National Prevention Project
Pre-ipertensione, pre-diabete, macrosimulazione
Perugia, 27 settembre 2015

Nuovi anticoagulanti orali e funzione renale

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VALUTAZIONE PRE-TERAPIA

PRE-

1. Valutazione clinica
   - Compliance
   - Farmaci
   - Eventi avversi
2. Esami ematochimici
   - Funzione renale
   - Funzione epatica
3. Ecografia
   - Eco cuore
   - Eco venoso

Compliance

Drugs don't work in patients who don't take them.

C. Everett Koop, M.D.

N Engl J Med 2005;353:487-97.

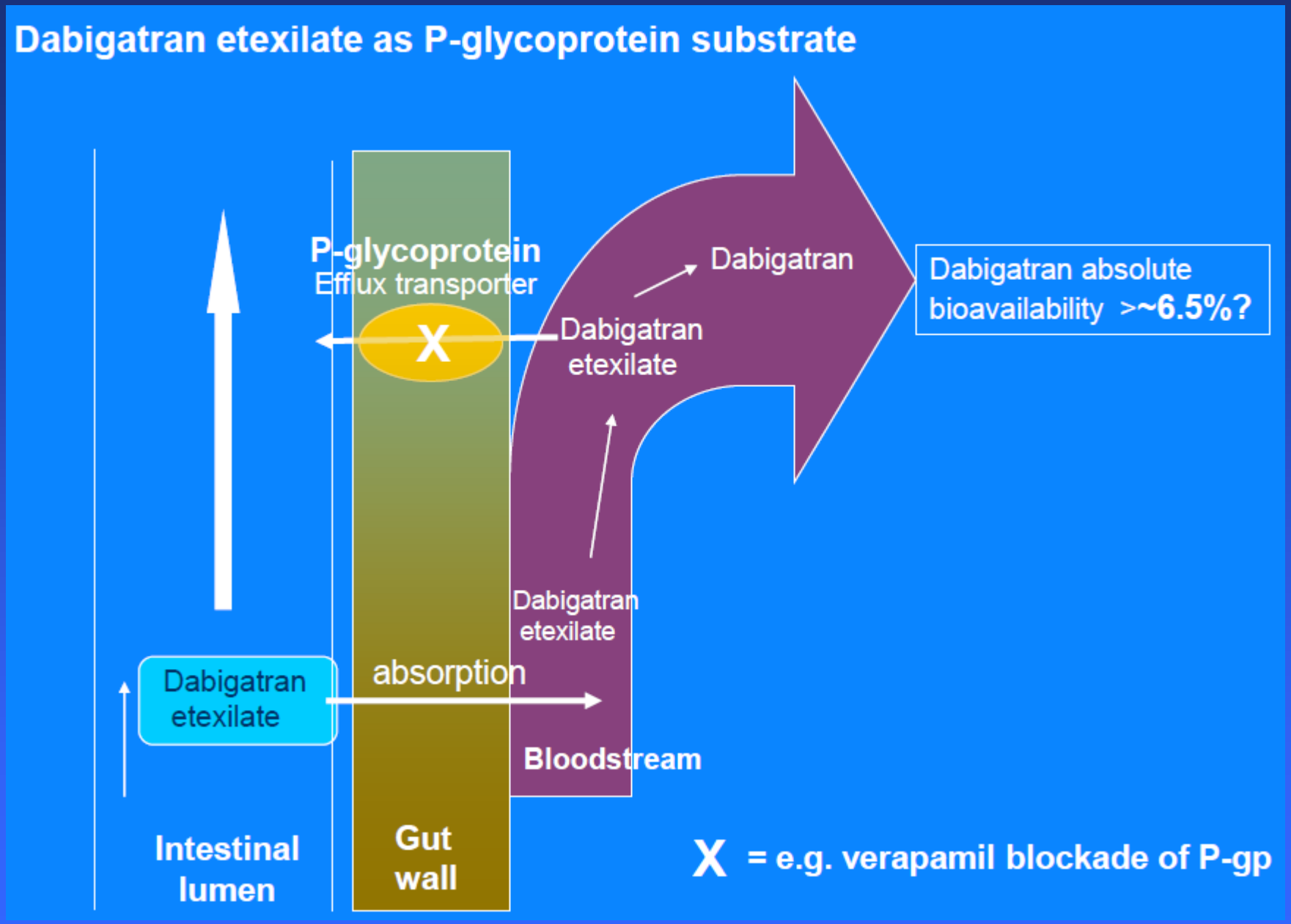
Dabigatran etexilate as P-glycoprotein substrate
P-glycoprotein
Efflux transporter
X
Dabigatran
Dabigatran etexilate
Dabigatran absolute bioavailability >~6.5%?
Dabigatran etexilate
absorption
Dabigatran etexilate
Bloodstream
Intestinal lumen
Gut wall
X = e.g. verapamil blockade of P-gp

Table 5 Effect on NOAC plasma levels ('area under the curve, AUC') from drug–drug interactions and clinical factors, and recommendations towards NOAC dosing

	Via	Dabigatran	Apixaban	Edoxaban[a]	Rivaroxaban
Atorvastatin	P-gp competition and CYP3A4 inhibition	+18%[29]	No data yet	No effect[30]	No effect[27,31]
Digoxin	P-gp competition	No effect[32]	No data yet	No effect[30]	No effect[27,33]
Verapamil	P-gp competition (and weak CYP3A4 inhibition)	+12–180%[24] (reduce dose and take simultaneously)	No data yet	+53% (SR)[30] (reduce dose by 50%)[a]	Minor effect (use with caution if CrCl 15–50 ml/min)
Diltiazem	P-gp competition and weak CYP3A4 inhibition	No effect[24]	+40%[SmPC]	No data yet	Minor effect (use with caution if CrCl 15–50 ml/min)
Quinidine	P-gp competition	+50%	No data yet	+80%[30] (reduce dose by 50%)[b]	+50%
Amiodarone	P-gp competition	+12–60%[24]	No data yet	No effect[30]	Minor effect (use with caution if CrCl 15–50 ml/min)
Dronedarone	P-gp and CYP3A4 inhibitor	+70–100% (US: 2 × 75 mg)	No data yet	+85% (reduce dose by 50%)[a]	No data yet
Ketoconazole; itraconazole; voriconazole; posaconazole	P-gp and BCRP competition; CYP3A4 inhibition	+140–150% (US: 2 × 75 mg)	+100%[SmPC]	No data yet	Up to +160%[27]
Fluconazole	Moderate CYP3A4 inhibition	No data yet	No data yet	No data yet	+42% (if systemically administered)[27]
Cyclosporin; tacrolimus	P-gp competition	No data yet	No data yet	No data yet	+50%
Clarithromycin; erythromycin	P-gp competition and CYP3A4 inhibition	+15–20%	No data yet	No data yet	+30–54%[26,27]
HIV protease inhibitors (e.g. ritonavir)	P-gp and BCRP competition or inducer; CYP3A4 inhibition	No data yet	Strong increase[SmPC]	No data yet	Up to +153%[27]
Rifampicin; St John's wort; carbamazepine; phenytoin; phenobarbital	P-gp/ BCRP and CYP3A4/CYP2J2 inducers	−66%[34]	−54%[SmPC]	−35%	Up to −50%
Antacids (H2B; PPI; Al-Mg-hydroxide)	GI absorption	−12–30%[22–24]	No data yet	No effect	No effect[21,25]
Other factors					
Age ≥80 years	Increased plasma level	No data yet			
Age ≥75 years	Increased plasma level	No data yet			
Weight ≤60 kg	Increased plasma level	See Table 7			
Renal function	Increased plasma level				
Other increased bleeding risk		Pharmacodynamic interactions (antiplatelet drugs; NSAID; systemic steroid therapy; other anticoagulants); history or active GI bleeding; recent surgery on critical organ (brain; eye); thrombocytopenia (e.g. chemotherapy); HAS-BLED ≥3			

