporre pazienti in terapia con NAO ad interventi invasivi.
- Pazienti che si presentino in emergenza con eventi trombotici o emorragici e senza chiare indicazioni in merito alla terapia. In queste circostanze, può essere utile conoscere la tipologia del NAO assunto, ed il dosaggio ematico attuale.
- Necessità di antagonizzare rapidamente l'effetto anticoagulante del farmaco.
- Pazienti con insufficienza renale o epatica, in cui il metabolismo dei NAO può essere alterato.
- Interazione con altri farmaci che possono ridurre o potenziare l'effetto dei NAO.
- Pazienti con estremi di peso (eccessiva magrezza o obesità).

Guida FCSA 2012

Quale test di laboratorio?

(alla seconda ora dopo la somministrazione o prima della somministrazione successiva?)

Dabigratan

- Si raccomanda l'esecuzione del Tempo di Trombina diluito (dTT), del tempo di ecarina (Ecaring Clotting Time, ECT) o del tempo di trombina (Thrombin Clotting Time, TCT).

Rivaroxaban

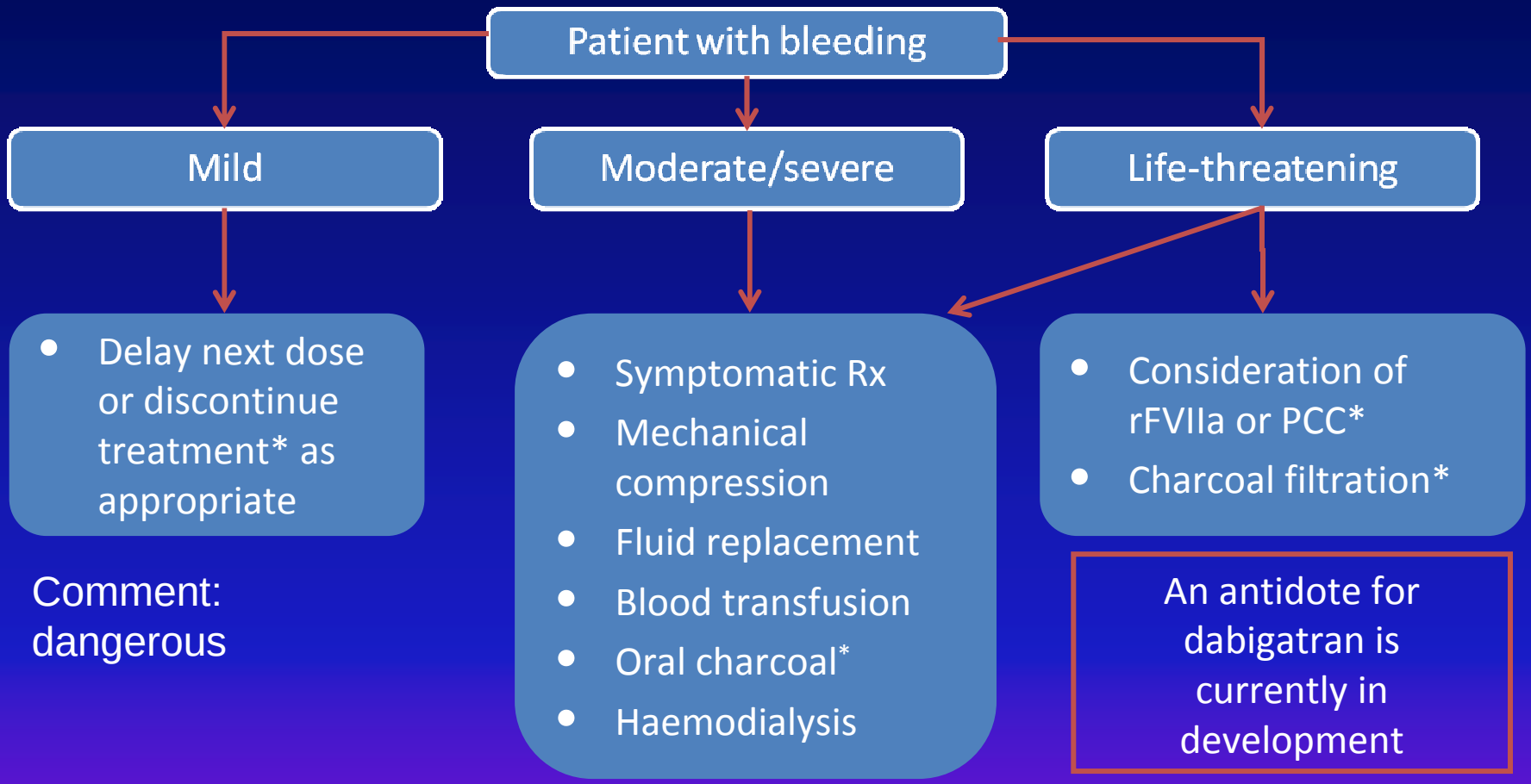
- Si raccomanda l'esecuzione dell'attività anti-FXa o del tempo di protrombina (PT).
- I risultati del PT devono essere espressi in termini di rapporto (paziente su normale), mentre è sconsigliata l'espressione in termini di INR

Altri suggerimenti pratici

- In caso di dimenticanza nell'assunzione di un NOA, non assumere la dose doppia il giorno dopo.

