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La gestione del paziente con i nuovi anticoagulanti orali

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Qualità della vita dei pazienti

Potenziali pro (e contro) per i pazienti

- Prevedibile e costante rapporto dose/effetto
- Non frequenti controlli periodici e prelievi ematici
- Risparmio di tempo e meno disagi di trasporto
- Meno interferenze con farmaci (e dieta)
- Semplicità del trattamento

(contro)

- Possibili problemi di aderenza alla terapia
- Possibile mancanza di punto di riferimento per problemi intercorrenti

Potenziale importante miglioramento:

Incremento della popolazione di pazienti con FA adeguatamente anticoagulati, superando molte limitazioni dell'attuale trattamento con AVK

Una importante porzione di pazienti con FA non vengono trattati o sono trattati in modo incongruo

Euro Heart Survey (2003-2004) =
intorno al 28% la percentuale di pazienti
con FA ad alto rischio “undertreated”

Aspetti pratici della gestione di pazienti in NAO

Attività essenziali per Il trattamento con AVK o NAO

AVK		NAO
Si	Visita di prescrizione (anamnesi e condizioni cliniche)	Si
Si	Giusta indicazione e dose (o INR)	Si
Si	Informazione/Educazione dei paz.	Si
Si	Routine controlli di lab. (esperti)	No
Si	Routine aggiustamento dose (esperti)	No
(No)	Controllo aderenza	Si
Si	Guida per condizioni a rischio/complic.	Si
No (routine)	Controllo clinico periodico	Si

Pharmacokinetic and pharmacodynamic characteristics of the NOACs

	Dabigatran	Apixaban	Rivaroxaban	Edoxaban
Target	IIa (thrombin)	Xa	Xa	Xa
Hrs to Cmax	0.5-2.0	3.0-4.0	2.0-4.0	1.0-2.0
Interactions	P-gp	P-gp and CYP3A4	P-gp and CYP3A4	P-gp
Half-Life	14-17 h	12-15h	9-13h	8-10h
Renal Elimination	80%	27%	33%	50%

Dabigatran etexilate for stroke prevention in patients with atrial fibrillation: Resolving uncertainties in routine practice

Menno V. Huisman[1]; Gregory Y. H. Lip[2]; Hans-Christoph Diener[3]; Martina Brueckmann[4]; Joanne van Ryn[5]; Andreas Clemens

Thromb Haemost 2012

Clinical management of rivaroxaban-treated patients

Walter Ageno, Annamaria Ferrari, Alessandro Filippi, Davide Imberti, Vittorio Pengo, Andrea Rubboli, Danilo Toni

Gualtiero Palareti (coordinatore)

Influence of CYP3A4 and P-gp inhibitors on rivaroxaban plasma concentration

Rivaroxaban +	CYP3A4 inhibition	P-gp inhibition	AUC x-fold increase	C_{max} x-fold increase	Clinically relevant
Ketoconazole 400 mg o.d.	Strong	Strong	2.6	1.7	YES
Ritonavir 600 mg b.i.d.	Strong	Strong	2.5	1.6	YES
Clarithromycin 500 mg b.i.d.	Strong	Moderate	1.5	1.4	No
Erythromycin 500 mg t.i.d.	Moderate	Moderate	1.3	1.3	No

Approved regimens in atrial fibrillation
Rivaroxaban

- 20 mg daily dose
- 15 mg daily in patients with CrCl 15 and 49 mL/min, but little experience exists for patients with severe renal insufficiency
- Contraindicated in Child B and C liver cirrhosis patients
- Contraindicated in patients aged <18 years old
- Contraindicated during pregnancy and breast-feeding

Rivaroxaban doses for acute treatment of DVT/PE

- 15 mg x 2 daily for 3 weeks
- Followed by 20 mg daily

What to do before starting treatment

- Order lab tests: aPTT, PT, full blood count, liver and renal function tests
- Calculate creatinine clearance (Cockroft-Gault formula)
- Collect drug history
- Consider dose reductions where appropriate

What to do before starting treatment 2

- Take time for adequate patient education
- Specific patient cards should be given
- A reference Thrombosis Center/specialist should be provided in case of problems

- Remember that rivaroxaban is contraindicated during pregnancy

From warfarin (W) to rivaroxaban (R)

a) INR ≤ 2 = switch immediately to R
b) INR between 2.0 - 3.0 = stop W and start R 48 h after the last W
c) INR >3.0 stop W and re-check INR 48 h after the last W

