UNIVERSITÉ DE GENÈVE
FACULTÉ DE MÉDECINE

HUG
Hôpitaux Universitaires de Genève

A propos des nouveaux anticoagulants

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Service d'Angiologie-Hémostase

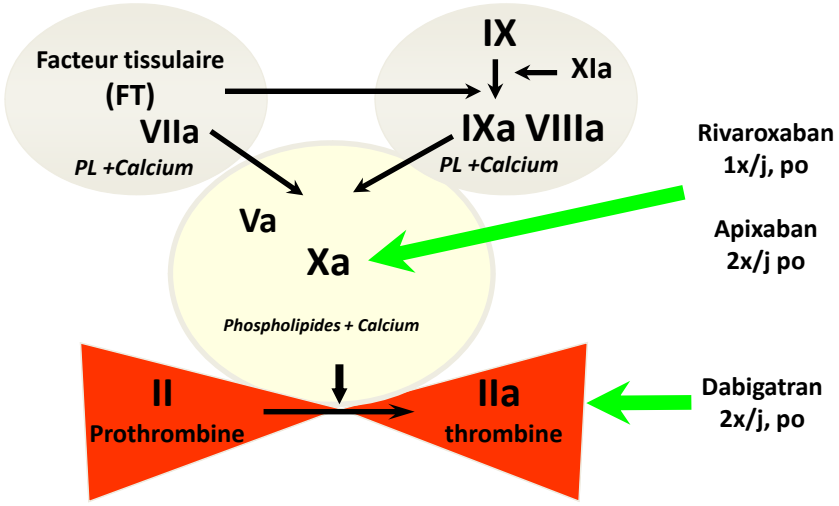
Pneumologie, 5 décembre 2012

Plan

- Nouveaux anticoagulants
- Principales études dans le traitement de la MTEV et la fibrillation atriale
- Questions et réponses (partielles)

Nouveaux anticoagulants

- anticoagulants spécifiques et directs -



Drôles de noms…

- **Rivaroxaban (Xarelto®, Bayer)**

  Xarelto : Xa ReguLation of Thrombosis Orally

- **Apixaban (Eliquis®, BMS/Pfizer)**

  E Liqui S : E pour equilibrium - Liqui pour liquid and S pour Stability

- **Dabigatran (Pradaxa®, Boehringer-I)**

Indication	FDA-EMEA approvals
DVT and PE prophylaxis	Dabigatran
in orthopedic surgery	Rivaroxaban
	Apixaban
AF	Dabigatran FDA 2010, EMEA 2011
	Rivaroxaban FDA 2011, EMEA 2011
DVT treatment	Rivaroxaban EMEA 2011
PE treatment	Rivaroxaban FDA 2012

SwissMedic : rivaroxaban admis comme traitement de la FA de la TVP (5 avril 2012), PE début 2013

Comparison

	Apixaban	Rivaroxaban	Dabigatran
Mechanism of action	direct FXa inhibitor	direct FXa inhibitor	direct FIIa inhibitor
Oral availability	~50 %	80 %	6.5 %
Route of administration	oral	oral	oral
Dosing	2x/day in all indications	1x/day (AF, DVT and PE)	1x/day (DVT prevention) 2x/day (VTE, AF)
Pro-drug	No	No	Yes
Food effect	No	No	No
Renal Clearance	~27 %	33 %	85 %
Mean Half-Life (T1/2)	~12h	7–11 h	14–17 h
Tmax	3 h	2–4 h	0.5–2 h
Drug interactions	CYP 3A4 and P-gp inhibitors CYP 3A4 inducers	CYP 3A4 and P-gp inhibitors CYP 3A4 inducers	P-gp inhibitors P-gp inducers