Farmaci

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Europace (2013) 15, 625–651
doi:10.1093/europace/eut083

Table 12 Recommendations concerning new onset AF in patients with a recent (<1 year) ACS

4. If a NOAC would be indicated, a FXa inhibitor might be preferred in view of the small but insignificant increase in the risk of myocardial infarction with dabigatran, but this needs to be weighed against the overall perceived clinical effect (which was not impacted for dabigatran)
5. If dabigatran would be indicated, a lower dose (110 mg bid) might be preferred, in combination with low-dose aspirin or with clopidogrel

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Europace (2013) 15, 625–651
doi:10.1093/europace/eut083

Insufficienza epatica

Apixaban

Child-Pugh C: controindicato

Child-Pugh A e B: da usare con cautela (senza aggiustamento dose)

Rivaroxaban

Child-Pugh B e C: controindicato

Dabigatran

Insufficienza epatica o malattia epatica che possa avere un qualsiasi impatto sulla sopravvivenza: controindicato

AST/ALT > 2 x ULN sono stati esclusi nello studio ROCKET-AF, ARISTOTELE e RELY-AF

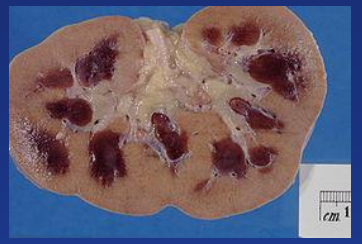
Bleeding Risk with Dabigatran in the Frail Elderly

TO THE EDITOR: Since July 1, 2011, the thrombin inhibitor dabigatran has been available in New Zealand for stroke prevention in patients with atrial fibrillation. There are no restrictions on prescribing, and access is free to patients through government funding. Approximately 7000 patients started treatment in the first 2 months.

Concerns from hematologists led to an audit of bleeding events that was initiated in collaboration with the Haematology Society of Australia

Table 1. Details of Episodes of Bleeding in 44 Patients Taking Dabigatran.*

Patient No.	Age	Sex	Weight	Daily Dose†	Site of Bleeding	Degree of Renal Impairment‡	Required Blood Products§
	yr		*kg*	*mg*			
1	65	M	129	300	Mucosal	Severe	No
2¶	71	M	NA	300	Hematuria	Moderate	No
3‖	77	M	60	300	Rectal	Moderate	Yes
4	78	F	NA	220	Rectal	Moderate	No
5‖	40	M	94	220	Rectal	Mild	Yes
6	65	F	79	300	Postoperative	Mild	Yes
7	71	M	75	300	Hematuria	Mild	No
8	74	M	100	220	Hematuria	Mild	No
9	75	F	NA	220	Rectal	Mild	Yes



INSUFFICIENZA RENALE

Stage	Description	GFR (mL/min/1.73 m^2)
I	Kidney damage with normal or increased GFR	> 90
II	Mild	60-89
III	Moderate	30-59
IV	Severe	15-29
V	End-stage and/or renal failure	< 15

HAS-BLED

(FA non valvolare)

H	**hypertension**
A	**abnormal renal/liver function**
S	**stroke**
B	**bleeding history predisposition**
L	**labile INR**
E	**elderly**
D	**drugs/alcohol**

Editorial

"R" for "Renal" and for "Risk"

Refining Risk Stratification for Stroke in Atrial Fibrillation

Impaired renal function contributes to increased risk of stroke via procoagulant and inflammatory pathways and changes in arterial compliance/stiffness.

Camm J et al. Circulation 2013; 127:169-71

Stroke and Bleeding in Atrial Fibrillation with Chronic Kidney Disease

Danish national registries

All patients discharged with NVAF between 1997 and 2008.

No Renal Disease (N=127,884)	Non–End-Stage Chronic Kidney Disease (N=3587)	Disease Requiring Renal-Replacement Therapy (N=901)

Stroke or systemic thromboembolism and bleeding associated with non–end-stage CKD and with end-stage chronic kidney disease

Olesen JB et al. NEJM 2012; 367:625-35

Stroke and Bleeding in Atrial Fibrillation with Chronic Kidney Disease

Bleeding

Event	No. of Person-yr	No. of Events	Event Rate per 100 Person-yr (95% CI)
Bleeding			
No renal disease	457,605	16,195	3.54 (3.48–3.59)
Non–end-stage CKD	12,515	1,097	8.77 (8.26–9.30)
Disease requiring renal-replacement therapy	2,734	243	8.89 (7.84–10.08)

Olesen JB et al. NEJM 2012; 367:625-35

Stroke and Bleeding in Atrial Fibrillation with Chronic Kidney Disease

Stroke or thromboembolism

Event	No. of Person-yr	No. of Events	Event Rate per 100 Person-yr (95% CI)
Stroke or thromboembolism			
No renal disease	461,734	16,648	3.61 (3.55–3.66)
Non–end-stage CKD	13,078	842	6.44 (6.02–6.89)
Disease requiring renal-replacement therapy	2,922	164	5.61 (4.82–6.54)

Olesen JB et al. NEJM 2012; 367:625-35

Predictor of **Stroke or thromboembolism** in **atrial fibrillation**

CHADS2 Risk	Score
CHF	1
Hypertension	1
Age > 75	1
Diabetes	1
Stroke or TIA	2

GFR < 60 ml/min 2

CHA2DS2-VASc Risk	Score
CHF or LVEF ≤ 40%	1
Hypertension	1
Age ≥ 75	2
Diabetes	1
Stroke/TIA/ Thromboembolism	2
Vascular Disease	1
Age 65 - 74	1
Female	1

Renal Dysfunction as a Predictor of Stroke and Systemic Embolism in Patients With Nonvalvular Atrial Fibrillation: Validation of the R2CHADS2 Index in the ROCKET AF (Rivaroxaban Once-daily, oral, direct factor Xa inhibition Compared with vitamin K antagonism for prevention of stroke and Embolism Trial in Atrial Fibrillation) and ATRIA (AnTicoagulation and Risk factors In Atrial fibrillation) Study Cohorts

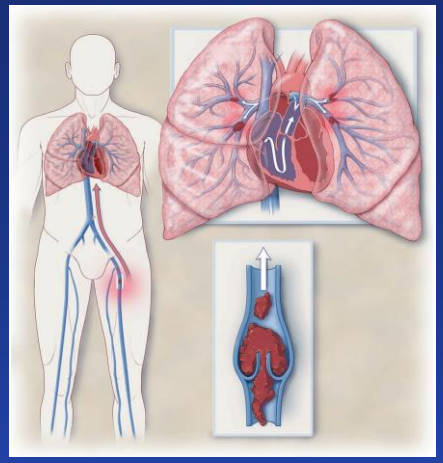
R_2CHADS_2 Score	Overall (All Patients)	
	n	Rate at 3 y†
0	6826	0.425
1	8317	1.274
2	6361	2.201
3	5331	2.288
4	4346	3.313
5	2615	4.857
6	1002	4.992
7	324	6.167
8	63	7.913

R_2CHADS_2 score in ATRIA Study Cohort

Piccini JP et al. Circulation 2013; 127:224-232

QUALE FARMACO per l'IRC?