- Istruire bene il paziente ed il medico di medicina generale in modo che il NOA non venga sospeso anche temporaneamente in caso di emorragie minori o trascurabili ancorchè vistose (es, emorragia congiuntivale)

Emorragie in pazienti trattati con dabigatran

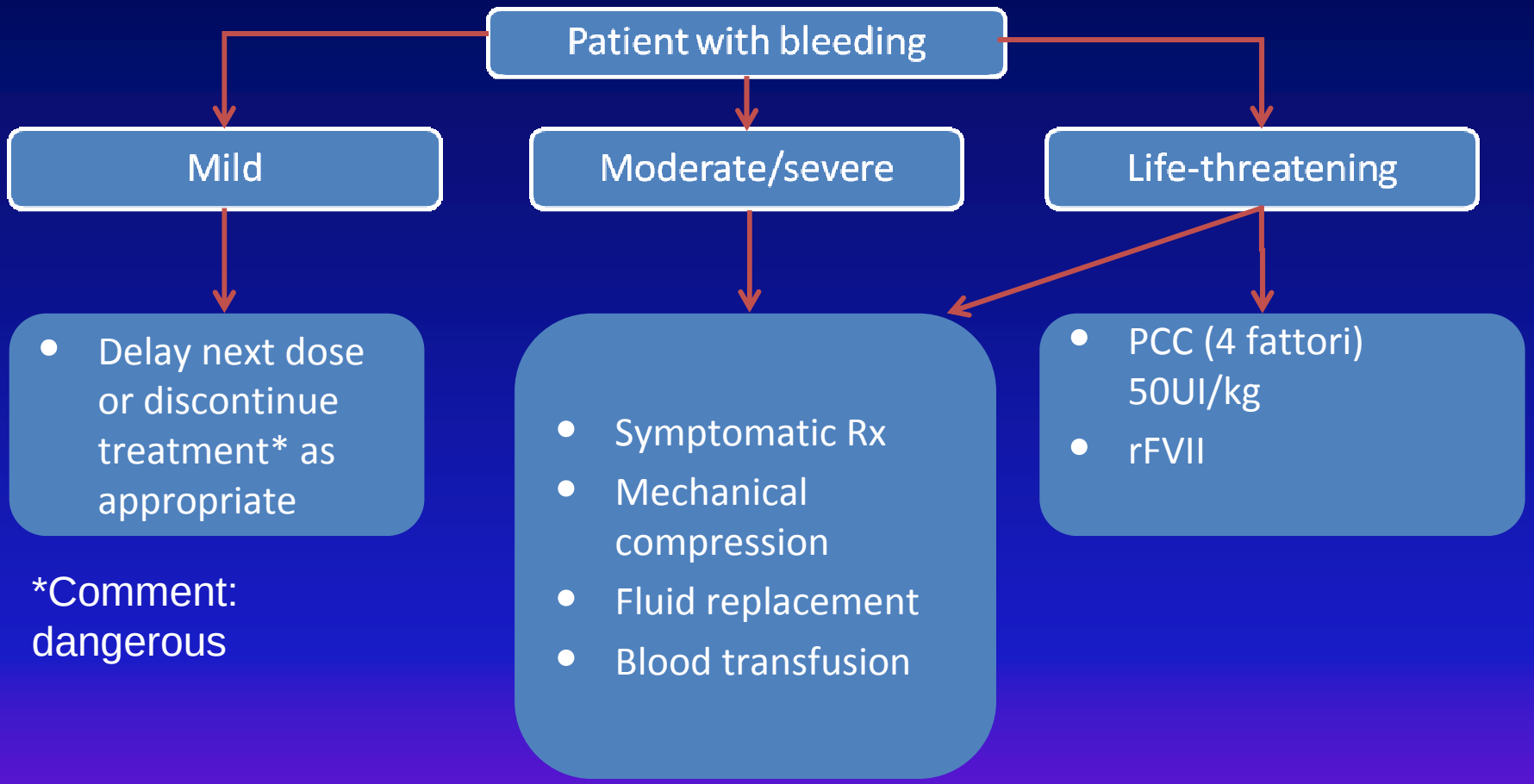


PCC = prothrombin complex concentrates; rFVIIa = recombinant Factor VIIa; Rx =treatment

*Recommendation based only on limited non-clinical data; there is no experience in volunteers or patients