Eikelboom et al. *Circulation* 2010;121:1523

New OAC: Drug interactions

	Dabigatran	Rivaroxaban, edoxaban, apixaban
P-glycoprotein inhibitors (amiodarone, phenotiazin, carboxylic acid, azole antifungals, verapamil, antimalarial, cyclosporine, thioxanthenes)	Yes	Yes
P-glycoprotein inducers (dexamethasone, rifampicin, St. John's Wort)	Yes	Yes
CYP3A4 inhibitors (phenotiazin, carboxylic acid, azole antifungals, verapamil, erythromycin, telithromycin, nefazodone, antimalarial, cyclosporine, thioxanthenes)	No	Yes
CYP3A4 inducers (carbamazepine, efavirenz, nevirapine, phenytoin, phenobarbitone, rifabutin, rifapentine, rifampicin, St. John's Wort, alcohol, eucalyptol)	No	Yes
NSAIDS (aspirin, naproxen, diclofenac)	Yes	Yes
Antiplatelet agents (clopidogrel)	Yes	Yes

Pengo et al. *Thromb Haemost* 2011; 106: 868

Plan

- Nouveaux anticoagulants
- Les études dans la FA et la MTEV
- Questions et réponses (partielles)

“Old” anticoagulants: heparins

- Administration parentérale
- Elimination rénale
- TIH
- Extraites de la muqueuse d’intestin de porc
  Chine, producteur de >50% des héparines
  contamination par des GAG persulfatés

A worker cleaned pig intestines in a Chinese village. Lining from the intestines is processed into crude heparin

"Old" anticoagulants: VKA

- Narrow therapeutic window
- Variability in dose response
- Numerous interactions with other drugs and diet
- Necessity of lab controls

"Warfarin is the drug we all love to hate"

Soff GA. *ATVB* 2012;32:569

	Venous thromboembolism (VTE) Prevention	VTE treatment	Atrial fibrillation	Acute coronary syndrome
Apixaban	Orthopedic ADVANCE-1 ADVANCE-2 ADVANCE-3 Medicine ADOPT IInd Prevention AMPLIFY-Ext NCT00633893	AMPLIFY	AVERROES ARISTOTLE	(APPRAISE) APPRAISE-2
Dabigatran	Orthopedic RE-NOVATE RE-MODEL RE-MOBILIZE IInd Prevention RE-MEDY RE-SONATE	RE-COVER	RE-LY	RE-DEEM
Rivaroxaban	Orthopedic RECORD I RECORD II RECORD III RECORD IV Medicine MAGELLAN IInd Prevention EINSTEIN-Ext	EINSTEIN-DVT EINSTEIN-PE	ROCKET-AF	ATLAS-TIMI 46 ATLAS-TIMI 51

New OAC and VTE

Dabigatran versus Warfarin in the Treatment of Acute Venous Thromboembolism
Sam Schulman, M.D., Clive Kearon, M.D., Ajay K. Kakkar, M.D., Patrick Mismetti, M.D., Sebastian Schellong, M.D., Henry Eriksson, M.D., David Baanstra, M.Sc., Janet Schnee, M.D., and Samuel Z. Goldhaber, M.D. for the RE-COVER Study Group
N Engl J Med 2009; 361:2342-2352 December 10, 2009

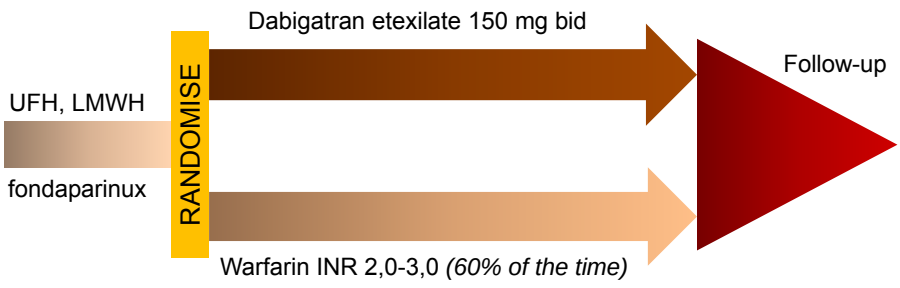
Oral Rivaroxaban for Symptomatic Venous Thromboembolism
The EINSTEIN Investigators
N Engl J Med 2010; 363:2499-2510 December 23, 2010