Utilizzo dei farmaci



Prevenzione secondaria/primaria FA e TEV

Profilassi del TEV

Terapia in acuto TEV

Terapia acuto SCA

FARMACI PARENTERALI

Eparina non frazionata

Eparina sodica e calcica

Eparina a basso peso molecolare

Enoxaparina, nadroparina, dalteparina

Pentasaccaride

Fondaparinux

Eparina non frazionata

VANTAGGI

aPTT da monitorare

SVANTAGGI

- **aPTT da monitorare**
- **In acuto: terapia e.v. (necessità assoluta di ricovero)**
- **In cronico: iniezioni s.c. multiple**
- **HIT più frequente**

Eparina a basso peso molecolare

VANTAGGI

Dosi ridotte/intermedie

SVANTAGGI

- **Attività anti-Xa non facile da dosare (4 ore dalla somministrazione)**
- **Si accumula nell'IR con Cl.Cr < 30 mL/min**

EBPM ed IR (ClCr < 30 mL/min): emorragie maggiori

ClCr < 30 mL/min	**5.0%**
ClCr > 30 mL/min	**2.4%**

OR 2.25 (CI 1.19-4.27)

Lim et al Annals Intern Med 2006

EBPM ed IR (ClCr < 30 mL/min): emorragie maggiori

- ***Enoxaparina a dosi terapeutiche standard*:**

ClCr < 30 mL/min	**8.3%**
ClCr > 30 mL/min	**2.4%**
OR	**3.88 (CI 1.78-8.45)**

- ***Enoxaparina a dosi terapeutiche aggiustate*:**

ClCr < 30 mL/min	**0.9%**
ClCr > 30 mL/min	**1.9%**
OR	**0.58 (CI 0.09-3.78)**

Lim et al Annals Intern Med 2006

ACCP 2012

If LMWH is chosen for patients with an eClCr< 30 mL/min,

1.anti-Xa monitoring and/or

2.dose reduction should be considered to ensure that there is no accumulation.

In the case of enoxaparin, for patients who have acute coronary syndromes or VTE is 50% of the usual dose

No specific recommendations have been made for other LMWH preparations.

Garcia et al. Chest 2012

If monitoring is required, the anti-Xa level is the recommended test

Table 6—*LMWH Target Ranges for the Treatment of VTE*

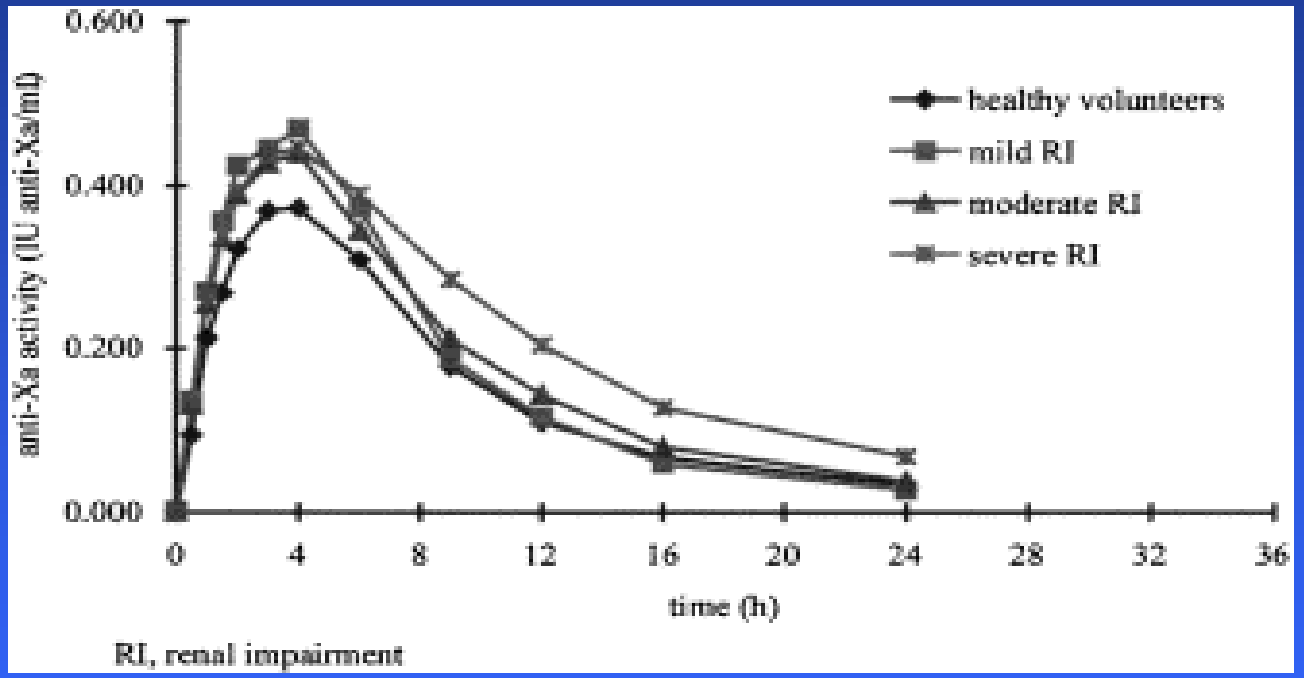
LMWH and Frequency of Administration	Target Range[a] (Anti-Xa units/mL)
Twice daily enoxaparin	0.6-1.0
Twice daily nadroparin	0.6-1.0
Once daily dalteparin	1.05
Once daily enoxaparin	>1.0
Once daily nadroparin	1.3
Once daily tinzaparin	0.85

See Table 4 legend for expansion of abbreviation.

[a]Measured 4 h after LMWH administration.

Garcia et al. Chest 2012

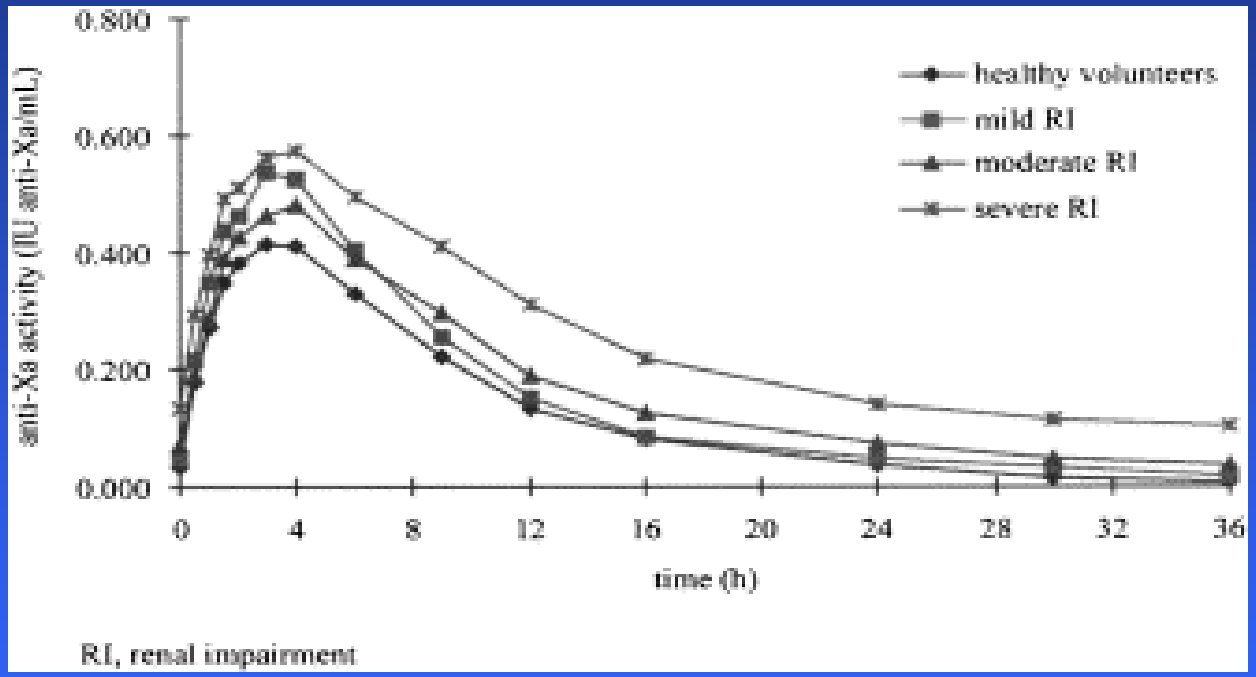
Dosi profilattiche di enoxaparina in pazienti con insufficienza renale