van Ryn J et al. Thromb Haemost 2010;103:1116–27

Emorragie in pazienti trattati con rivaroxaban

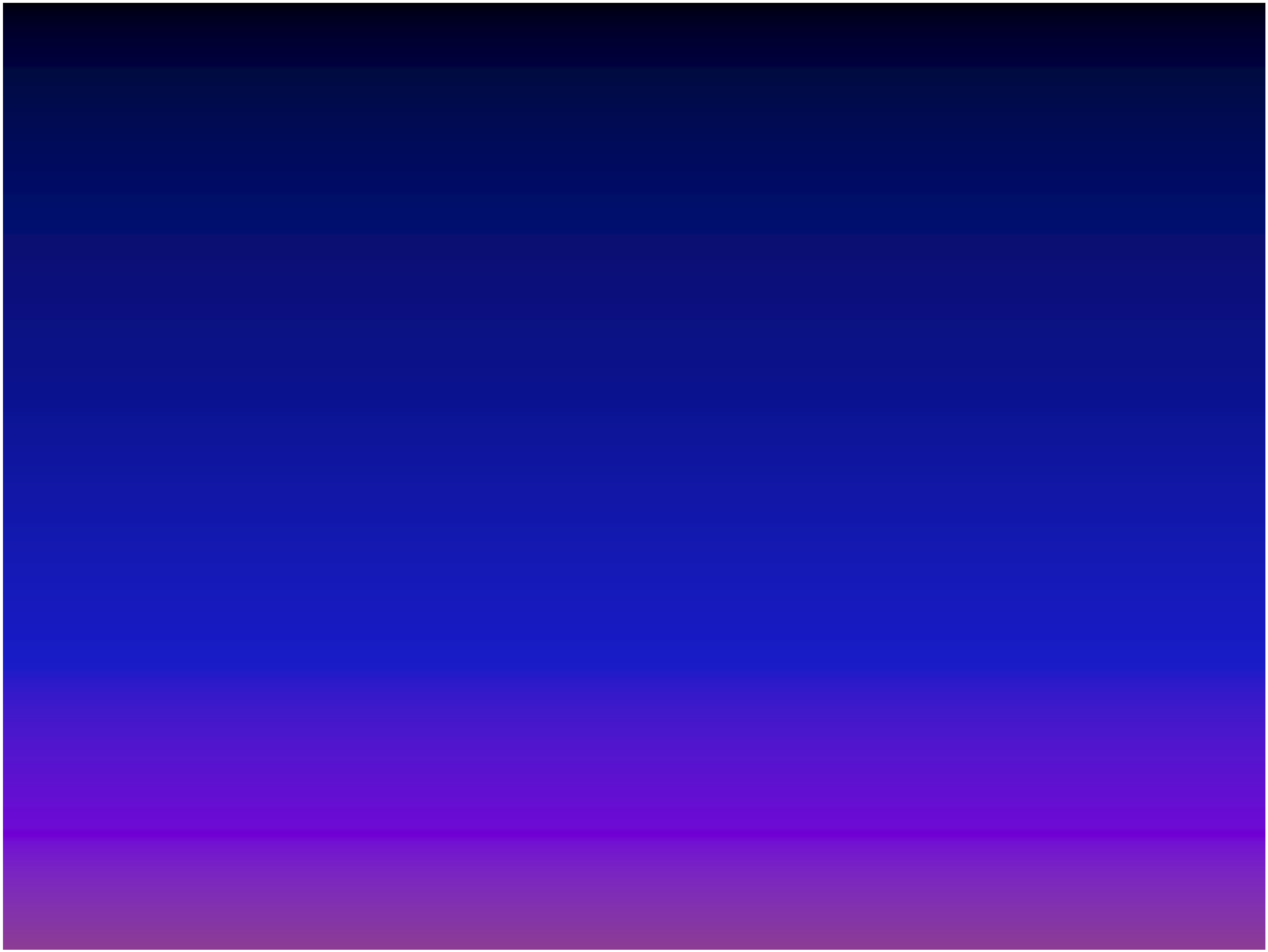


*Comment: dangerous

PCC = prothrombin complex concentrates; rFVIIa = recombinant Factor VIIa; Rx =treatment

Raccomandazioni per il follow up dei pazienti trattati con NAO

- E’ opportuno che questi pazienti entrino in un registro che raccolga le caratteristiche di pazienti ed il tipo di trattamento
- Che vi sia una registrazione puntuale degli eventi trombotici ed emorragici e della mortalità
- I pazienti che mancano ad una visita di controllo andrebbero rintracciati direttamente o tramite il MMG con individuazione della causa del mancato controllo
- Un registro di questo genere (START Registry) è attivo dal 2011, ma ha arruolato finora solo soggetti trattati con VKA data la indisponibilità in Italia dei NAO



Switching patients to dabigatran

Warfarin to dabigatran

Parenteral to dabigatran

Start dabigatran up to 2 hours before next parenteral drug dose

Continuous infusions to dabigatran

Start dabigatran at time of discontinuation of continuous infusion

INR = international normalized ratio

Huisman M et al. Thromb Haemost doi:10.1160/TH11-10-0718

If a patient misses a dose

The 6-hour rule	
Time since missed dose	*Recommendation*
<6 hours	The patient should take the ‘missed’ dose
>6 hours	The patient should wait until their next scheduled dose

Huisman M et al. Thromb Haemost doi:10.1160/TH11-10-0718

Temporary discontinuation for elective surgery

When to stop dabigatran:

Renal function (CrCl in mL/min)	Standard bleeding risk	High bleeding risk*
≥80	24 hours before	2 days before
≥50 to <80	1–2 days before	2–3 days before
≥30 to <50	2–3 days before (>48 hours)	4 days before

- Due to the fast onset and offset of action of dabigatran no bridging therapy is required for the majority of interventions
- Following surgery, dabigatran should be restarted as soon as possible after haemostasis has been achieved

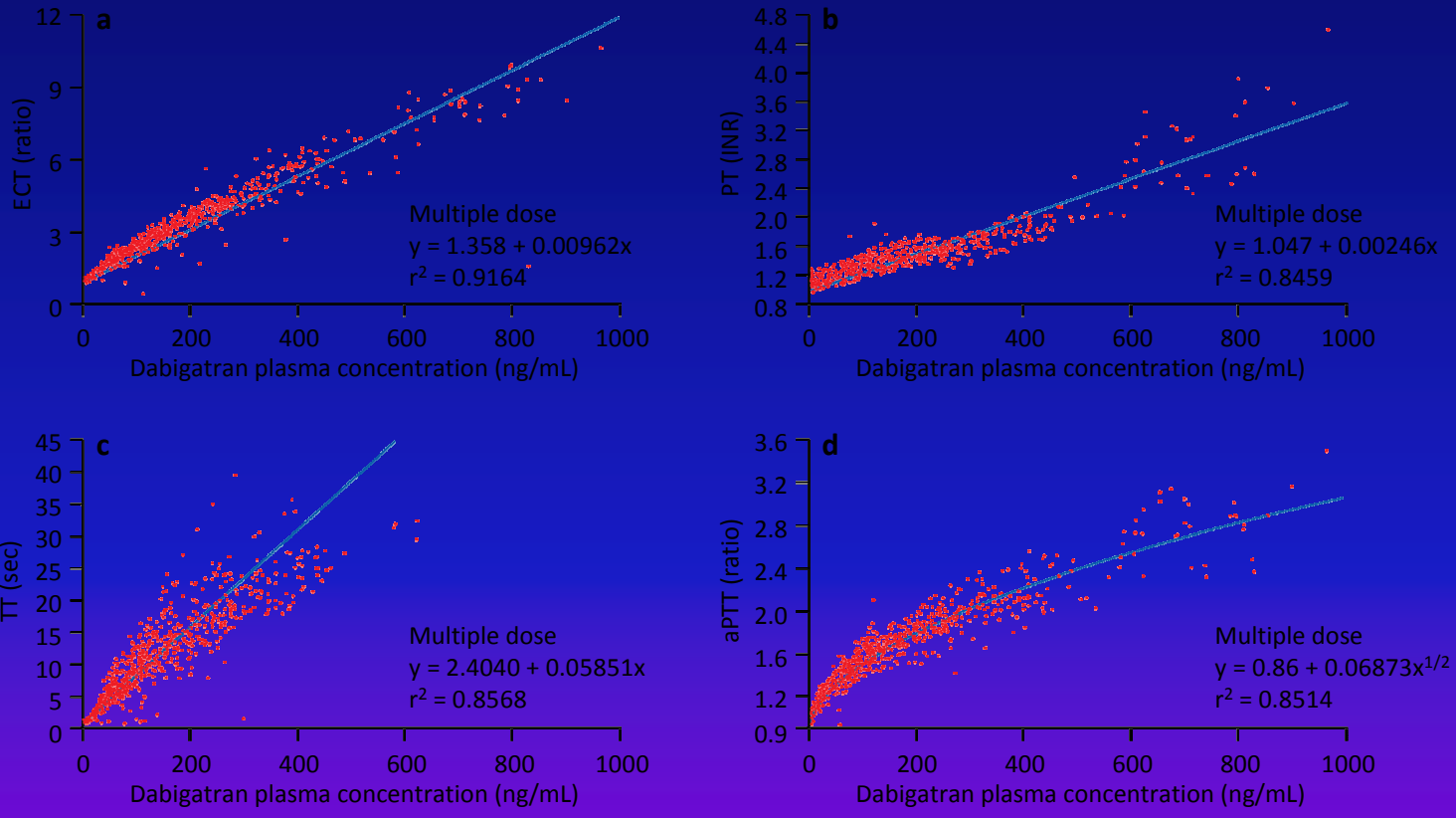
*Type of surgery associated with a high risk of bleeding include but are not limited to cardiac surgery, neurosurgery, abdominal surgery, or surgeries involving a major organ. Other procedures such as spinal anaesthesia may require complete haemostatic function