Oral Rivaroxaban for the Treatment of Symptomatic Pulmonary Embolism. N Engl J Med 2012;366;1287-1297 March 26, 2012

Recover Trial

Dabigatran vs warfarin for acute VTE treatment

- Randomised control, double-blind, non-inferiority trial (n= 2'539)



RE-COVER Trial – Results

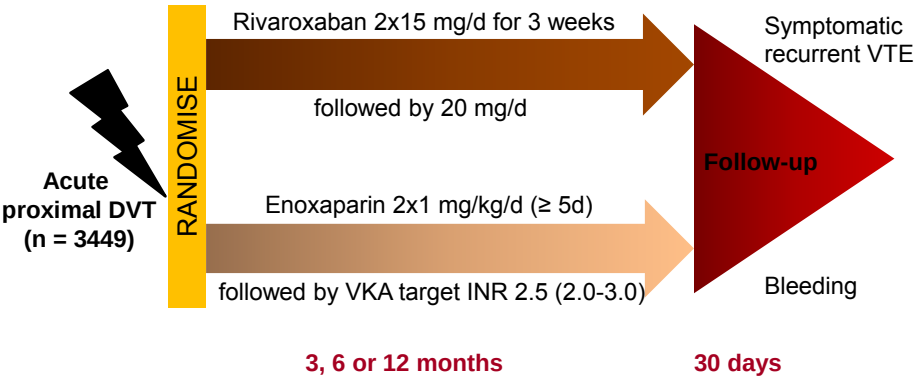
1) Comparable efficacy in the reduction of recurrent VTE and deaths related to VTE

2) Similar safety profil

- Overall bleeding > in warfarin-treated patients
- Major bleeding similar in the two groups

Schulman S et al. *NEJM* 2009;361:2342

Rivaroxaban – EINSTEIN-DVT Study



- Non-inferiority confirmed for DVT treatment
- Efficacy (2.1% vs 3.0%; HR 0.68; 0.44-1.44); safety (8.1% vs 8.1%)

EINSTEIN Investigators. *NEJM* 2010;363:2499

Initiation of treatment

A major difference:

- Dabigatran: heparin
- Rivaroxaban, apixaban: no heparin

And DVT and PE are outpatient diseases…

9th ACCP Guidelines (2012)

Inpatient or outpatient treatment?

2.7. In patients with acute DVT of the leg and whose home circumstances are adequate, we recommend initial treatment at home over treatment in hospital (Grade 1B).

Remarks: The recommendation is conditional on the adequacy of home circumstances: well-maintained living conditions, strong support from family or friends, phone access, and ability to quickly return to the hospital if there is deterioration. It is also conditional on the patient feeling well enough to be treated at home (eg, does not have severe leg symptoms or comorbidity).

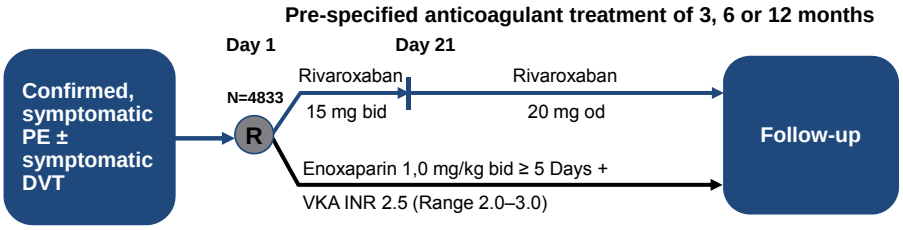
5.5. In patients with low-risk PE and whose home circumstances are adequate, we suggest early discharge over standard discharge (eg, after first 5 days of treatment) (Grade 2B).