Livelli medi plasmatici di attività anti Xa, giorno 1

Sanderkink et al Thromb Res 2002

Dosi profilattiche di enoxaparina in pazienti con insufficienza renale



Livelli medi plasmatici di attività anti Xa, giorno 4

Sanderkink et al Thromb Res 2002

Bioaccumulation of dalteparin at a prophylactic dose in patients with impaired renal function

- 42 patients from medical and surgical wards
- Dalteparin administered at prophylactic doses
- Peak anti-Xa at 4±1 hours from day 1

- No bioaccumulation >30% detected up to day 10 in patients with severe renal insufficiency

Schmid P et al JTH 2009

ACCP 2012

- When given in prophylactic doses, LMWH has **not** been shown to **increase the risk of bleeding** complications, irrespective of the degree of impairment of renal function.

- For patients with a **CrCl<30 mL/min** who require pharmacologic VTE prophylaxis, manufacturer of **enoxaparin** recommends that **30 mg once daily be used**

- For other LMWHs, dosing recommendations cannot be made in the setting of renal insufficiency.

Garcia et al. Chest 2012

Fondaparinux

VANTAGGI

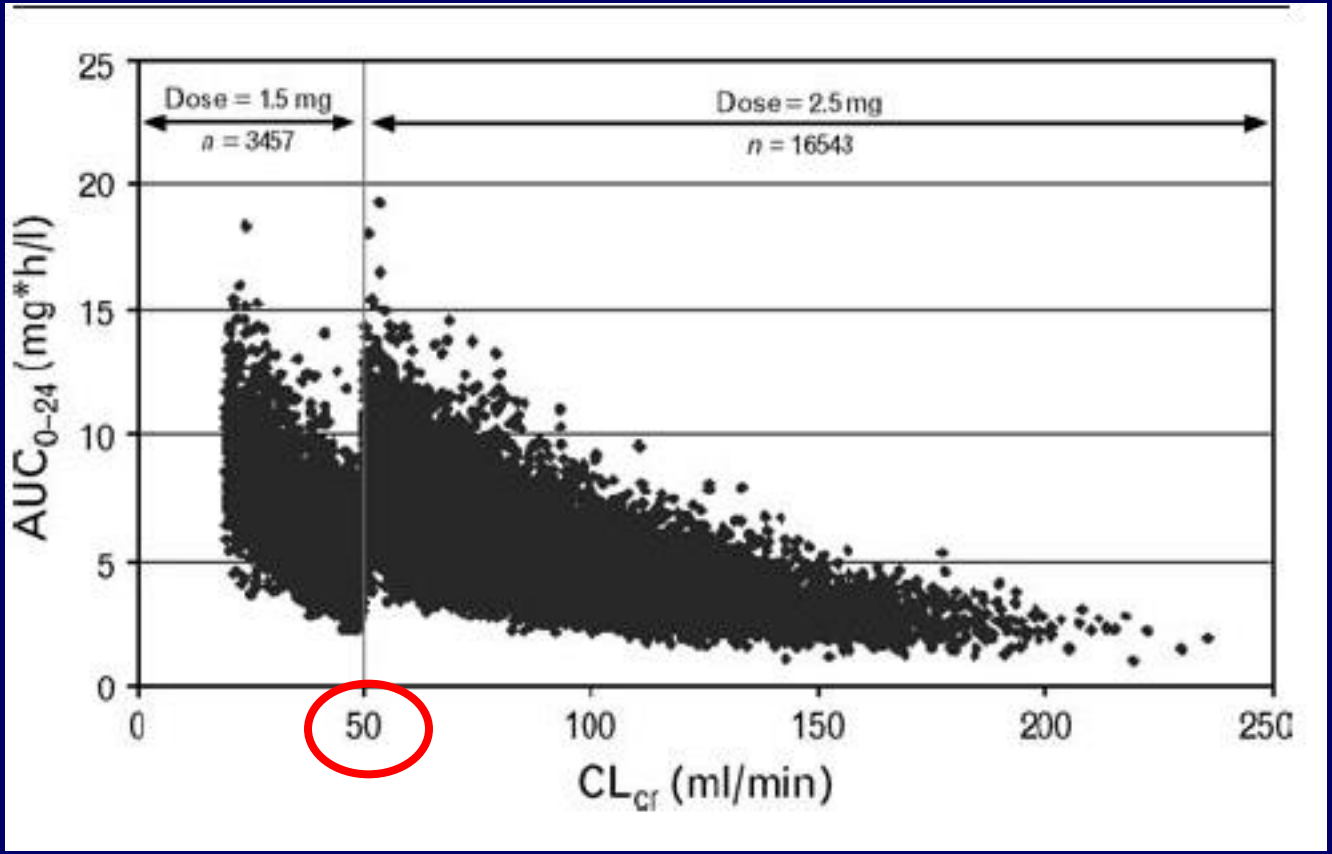
?

SVANTAGGI

Emivita più lunga (17-20 ore)

Controindicato con Cl.Cr < 30 ml/min e cautela fra 30 e 50 ml/min (come ridurre la dose ??)