CrCl = creatinine clearance

Huisman M et al. Thromb Haemost doi:10.1160/TH11-10-0718

but in certain emergency situations it may be advisable to assess coagulation status

Close correlation between dabigatran plasma concentration and degree of anticoagulant effect



INR is not sufficiently sensitive and cannot be recommended

ECT = ecarin clotting time; PT = prothrombin time; TT = thrombin time; aPTT = activated partial thromboplastin time

van Ryn J et al. Thromb Haemost 2010;103:1116–27

Interpretation of coagulation assays to assess bleeding risk: aPTT

Activated partial thromboplastin time (aPTT)

May be useful in determining an excess of anticoagulant activity[1,2]

Clinically relevant measurement

An aPTT >80 seconds at trough (when the next dose is due) is associated with a higher risk of bleeding[1,3]

INR = international normalized ratio

1. van Ryn J et al. Thromb Haemost 2010; 103:1116–1127; 2. Liesenfeld K-H et al. Br J Clin Pharmacol 2006; 62:527–537; 3. Huisman M et al. Thromb Haemost doi:10.1160/TH11-10-0718

Tests that assess the risk of bleeding – TT

Thrombin time (TT) test

The TT test measure will depend on the coagulometer and on the thrombin lot used

It is therefore advisable to use the calibrated Hemoclot® Thrombin Inhibitor assay* (a diluted TT assay) with dabigatran standards

Clinically relevant measurement

A TT measure (calibrated Hemoclot® thrombin inhibitor assay) of >200 ng/mL dabigatran plasma concentration (approximately >65 seconds) prior to the next drug intake after 150 mg BID dosing (trough measure, i.e. 10–16 hours after the previous dose) is associated with a higher risk of bleeding

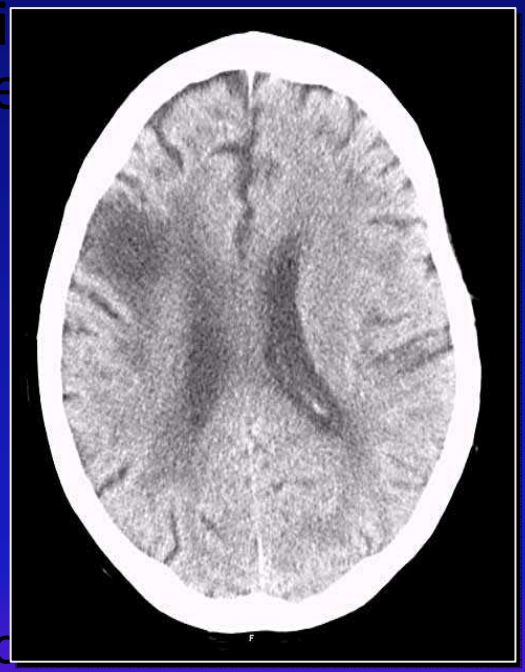
A normal TT measurement indicates no clinically relevant anticoagulant effect of dabigatran

* Hyphen BioMed, Neuville-sur-Oise, France; BID = twice daily;
van Ryn J et al. Thromb Haemost 2010;103:1116–27

Thrombolysis in patients with acute ischaemic stroke

Intravenous administration of rtPA is effective if given to eligible patients within 4.5 hours of symptom onset

- The use of thrombolysis in patients receivi concurrent dabigatran has not been studie
  - May increase the risk of bleeding
- In patients considered candidates for thrombolysis measurement of the aPTT, or TT are appropriate initial tests
  - A normal result for one of these assays generally indicates that the bleeding risk is lo



aPTT = activated partial thromboplastin time; ECT = ecarin clotting time; INR = international normalized ratio; TT = thrombin time; rtPA = recombinant tissue plasminogen activator

Huisman M et al. Thromb Haemost doi:10.1160/TH11-10-0718

Utilizzo di agenti fibrinolitici per il trattamento dell'ictus ischemico acuto

Può essere considerato l'utilizzo di agenti fibrinolitici per il trattamento dell'ictus ischemico acuto se il paziente presenta un dTT, ECT o un aPTT al di sotto del limite superiore dei valori normali, in accordo all'intervallo di riferimento locale.