Remarks: Patients who prefer the security of the hospital to the convenience and comfort of home are likely to choose hospitalization over home treatment.

Kearon et al. *Chest* 2012; 141 Suppl: 419s-494s

EINSTEIN PE: Study design

Randomised, open, event-driven, non-inferiority trial
Possible 48 h treatment with heparin/fondaparinux or 1 VKA dosis before randomisation



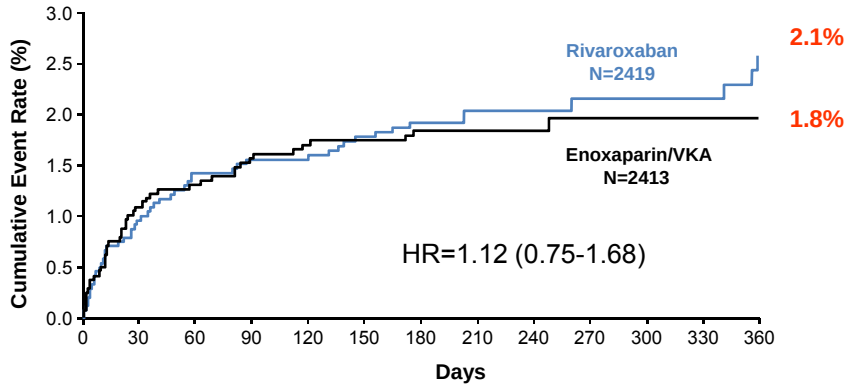
- **Main efficacy endpoint:** recurrent symptomatic VTE
- **Main safety endpoint:** major and clinically relevant non-major bleeding

Einstein-PE. *NEJM* 2012;366:1287

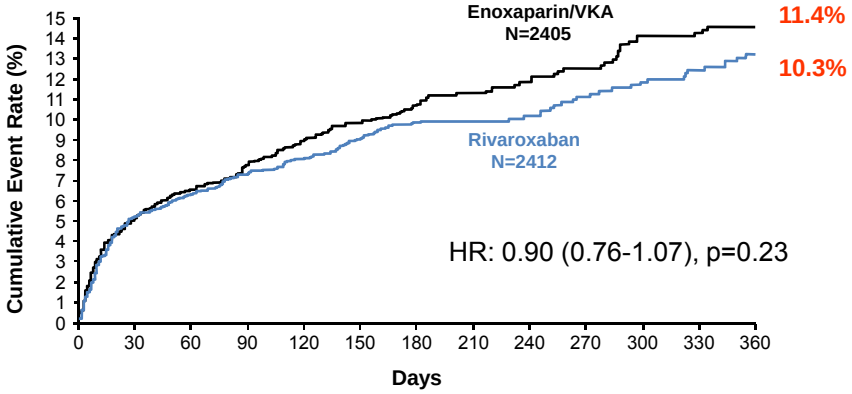
Patients characteristics

- Median age 58 years
- 14% > 100 kgs
- 8% creatinine clearance 30 to 49 mL/min
- All types of PE were included, except those for whom fibrinolytic therapy was planned
  - 1173 (25%) patients had extensive disease (multiple lobes and >25% of entire pulmonary vasculature)
  - 608 (13%) had limited PE (< 25% of vasculature of a single lobe)
- 12% admitted to intensive care unit
- 64% unprovoked PE