Pharmacokinetic and clinical data supporting the use of fondaparinux 1.5 mg once daily in the prevention of venous thromboembolism in renally impaired patients



Turpie AG et al, Blood Coag Fibrinol 2009

FARMACI ORALI

Inibitori diretti del fattore Xa

Apixaban, rivaroxaban

Inibitori diretti della trombina

Dabigatran

Antagonisti della Vitamina K

Warfarin, acenocumarolo

Antagonisti della vitamina K

VANTAGGI

INR da monitorare

SVANTAGGI

No terapia acuto

No dosaggi intermedi/profilattici

Antagonisti della vitamina K

INS. EPATICA

Alterazione dell'INR

-Difficoltà alla gestione del warfarin

-Maggiore sensibilità al warfarin

INS. RENALE

No problemi

(ad escrezione renale, ma INR per monitorare)

NOAc

(new oral anticoagulants)

DOAc

(direct oral anticoagulants)

Indicazioni approvate
(fascia A, settembre 2015, in Italia)

1. **Profilassi** del **TEV** in chirurgia protesica di **anca** e **ginocchio**

(apixaban, dabigataran, rivaroxaban)

2. Prevenzione del cardioembolismo in pazienti con **FA non-valvolare**

(apixaban, rivaroxaban, dabigatran)

3. **Trattamento** in acuto e **prevenzione** della **TVP** ed **EP** (apixaban, rivaroxaban, dabigatran)

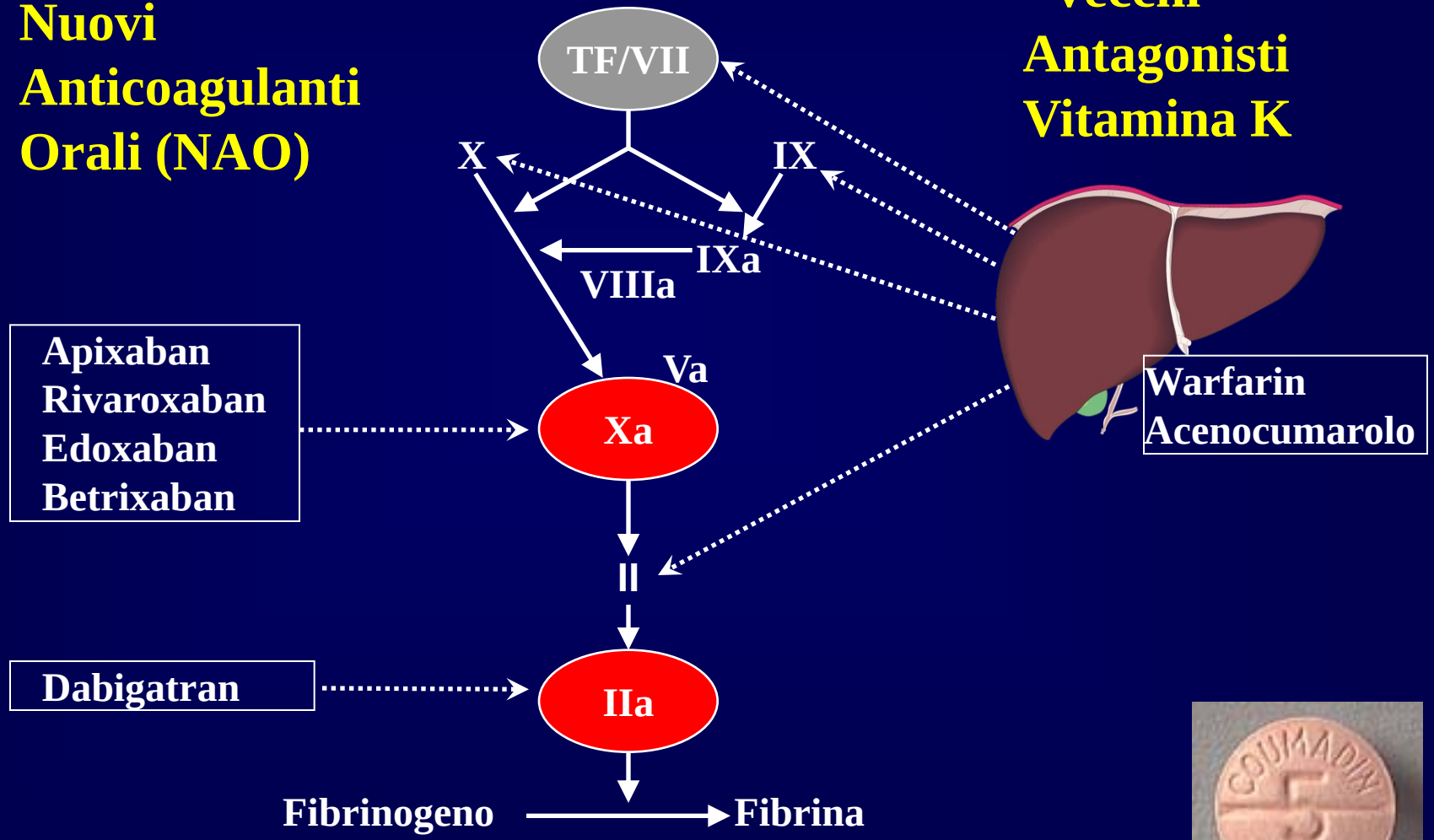
Confronto tra i nuovi farmaci anticoagulanti orali: Dabigatran, Rivaroxaban e Apixaban

	Dabigatran	Rivaroxaban	Apixaban
Target	IIa (thrombin)	Xa	Xa
Profarmaco	si	no	no
Cmax (ore)	0,5-2	2-4	1-3
Biodisponibilità	6,5%	80-100%	66%
Metabolismo (Cit. P450)	No	32%	15%
Emivita (ore)	12-14	7- 13	8-13
Profarmaco	SI	NO	NO
Eliminazione renale	80%	33%	25%
Interazione farmacologica	Rifampicina, chinidina, amiodarone, potenti inibitori P-gp	CYP3A4 e P-gp	CYP3A4 e P-gp
Monitoraggio (routine)	No	No	No

Nuovi e "Vecchi"

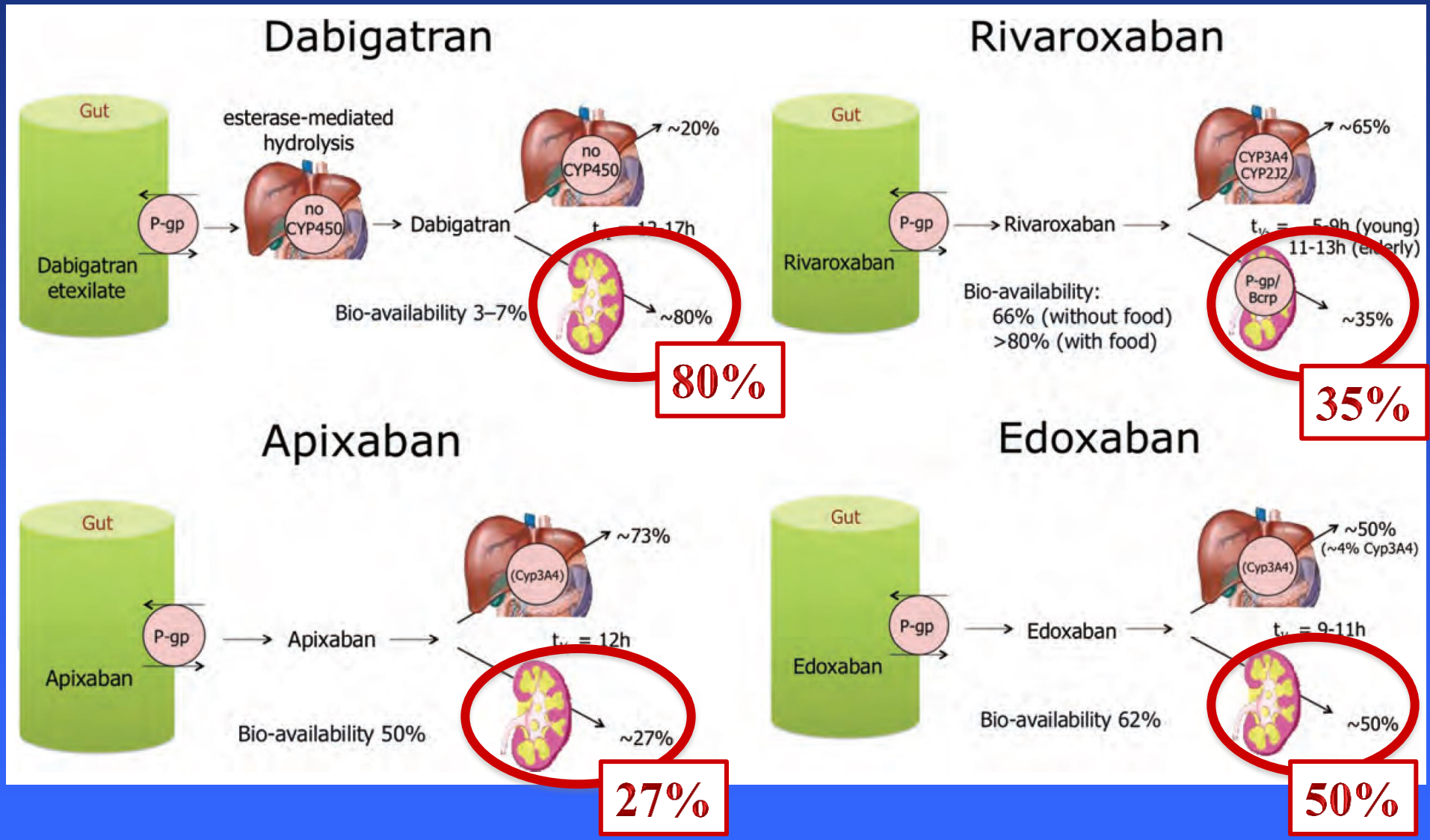
Nuovi Anticoagulanti Orali (NAO)