Practical issues

- **Food intake slightly increases absorption rates and reduces inter-individual variability: 15-20 mg daily doses should be taken with food**
- **In patients taking rivaroxaban once daily, missed dose can be taken as soon as possible on the same day, doubling the dose on the day after is not recommended**
- **DVT patients on 15 mg bid treatment can take the two 15 mg doses together if the first dose was missed**

What to do during treatment

- Ensure drug adherence
- Plan the following lab examinations 3 months after treatment is started and then at least twice a year:
  - Full blood count
  - Creatinine clearance
  - Liver function

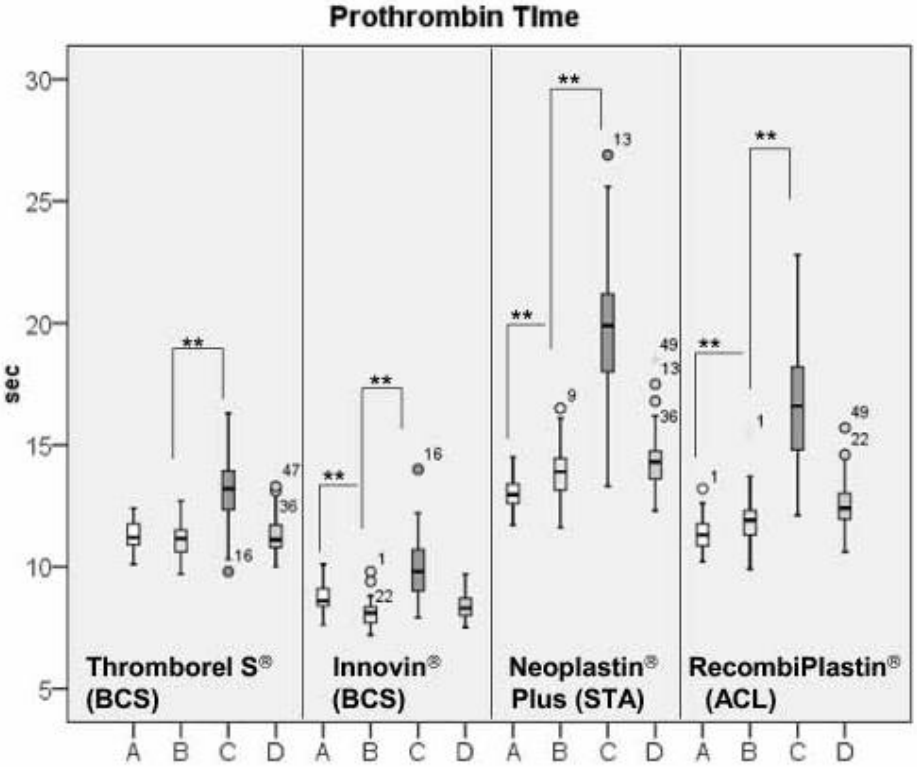
How to assess anticoagulant activity in rivaroxaban-treated pts

- PT assay, with specific reagents
- Anti-Xa activity (chromogenic assay)

Rivaroxaban differentially influences *ex vivo* global coagulation assays based on the administration time

Thromb Haemost 2011

Helen Mani; Christian Hesse; Gertrud Stratmann; Edelgard Lindhoff-Last



Influence of rivaroxaban on the prothrombin time (measured in seconds) for plasma samples of patients undergoing major orthopaedic surgery receiving 10 mg of rivaroxaban daily.

A: before surgery

B: before rivaroxaban at day 4–5 postoperatively,

C: 2 h after rivaroxaban intake,

D: 12 h after rivaroxaban intake. ** p< 0.001.

Journal of Thrombosis and Haemostasis, **10**: 1433–1436 **2012** DOI: 10.1111/j.1538-7836.2012.04784.x

OFFICIAL COMMUNICATION OF THE SSC

Report of the Subcommittee of Control of Anticoagulation on the determination of the anticoagulant effects of rivaroxaban

J. HARENBERG,* S. MARX,* C. WEISS,† R. KRÄMER,‡ M. SAMAMA,§ and S. SCHULMAN¶, ON BEHALF OF THE WORKING PARTY: METHODS TO DETERMINE RIVAROXABAN OF THE SUBCOMMITTEE ON CONTROL OF ANTICOAGULATION OF THE ISTH

STA Neoplastin Plus is the most precise method for determination of the anticoagulant rivaroxaban in human plasma.