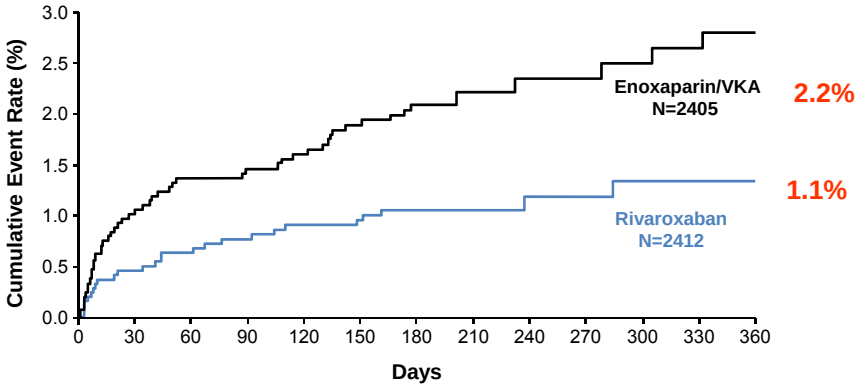
EINSTEIN PE: primary efficacy



Safety: clinically significant bleeding



EINSTEIN PE: major bleeding



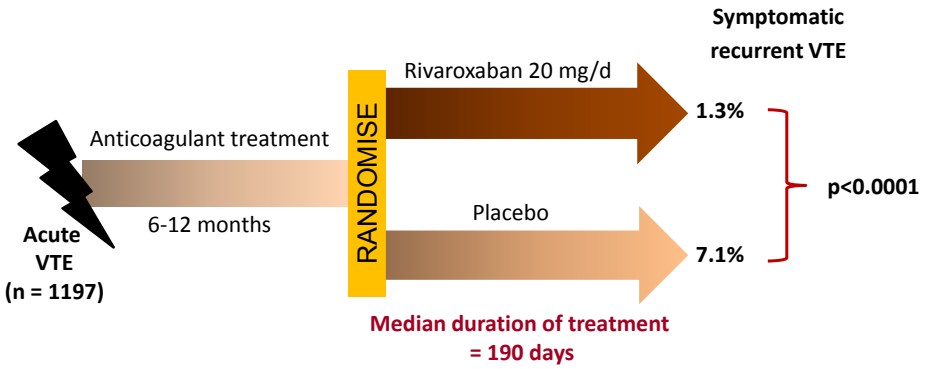
HR: 0.49 (0.31-0.79), p=0.0032

9th ACCP Guidelines (2012)

Duration of anticoagulant treatment following DVT/PE (III Bleeding risk)

Condition	Recommendation Grade
Proximal DVT or PE	3 months (1B)
First provoked proximal DVT or PE	3 months (1B if surgical, 2B if non-surgical and low or moderate bleeding BR risk)
First unprovoked proximal DVT or PE	Extended if BR low or moderate (2B), 3 months if BR high (1B)
Proximal DVT or PE associated with active cancer Treatment with LMWH VKA rather than dabi/rivaroxaban	Extended if BR low or m moderate (1B), if BR high (2B) 2B 2B
Extensive superficial phlebitis	Prophylaxtic LMWH (2B), fondaparinux compared with LMWH (2C)

Rivaroxaban – EINSTEIN-Extension Study



- **82% relative risk reduction in the recurrence of VTE**
  - ✓ NNT = 15 to prevent 1 recurrent VTE event
  - ✓ 34 recurrent events prevented at a cost of 4 major bleeds

EINSTEIN Investigators. *NEJM* 2010;363:2499

Plan

- Nouveaux anticoagulants
- Les études dans la MTEV et la FA
- Quelques questions

Questions

1. Laboratory controls?
2. Which tests?
3. Monitoring of renal function?
4. Safe for patients > 80 years?
5. Before a surgery?
6. Bleeding and antidote?
7. New OAC or VKA?
8. Cost?
9. Situation in Switzerland?

Q1) Is laboratory control ever indicated?

Might require lab. control for patient management

- Patients presenting with adverse events (thrombosis or hemorrhage)
- Immediate reversal of anticoagulation (surgery)
- Renal failure
- Main drug-drug interactions
- Adherence

What is the adherence of treatment in the absence of systematic control?

- After a dramatic event such as ACS, after 6-12 months continuous use of aspirin drops to 71%, β-blockers 46% and statins 44%, adherence to all three medications 21%

  Newby LK et al. *Circulation* 2006;113:203

- This scenario is worst in condition like AF which is often an asymptomatic chronic disease
- Non adherence in elderly with AF up to 75%

  Doggrell SA. *Drugs Aging* 2010;27:239

- Laboratory control: an advantage of VKA?