RCP, 2012

When to start dabigatran after an acute stroke?

Stroke Severity	Restart dabigatran
TIA	As soon as imaging has excluded a cerebral haemorrhage
Mild Stroke	3–5 days after symptom onset
Moderate Stroke	5–7 days after stroke onset
Severe Stroke	2 weeks after stroke onset

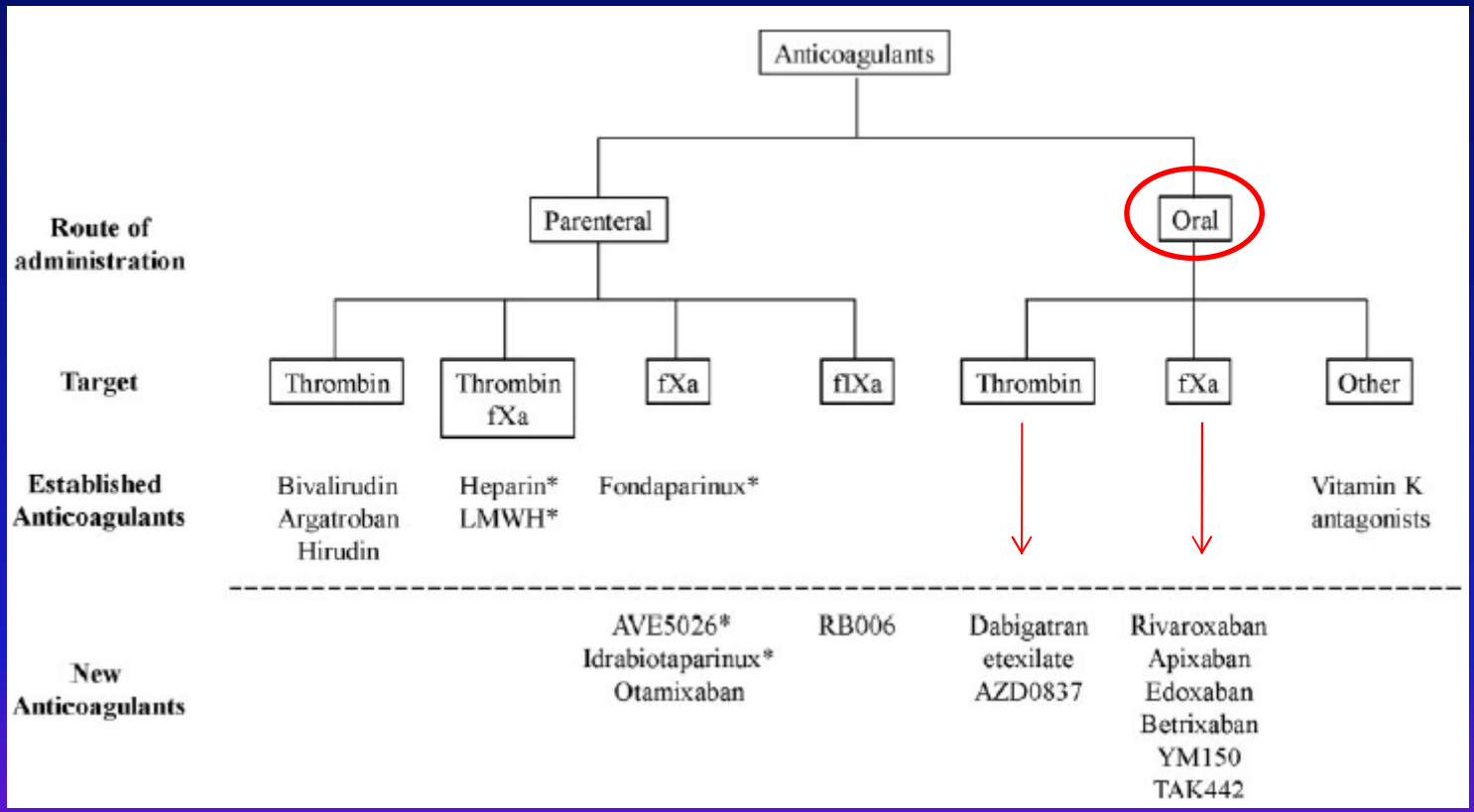
TIA = transient ischaemic attack

Huisman M et al. Thromb Haemost doi:10.1160/TH11-10-0718

A practical guide to Dabigatran therapy: important Topics

- How to pick the right dose?
- How to switch to dabigatran?
- How to manage interruptions?
- How to measure the anticoagulant effect?
- How to manage acute ischaemic stroke?
- How to manage bleeding?

Anticoagulants



John W. Eikelboom, ***Circulation. 2010;121:1523-1532.***

Novel oral anticoagulants

	Dabigatran	Rivaroxaban	Apixaban	Edoxaban	Betrixaban
Target	IIa	Xa	Xa	Xa	Xa
Hours to Cmax	2	2-4	1-3	1-2	NR
Prodrug	Yes	No	No	No	No
CYP metabolism	No	32%	15%	NR	No
Bioavailability	7%	80%	66%	>45%	34%-47%
Tranporters	Pgp	Pgp	Pgp	Pgp	Pgp
Protein binding	35%	>90%	87%	55%	NR
Half-life (hours)	12-14	9-13	8-15	8-10	19-20
Renal elimination	80%	66%	25%	35%	<5%
Linear PK	Yes	No	Yes	Yes	Yes
Dosing	Twice a day	Once a day	Twice a day	Once a day	Once a day