Other thromboplastin reagents remain to be investigated.

Some chromogenic assays precisely determined rivaroxaban in plasma.

Journal of Thrombosis and Haemostasis, **10**: 1433–1436 **2012** DOI: 10.1111/j.1538-7836.2012.04784.x

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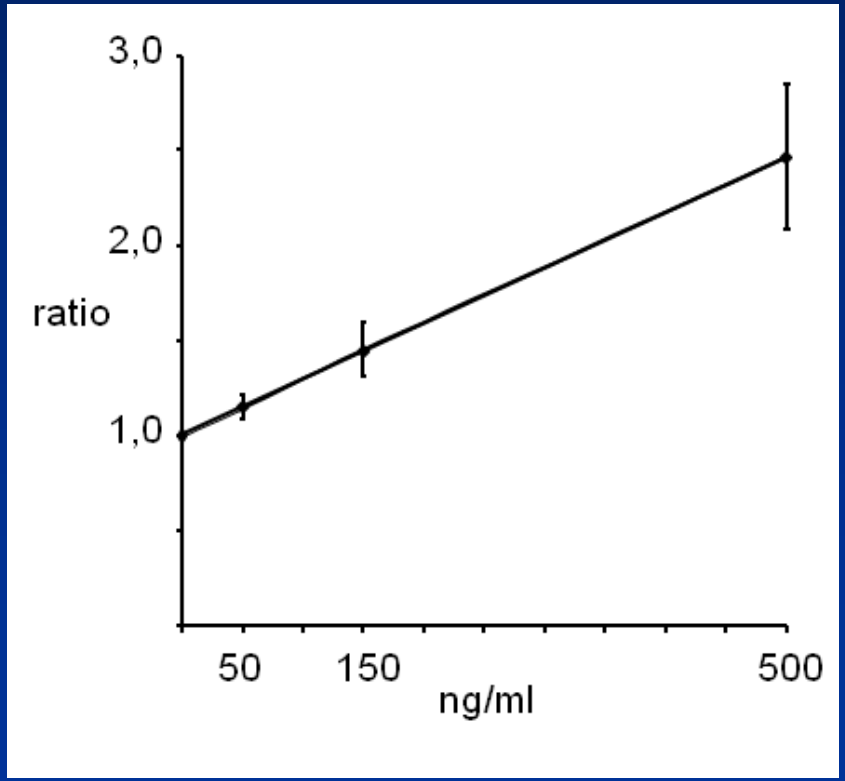
Relationship between PT-ratio using Neoplastin Plus and rivaroxaban levels



Anticoagulant Monitoring

- Bleeding
- Before surgery or invasive procedure
- Overdose
- Concomitant drugs that may have affected exposure to the NOAC
- Extremes of body weight
- Deteriorating renal function
- Assessment of compliance

What to do in case of co-administration of antiplatelet agents

- No contraindications, but prefer low doses (i.e. ASA ≤100 mg/day or clopidogrel 75 mg)
- Keep duration of combined treatment as short as possible
- No data on combined treatment of rivaroxaban and prasugrel or ticagrelor
- Very little experience with triple therapy, consider lower dose of rivaroxaban (15 mg/day)

Management of pts treated with R in case of planned surgery/procedures

Normal renal function and standard bleeding risk =
R stopped 24 hours before

Moderate renal impairment (CrCl 30-49 ml/min) and high bleeding risk =
R stopped 48 hours before and PT checked

if PT is prolonged postpone the procedure

Re-start R the day of procedure (after ≥ 12 hours) with a lower dose (R 15 mg/day or 10 mg/day)

If oral therapy is impossible in the post-surgery period =
LMWH first, and R after