"Vecchi" Antagonisti Vitamina K



Adapted from Weitz & Bates, *J Thromb Haemost* 2007

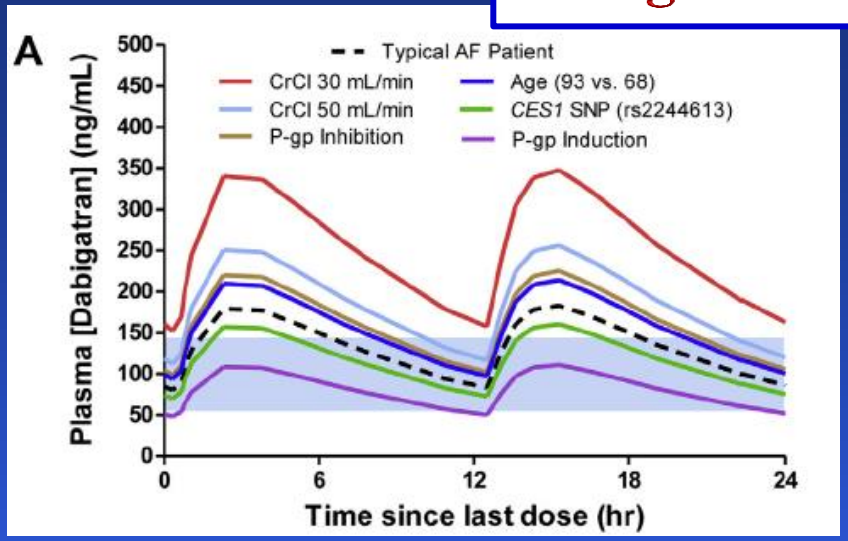
European Heart Rhythm Association Practical Guide on the use of new oral anticoagulants in patients with non-valvular atrial fibrillation



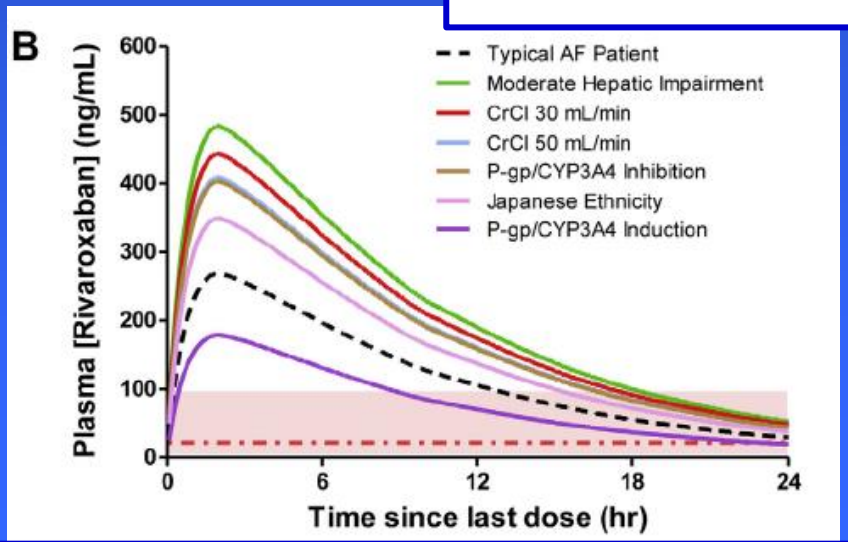
Heidbuchel H. Europace 2013; 15: 625-651

Importance of Pharmacokinetic Profile and Variability as Determinants of Dose and Response to Dabigatran, Rivaroxaban, and Apixaban

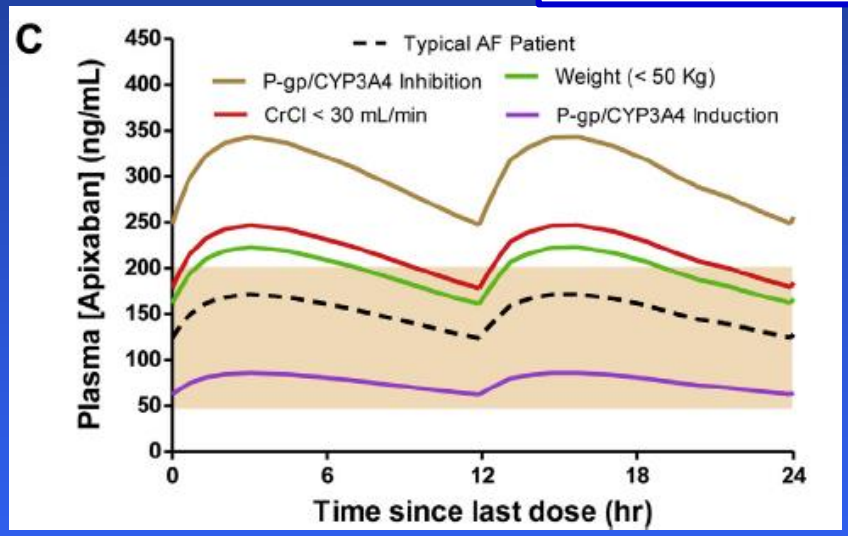
Dabigatran



Rivaroxaban



Apixaban



Gong IY et al. Can J Cardiol 2013; 29:S24-33

CHE FARE ?