I wonder…

- If for patients who require long term new OAC a laboratory control should not be performed?
- Possible advantages: improving adherence and, in a non acute situation, get an idea of the level of anticoagulation of an individual patient which can be used in case of complication
- Of note: a patient with a low compliance of VKA will not improve his/her compliance with the new OAC (≠ from a patient with unstable INR)

Q2) Tests and NOAC, what a lung specialist should know?

PT and aPTT are modified, they give an idea on the effects of NOAC but are not really appropriate for measuring and furthermore are not specific

Other coagulation tests are also modified and the choice of reagents is crucial

Some simple tests can be performed, dTT for dabigatran and anti-Xa for rivaroxaban

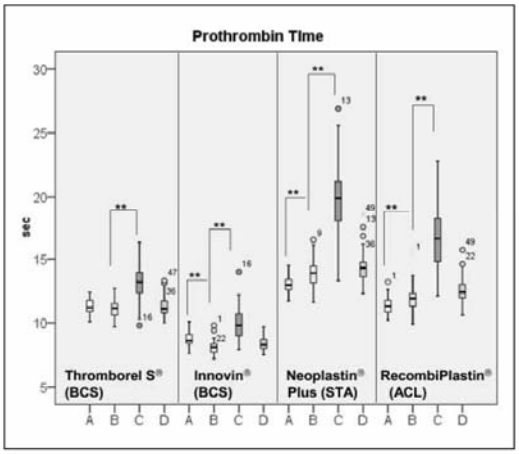


Figure 1: The time-dependent influence of rivaroxaban on the prothrombin time (measured in seconds) for plasma samples of 47 patients undergoing major orthopaedic surgery receiving 10 mg of rivaroxaban daily. A: before surgery, B: before intake of rivaroxaban dose at day 4–5 postoperatively, C: 2 h after rivaroxaban intake, D: 12 h after rivaroxaban intake. ** p< 0.001.

Summary:

- reagent dependent
- peak after 2h
- **no residual effect after 12h after 10 mg riva**

Mani et al. *Thromb Haemost* 2011;106:156

Q3) Should renal function be monitored?

- Normal renal function: no monitoring
- Mild renal failure: periodic (every year) evaluation
- Moderate renal failure: dose reduction and periodic (every six months) evaluation
- Severe renal impairment: dabigatran contraindicated

⇒ Yes, renal function must be known before prescribing NOAC and needs to be monitored afterwards in selected patients

Pengo et al. *Thromb Haemost* 2011;106:868

Underascertainment of impaired kidney function in older adults with normal serum creatinine