On March 2011 Merk decided to abandon betrixaban

Modified from:
Ericksson BI, Clin Phatmacokinet 2009
Ruff CR, Am Heart J 2010

Advantages using New Anticoagulants

Rapid onset of action

Predictable anticoagulant effect

Specific coagulation enzyme target

Low potential for food interactions

Low potential for drug interactions

No need for bridging

No need for routine coagulation monitoring

Low risk of off-target adverse effects

No dietary precautions

Few drug restrictions

Eikelboom JW, Circulation 2010

Rivaroxaban versus Warfarin in Nonvalvular Atrial Fibrillation

Manesh R. Patel, M.D., Kenneth W. Mahaffey, M.D., Jyotsna Garg, M.S., Guohua Pan, Ph.D., Daniel E. Singer, M.D., Werner Hacke, M.D., Ph.D., Günter Breithardt, M.D., Jonathan L. Halperin, M.D., Graeme J. Hankey, M.D., Jonathan P. Piccini, M.D., Richard C. Becker, M.D., Christopher C. Nessel, M.D., John F. Paolini, M.D., Ph.D., Scott D. Berkowitz, M.D., Keith A.A. Fox, M.B., Ch.B., Robert M. Califf, M.D., and the ROCKET AF Steering Committee, for the ROCKET AF Investigators*

Apixaban versus Warfarin in Patients with Atrial Fibrillation

Christopher B. Granger, M.D., John H. Alexander, M.D., M.H.S., John J.V. McMurray, M.D., Renato D. Lopes, M.D., Ph.D., Elaine M. Hylek, M.D., M.P.H., Michael Hanna, M.D., Hussein R. Al-Khalidi, Ph.D., Jack Ansell, M.D., Dan Atar, M.D., Alvaro Avezum, M.D., Ph.D., M. Cecilia Bahit, M.D., Rafael Diaz, M.D., J. Donald Easton, M.D., Justin A. Ezekowitz, M.B., B.Ch., Greg Flaker, M.D., David Garcia, M.D., Margarida Geraldes, Ph.D., Bernard J. Gersh, M.D., Sergey Golitsyn, M.D., Ph.D., Shinya Goto, M.D., Antonio G. Hermosillo, M.D., Stefan H. Hohnloser, M.D., John Horowitz, M.D., Puneet Mohan, M.D., Ph.D., Petr Jansky, M.D., Basil S. Lewis, M.D., Jose Luis Lopez-Sendon, M.D., Prem Pais, M.D., Alexander Parkhomenko, M.D., Freek W.A. Verheugt, M.D., Ph.D., Jun Zhu, M.D., and Lars Wallentin, M.D., Ph.D., for the ARISTOTLE Committees and Investigators*

Rely 2009

Rocket 2011

Aristotele 2011

Characteristics of randomized patients

Risk factors	Dabigatran 110mg N= 6015	Dabigatran 150mg N=6076	Rivaroxaban 20mg N=7131	Apixaban 5 mg N=9120
Age (years)	71 4 ± 8.6	71.5 ± 8.8	73 (65-78)**	70 (63-76)**
Female sex (%)	35.7	35.8	39.7	35.5
Weight (Kg)	82.9 ± 19.9	82.5 ± 19.4	28.3 (25.2-32.1)**§	82 (70-96)**
Prior stroke or embolism %	19.9	20.3	54.9	19.2
Heart failure %	32.2	31.8	62.6	35.5
Diabetes %	23.1	23.4	40.4	25.0
Hypertension %	78.8	78.9	91.3	87.3
CHADS2 score (mean)	2.1 ± 1.1	2.2 ± 1.2	3.48 ± 0.94	2.1 ± 1.1

**median (interquartile range) ; § Body Mass Index.

Dabigatran Rivaroxaban Apixaban for Stroke prevention in AF

EFFICACY

- Non inferiority Vs Warfarin in stroke and peripheral embolism prevention: YES

- Superiority:

  Dabigatran 150mg/bid

  Apixaban 5mg/bid

Dabigatran Rivaroxaban Apixaban for Stroke prevention in AF

SAFETY

- Signifantly less major bleeding:
  - Dabigatran 110mg/bid*
  - Apixaban

- Signifantly less cerebral bleeding :
  - Dabigatran 110mg/bid and 150mg/bid
  - Rivaroxaban
  - Apixaban

Dabigatran Rivaroxaban Apixaban for Stroke prevention in AF

Death from any cause

Clinical Events	Study	Drugs	%/y NOA	%/y W	Relative Risk (95%CI)	P value
Death from any cause	RE-LY	Dabigatran 110	3,75	4,13	0,91 (0,80-1,03)	0,13
		Dabigatran 150	3,64	4,13	0,88 (0,77-1,00)	0,051
	ROCKET-AF	Rivaroxaban	4,5	4,9	0,92 (0,82-1,03)	0,15
	ARISTOTELE	Apixaban	3,52	3,94	0,89 (0,80-0,99)	0,047

Potential problems using New Anticoagulants

Adherence and persistence to treatment: very important in light of the short half-life of new oral anticoagulants

Renal Function

Treatment of major or life threatening bleeding

Potential drug interactions

Side-effects and potential drop-out

Costs

Medication adherence?

After acute coronary syndrome:

Continuous use of drugs after 6-12 months

-Aspirin 71%

-beta-blockers 46%

-statins 44%

-All the three medications 21%

Newby LK, Circulation 2006

What can be practically done to improve adherence/persistence?

Systematic follow-up visits **(Grade B recommendation)** **at least** every six months (check for adverse events, renal function, dyspepsia) by either:

- Prescribing physician
- General practitioner
- Thrombosis center physician
- Community pharmacist (refill frequency)
- Caregivers

Pengo V et al. Thromb Haemost 2011

Renal function

Patients with creatinine clearance < 30ml/min were excluded from dabigatran and rivaroxaban trials; those with a creatinine clearance < 25ml/min were excluded from apixaban trial

Patients with creatinine clearance 30 to 50 ml/min received reduced dose in Rocket-AF (15mg/qd). Patients with a serum creatinine level of 1.5 mg per deciliter (133 µmol per liter) or more received a reduced dose of apixaban (2.5mg/bid)

Control of renal function?