1. Ridurre la dose per FAnv

Rivaroxaban

Scheda tecnica: non riduzione fino a 15 ml/min

Studio EINSTEIN: 15 pz con eGFR < 30 ml/min
235 pz con eGFR 30 << 50 ml/min

LG ESC 2014: controindicato se eGFR < 30 ml/min

Insufficienza renale

New oral anticoagulants (rivaroxaban, apixaban, dabigatran, edoxaban) are not recommended in patients with severe renal impairment.[f]	III	A

ESC Guidelines. Eur Heart J 2014;Sept

Apixaban

FA

Cl. Creat. 15-29 ml/min: ridurre dose a 2.5 mg x 2

Cl. Creat. 30-50 ml/min: ridurre se almeno 2 fra

> 80 aa, < 60 Kg, creatinina > 1.5 mg/dl

(sotto i 25 ml/min e/o crea> 2.5 mg/dL, non inclusi nello studio ARISTOTLE)

Profilassi TEV: Non è necessario alcun aggiustamento della dose in pazienti con insufficienza renale lieve o moderata

Terapia TEV: 10 x 2 mg per 1 settimana, poi 5 mg x 2. 2,5 mg x 2 per il lungo termine

Rivaroxaban

Se clearence della creatinina 15-49 ml/min:

FA: ridurre dose a 15 mg

(sotto i 30 ml/min, non inclusi nello studio ROCKET-AF)

Profilassi TEV: Non è necessario alcun aggiustamento (10 mg) fino a 30 ml/min

Terapia TEV: 15 mg x 2 per 3 settimane (dose piena), poi valutare se proseguire con 20 mg/die o 15 mg/die a seconda del rischio emorragico

Dabigatran

Se clearence della creatinina

30-50 ml/min:

FA: valutare se passare a 110 mg x 2

Profilassi TEV: 150 mg x 1 (dose ridotta)

(first dose 75 mg)

2. Sospendere prima per CH

Table 9 Last intake of drug before elective surgical intervention

	Dabigatran		Apixaban		Edoxaban[a]		Rivaroxaban	
	No important bleeding risk and/or adequate local haemostasis possible: perform at trough level (i.e. ≥12 h or 24 h after last intake)							
	Low risk	High risk	Low risk	High risk	Low risk	High risk	Low risk	High risk
CrCl ≥80 ml/min	≥24 h	≥48 h	≥24 h	≥48 h	No data	No data	≥24 h	≥48 h
CrCl 50–80 ml/min	**≥36 h**	**≥72 h**	≥24 h	≥48 h	No data	No data	≥24 h	≥48 h
CrCl 30–50 ml/min[b]	**≥48 h**	**≥96 h**	≥24 h	≥48 h	No data	No data	≥24 h	≥48 h
CrCl 15–30 ml/min[b]	Not indicated	Not indicated	**≥36 h**	**≥48 h**	No data	No data	**≥36 h**	**≥48 h**
CrCl <15 ml/min	No official indication for use							

Bold values deviate from the common stopping rule of ≥24 h low risk, ≥48 h high risk.

[a]No EMA approval yet. Needs update after finalisation of SmPC.

[b]Many of these patients may be on the lower dose of dabigatran (i.e. 110 mg BID) or apixaban (i.e. 2.5 mg BID), or have to be on the lower dose of rivaroxaban (15 mg QD).

Low risk = surgery with low risk of bleeding; high risk = surgery with high risk of bleeding. See also Table 10.

CrCl, creatinine clearance.

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Europace (2013) 15, 625–651
doi:10.1093/europace/eut083

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Perioperative Bridging Anticoagulation in Patients with Atrial Fibrillation

James D. Douketis, M.D., Alex C. Spyropoulos, M.D., Scott Kaatz, D.O., Richard C. Becker, M.D., Joseph A. Caprini, M.D., Andrew S. Dunn, M.D., David A. Garcia, M.D., Alan Jacobson, M.D., Amir K. Jaffer, M.D., M.B.A., David F. Kong, M.D., Sam Schulman, M.D., Ph.D., Alexander G.G. Turpie, M.B., Vic Hasselblad, Ph.D., and Thomas L. Ortel, M.D., Ph.D., for the BRIDGE Investigators*

ABSTRACT

BACKGROUND

It is uncertain whether bridging anticoagulation is necessary for patients with atrial fibrillation who need an interruption in warfarin treatment for an elective operation or other elective invasive procedure. We hypothesized that forgoing

From St. Jo
(J.D.D.) and
(J.D.D.) an
Center (S.S

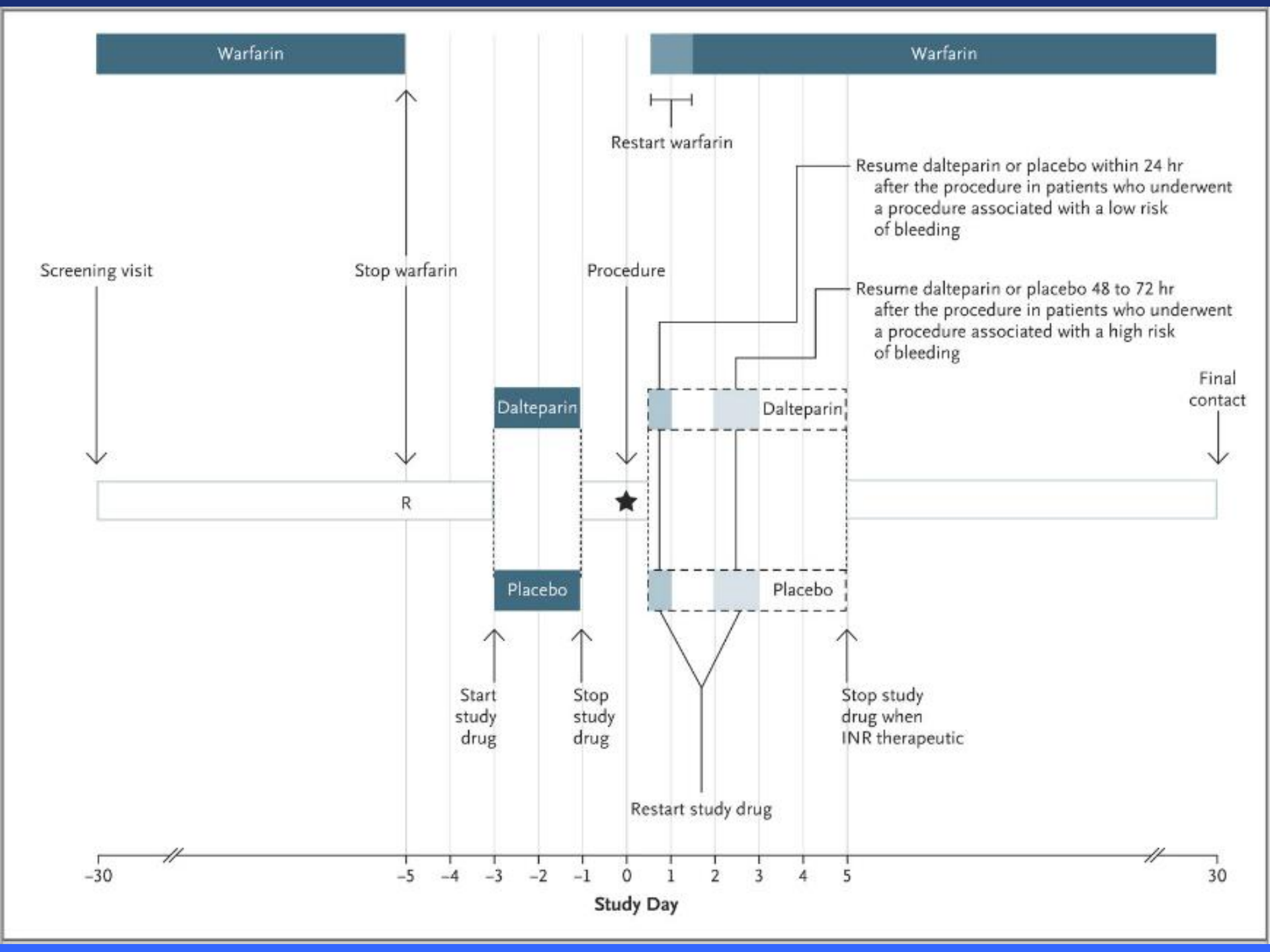

Warfarin
Warfarin
Restart warfarin
Resume dalteparin or placebo within 24 hr after the procedure in patients who underwent a procedure associated with a low risk of bleeding
Resume dalteparin or placebo 48 to 72 hr after the procedure in patients who underwent a procedure associated with a high risk of bleeding
Screening visit
Stop warfarin
Procedure
Final contact
Dalteparin
Dalteparin
R
Placebo
Placebo
Start study drug
Stop study drug
Stop study drug when INR therapeutic
Restart study drug
−30
−5
−4
−3
−2
−1
0
1
2
3
4
5
30
Study Day

Table 3. Study Outcomes.