660 participants aged 65 to 92 with normal serum creatinine

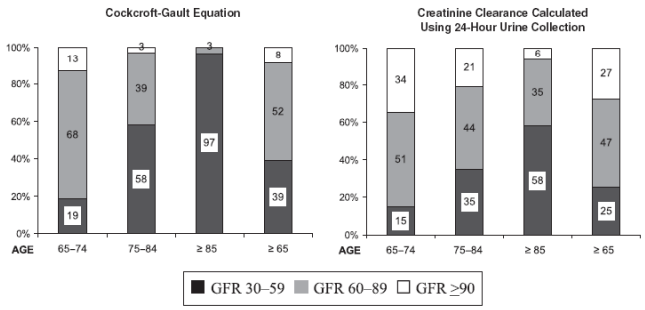


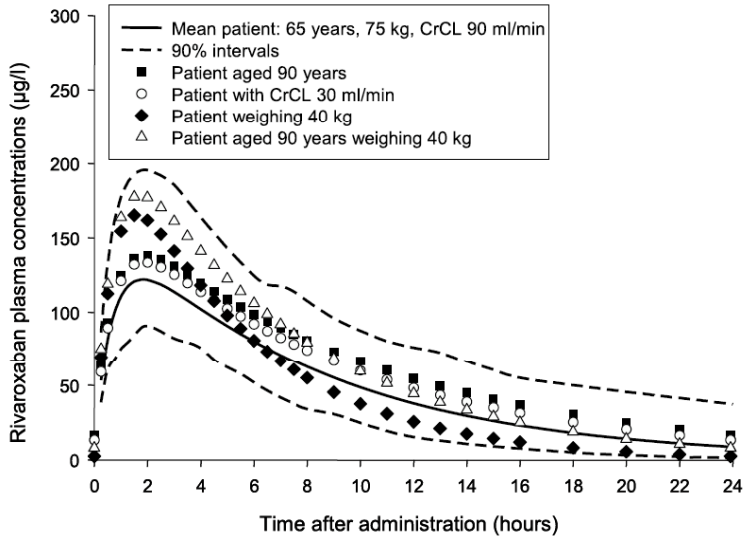
Figure 1. Distribution of three levels of glomerular filtration rate (GFR) (mL/min), estimated with both the Cockcroft–Gault equation and creatinine clearance calculated using 24-hour urine collection in a population of people aged 65 and older with normal serum creatinine values, with and without stratification according to age.

Female sex (P 0.001) and normal or underweight (P 0.05) were factors associated with high risk of misclassification

Giannelli et al. *J Am Geriatr Soc* 2007;55:816

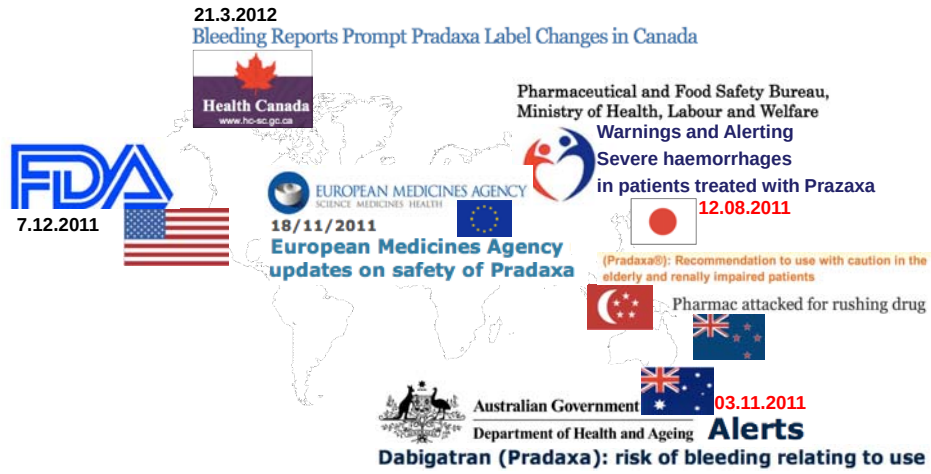
Q4) Is new OAC prescription safe in very (>80 years) elderly patients?

Rivaroxaban (10mg) after hip replacement



Mueck et al. *Thromb Haemost* 2008;32:569

Safety Alerts



Nov.2011 Reuters Boehringer says about 260 deaths related to Pradaxa

Bleeding risk with dabigatran

- 2 months follow-up study after approval for atrial fibrillation in New-Zealand
- 78 episodes of bleeding in 44 patients (23/44 GI bleeds)
- Four major factors: impaired renal function, patient age, prescriber errors (switch from warfarin without INR<2 and use of drugs with Cr Cl <30/min) and complications from the lack of a reversal agent
- 2/3 of patients >80 yrs; 50% weighed < 60 kgs; 50% moderate (Cr Cl 30-50 ml/min) or severe renal impairment
- RE-LY: mean age 71 yrs; mean weight 83 kg; Cr Cl 68 ml/min (< 20% Cr Cl < 50 ml/min)