Periodic (at least every year) evaluation of renal function especially in the elderly and fragile patients.

Major or life-threatening bleeding

No antidote

Laboratory tests?

Fresh Frozen Plasma?

Prothrombin complex concentrate?

Recombinant Activated factor VII (rFVIIa)?

Laboratory tests

- Importance to know which one of the new anticoagulants is taken

- Ecarin Clotting Time (ECT) or aPTT (if ECT is not available) for dabigatran or diluted thrombin time (dTT) should be recommended

- Prothrombin Time (PT) for rivaroxaban and for apixaban should be recommended

- It is recommended to do testing after 2–3 months from the initiation of the therapy in order to have a steady-state laboratory value that may be useful in the future if adverse clinical events will occur.

How should patients with major or life-threatening bleeding be treated?

- Direct thrombin inhibitors are hardly counteracted by PCC or FFP. Dabigatran could be adsorbed via haemoperfusion over a charcoal filter. In case of major-life threatening bleeding, haemodialysis is a therapeutic option .

- Direct FXa inhibitors could be (partially) antagonised by nonactivated four-factor PCCs. They contain factor II-VII-IX-X and dosage could be 50UI/Kg by one-shot administration.

Eerenberg ES, ***Circulation. 2011;124:1573-1579***

Drugs affecting the efflux tranporter P-glycoprotein and the cytocrome 450 metabolism

Dabigatran
Rivaroxaban
Apixaban

Rivaroxaban
Apixaban

P-gp inhibitors	P-gp inducers	P-gp substrate	CYP3A4 inhibitors	CYP3A4 inducers	CYP3A4 substrate
Amiodarone	Dexamethasone	Digoxin	Phenotiazin	Carbamazepine	Midazolam
Phenotiazin	Rifampicin	Atorvastatin	Carboxylic Acid	Efavirenz	Atorvastatin
Carboxylic acid	St. John's Wort		Verapamil	Nevirapine	
Azole antifungals	Carbamazepine		Azole antifungals	Phenytoin	
Verapamil	Phenytoin		Erythromycin	Phenobarbital	
Antimalarial			Telithromycin	Rifabutin	
Cyclosporine			Nefazodone	Rifapentine	
Thioxanthenes			Antimalarial	Rifampicin	
Ketoconazole			Cyclosporine	St. John's wort	
Quinidine			Thioxanthenes	Alcohol	
			Ketoconazole	Eucalyptol	

General recommendations before starting new OAC (I)

New oral anticoagulants may be prescribed by specialists in cardiology, neurology, internal medicine, or by Thrombosis Centres (treatment plan). Before prescribing the following steps should be followed:

- Comply with the indications and contraindications of individual new OAC.
- Explain to the patient the characteristics of various available drugs.
- Take into account the patient preferences in the choice of treatment. Once the treatment is chosen then it is needed to make a correct and complete information and patient education.

Pengo V et al. Thromb Haemost 2011

General recommendations before starting new OAC (II)

- Arrange personally the follow-up or through the support of Thrombosis Centres or by express agreement with the general practitioner (GP).
- Advise the patient to keep a personal identification card, containing personal information, the type of anticoagulant treatment in progress, an address reference with telephone number for contact by the patient in case of need or by another physician for any emergency.
- Check blood cell count, PT, APTT, liver function tests and the creatinine clearance in all subjects over 75 years of age.

START Registry

- Independent
- Open to everyone
- Multisponsored
- Involves the construction of the central database, and its connection with the peripheral database of participating centers
- Prospectively records the events in naive patients treated with anticoagulants both old and new

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Which patients with AFib should be prioritized in taking the new oral anticoagulants?

- Patients with unstable INR
- Patients with history of intracranial bleeding
- Patients willing to be prescribed the new drugs.
- Patients with logistic problems
- Patients in whom warfarin was not prescribed