Outcome	No Bridging (N=918)	Bridging (N=895)	P Value
	number of patients (percent)		
Primary			
Arterial thromboembolism	4 (0.4)	3 (0.3)	0.01*, 0.73†
Stroke	2 (0.2)	3 (0.3)	
Transient ischemic attack	2 (0.2)	0	
Systemic embolism	0	0	
Major bleeding	12 (1.3)	29 (3.2)	0.005†
Secondary			
Death	5 (0.5)	4 (0.4)	0.88†
Myocardial infarction	7 (0.8)	14 (1.6)	0.10†
Deep-vein thrombosis	0	1 (0.1)	0.25†
Pulmonary embolism	0	1 (0.1)	0.25†
Minor bleeding	110 (12.0)	187 (20.9)	<0.001†

3. Calcolare sempre il filtrato glomerulare

Cockgroft–Gault

$$\frac{(140 - \text{età [anni]}) \times \text{peso [kg]} \; (\times 0{,}85 \text{ se femmina})}{72 \times \text{creatinina sierica [mg/dl]}}$$

4. Vedere il paziente più spesso

POST-

1. Valutazione clinica

   Compliance (educazione !!)

   Farmaci

2. Esami ematochimici

3. Prossimo controllo

EHRA PRACTICAL GUIDE

Table 2 Checklist during follow-up contacts of AF patients on anticoagulation

	Interval	Comments
1. Compliance	Each visit	• Instruct patient to bring remaining medication: note and calculate average adherence • Re-educate on importance of strict intake schedule • Inform about compliance aids (special boxes; smartphone applications; . . .)
2. Thrombo-embolism	Each visit	• Systemic circulation (TIA, stroke, peripheral) • Pulmonary circulation
3. Bleeding	Each visit	• 'Nuisance' bleeding: preventive measures possible? (PPI; haemorrhoidectomy; . . .). Motivate patient to diligently continue anticoagulation • Bleeding with impact on quality-of-life or with risk: prevention possible? Need for revision of anticoagulation indication or dose?
4. Other side effects	Each visit	• Carefully assess relation with NOAC: decide for continuation (and motivate), temporary cessation (with bridging), or change of anticoagulant drug.
	Yearly	• Haemoglobin, renal and liver function
	6 monthly	• Renal function if CrCl 30–60 ml/min, or if on dabigatran and >75 years or fragile
	3 monthly	• If CrCl 15–30 ml/min
	On indication	• If intercurring condition that may impact renal or hepatic function

TIA, transient ischaemic attack; PPI, proton pump inhibitor; CrCl, creatinine clearance (preferably measured by the Cockroft method).

EUROPEAN SOCIETY OF CARDIOLOGY®
Europace (2013) 15, 625–651
doi:10.1093/europace/eut083

SE …

1. Insufficienza renale severa intercorrente

2. Emorragia

3. Intervento chirurgico

1. SE …

Febbre

Infezione

Vomito

Diarrea

Digiuno

Rifiuto di alimentarsi

Anoressia

Bleeding Risk with Dabigatran in the Frail Elderly

TO THE EDITOR: Since July 1, 2011, the thrombin inhibitor dabigatran has been available in New Zealand for stroke prevention in patients with atrial fibrillation. There are no restrictions on prescribing, and access is free to patients through government funding. Approximately 7000 patients started treatment in the first 2 months.

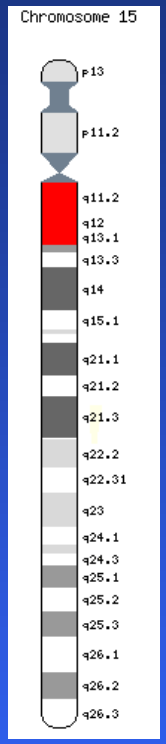
Concerns from hematologists led to an audit of bleeding events that was initiated in collaboration with the Haematology Society of Australia

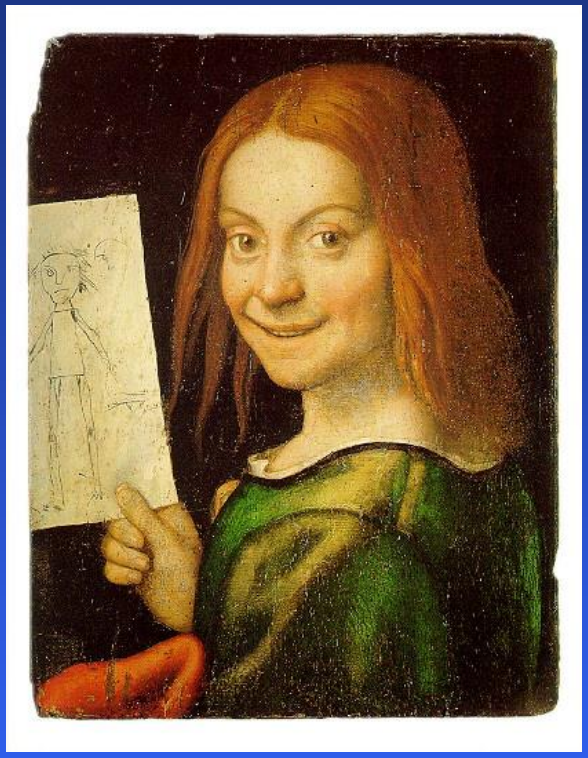
Table 1. Details of Episodes of Bleeding in 44 Patients Taking Dabigatran.*

Patient No.	Age	Sex	Weight	Daily Dose†	Site of Bleeding	Degree of Renal Impairment‡	Required Blood Products§
	yr		*kg*	*mg*			
1	65	M	129	300	Mucosal	Severe	No
2¶	71	M	NA	300	Hematuria	Moderate	No
3‖	77	M	60	300	Rectal	Moderate	Yes
4	78	F	NA	220	Rectal	Moderate	No
5‖	40	M	94	220	Rectal	Mild	Yes
6	65	F	79	300	Postoperative	Mild	Yes
7	71	M	75	300	Hematuria	Mild	No
8	74	M	100	220	Hematuria	Mild	No
9	75	F	NA	220	Rectal	Mild	Yes

CONCLUSIONI

DON'T *'FILL AND FORGET'*





"Boy with a Puppet" or "A child with a drawing" by
Giovanni Francesco Caroto, Castelvecchio Museum, Verona
Italy

The Angelman Syndrome

1965, Verona

”I may not speak, but I have much to say”

The ‘Angel’ Pietro