Management of pts treated with R in case of emergency procedures/surgery

Procedures at low bleeding risk =

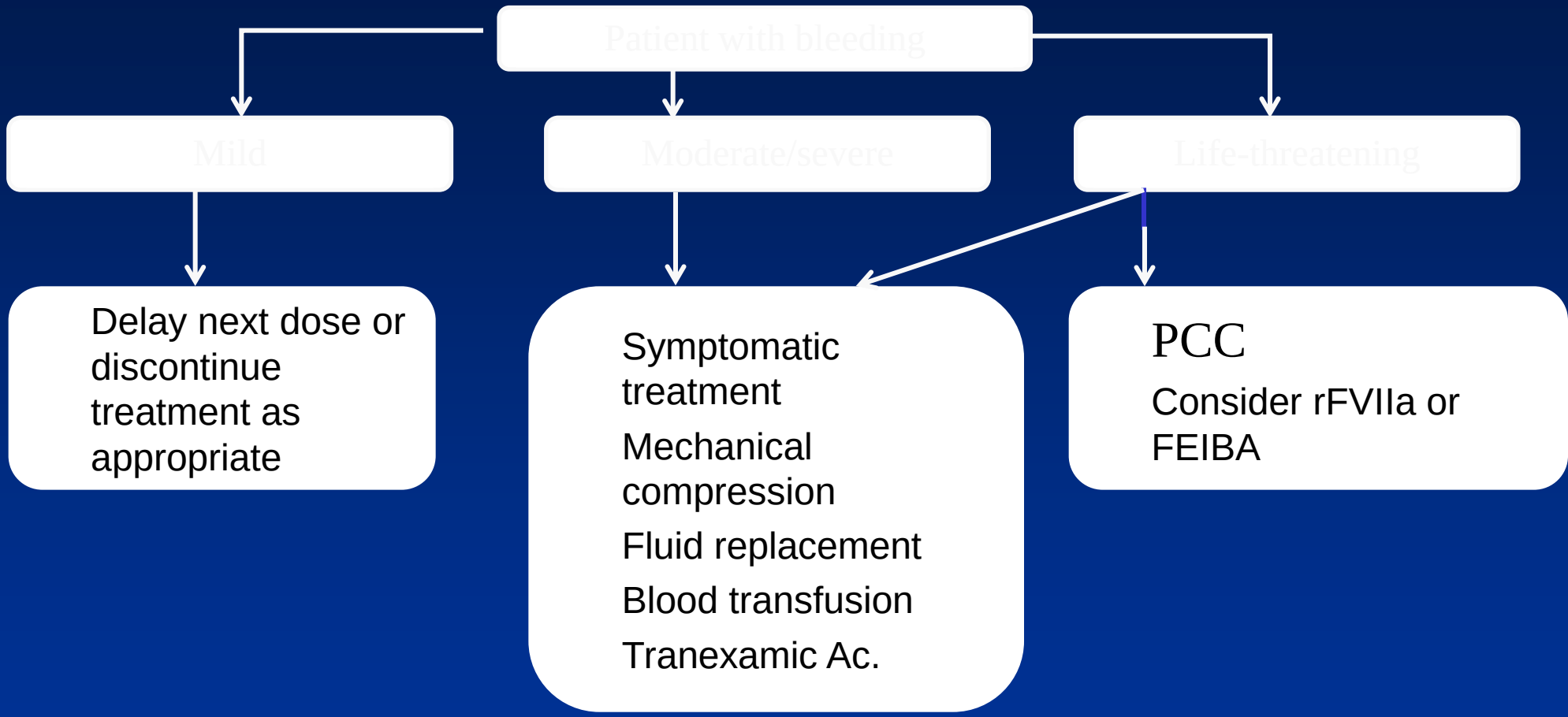
R administration is continued

In other cases =

useful PT test and renal function tests in emergency;

interrupt R and consider prothrombin complex concentrate

Algorithm for bleeding management



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

What to do in case of severe bleeding-1

- adequate venous line, complete coagulation and routine blood tests (including CrCl)
- general resuscitation procedures (if necessary)
- compressive or invasive haemostatic procedures (if possible)
- clinical history of patient and information on treatment (dose, last administration, etc.)
- ensure that treatment has been stopped

What to do in case of severe bleeding-2

Restore normal coagulation levels through:

- Intravenous (i.v.) administration of PCC (50 Ul/kg)
- Tranexamic Ac., 10-30 mg/kg i.v., repeated every 6-8 hours
- Transfusion therapy = FFP and RCB concentrates; consider cryoprecipitate
- rFVIIa (Novo-Seven), at recommended dose of 90 μg/kg,
- Activated PCC (FEIBA, Baxter), suggested dose of 30 U.F./kg,
- Desmopressin (DDAVP), at a dose of 0.3 μg/kg