Dabigatran Rivaroxaban Apixaban for Stroke prevention in AF

TTR accounts for the standard of care in warfarin arm

	Dabigatran	Rivaroxaban	Apixaban
Warfarin TTR (%)	64	55	62.2

Local standards of care affect the benefits of use of new treatment alternatives

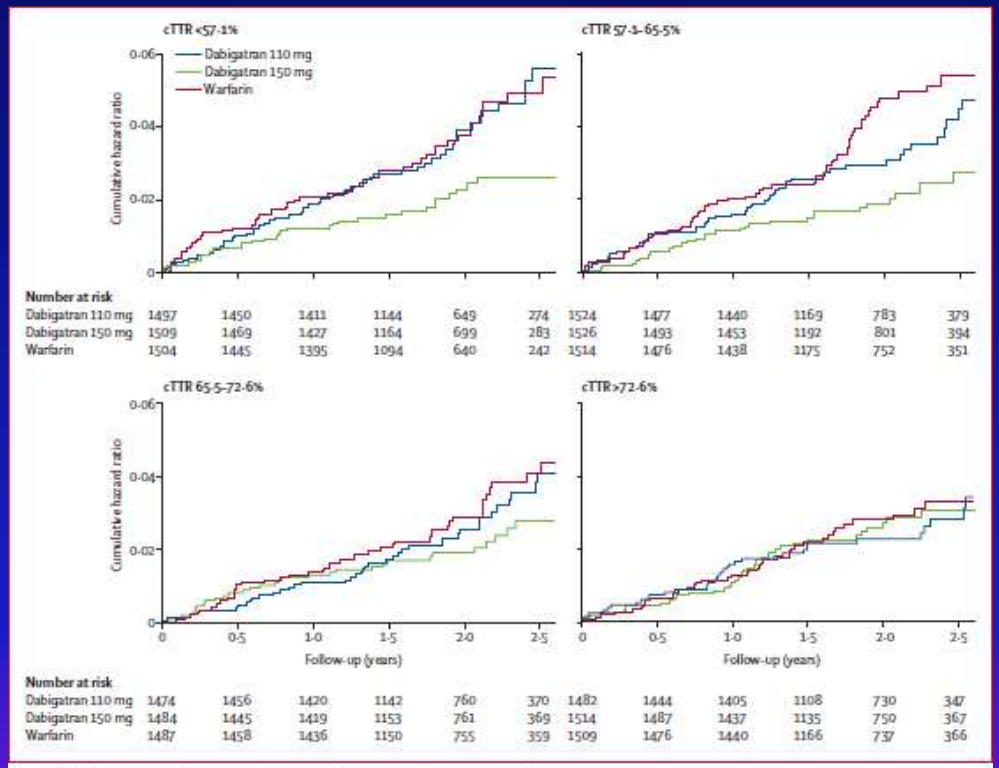

Figure 2: Time to primary outcome in each quartile of centre's mean time in therapeutic range
cTTR=centre's mean time in therapeutic range.

Wallentin L, Lancet 2010

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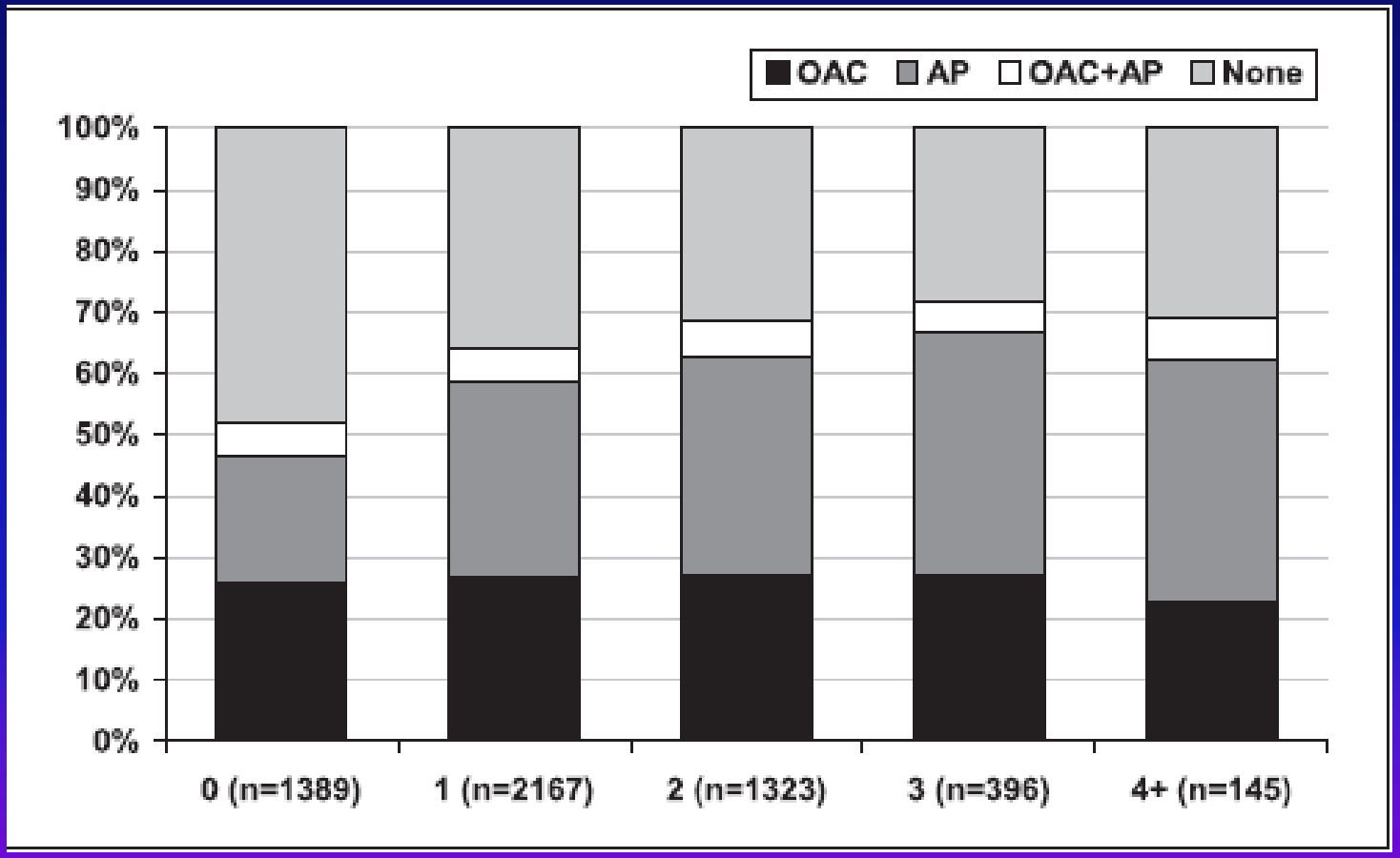
Management of AF in Italian primary care



Mazzaglia G, Thromb Haemost 2010

Use of aspirin in AFib according to age

	All	n (%)[a] on AP	Adjusted OR OR[b] (95% CI)	P-values[c]
Age groups				<0.001
30–64	1140	279 (24.4)	1.00	
65–74	1698	573 (33.7)	1.39 (1.15–1.67)	
75–84	1946	784 (40.3)	1.81 (1.57–2.10)	
≥85	636	328 (51.6)	2.95 (2.30–3.78)	

Mazzaglia G, Thromb Haemost 2010

Patients in whom the new drugs may not replace coumarins.

- Patients with severe renal failure
- Patients with both a stable INR and a low bleeding risk
- Patients who scarcely adhere to treatment

Dabigatran Rivaroxaban Apixaban for Stroke prevention in AF

Results

	Dabigatran	Rivaroxaban	Apixaban
Premat discont (%)	15	24	25

Back to warfarin? A different NOA?