Harper et al. *NEJM* 2012;336:864

Questions

1. Laboratory controls?
2. Which tests?
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8. Cost?
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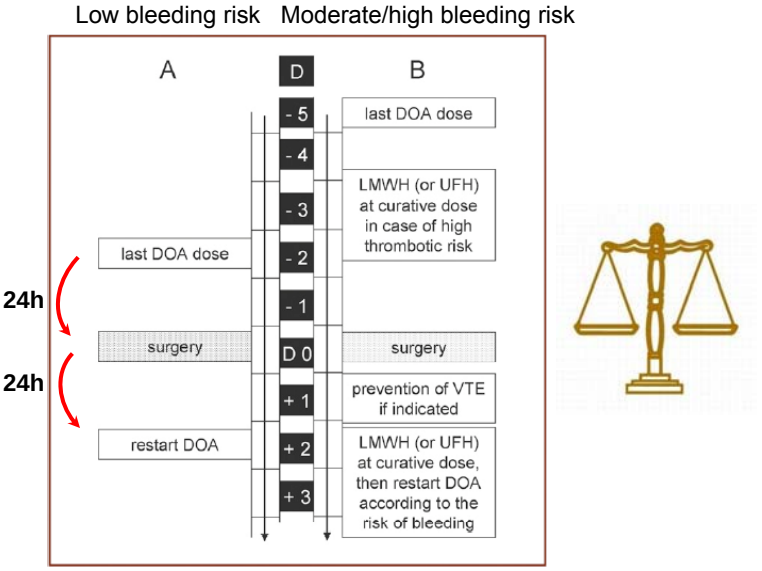
What to do before surgery ?

GIHP Groupe d'intérêt en hémostase péri-opératoire

What to do before surgery ?

Low bleeding risk Moderate/high bleeding risk



Sié P et al, *Arch Cardiovasc Dis* 2011;104:669

What to do before surgery ?

Calculated creatinine clearance, mL/min	Half-life, hours	Timing of last dose before surgery: Standard risk of bleeding*	Timing of last dose before surgery: High risk of bleeding†
Dabigatran			
> 80	13 (11-22)	24 h	2 d
> 50- ≤ 80	15 (12-34)	24 h	2 d
> 30- ≤ 50	18 (13-23)	2 d	4 d
≤ 30	27 (22-35)	4 d	6 d
Rivaroxaban			
> 30	12 (11-13)	24 h	2 d
< 30	Unknown	2 d	4 d

*Examples are cardiac catheterization, ablation therapy, colonoscopy without removal of large polyps, and uncomplicated laparoscopic procedures, such as cholecystectomy.

†Examples are major cardiac surgery, insertion of pacemakers or defibrillators (resulting from the risk for pocket hematoma), neurosurgery, large hernia surgery, and major cancer/urologic/vascular surgery.

Schulman S et al, *Blood* 2012;119:3016

Q6) How should patients with major bleeding be treated?

- Half-life not short enough to avoid problems in case of massive hemorrhage
- Direct thrombin inhibitors are hardly counteracted by PCC or FFP. Hemoperfusion over a charcoal filter and hemodialysis are options
- Direct Xa inhibitors could partially be antagonized by non activated PCCs. They contain FII-VII-IX-X and dosage could be 50 IU/kg in one-shot
- FVIIa may-be used off-label with a potential risk of thrombosis

Q7) In which patients should new OAC be prioritized in replacing VKAs?

- Patients on VKA with a time spent in therapeutic range < 50% (↑ risk in RE-LY)
- Patients with a $CHADS_2 \geq 2$
- Patients with a history of cerebral bleeding
- Patients at high risk of stroke
- Patients who wish to take the new OAC or are unwilling to perform frequent blood testing
- Logistic problems or polymedications

Better with VKA?

- For patients who are both with a stable INR and a low bleeding risk, keep VKA
- Also those who prefer to continue with VKA after complete information on the pros and cons of the NOAC
- In case of severe renal failure these two new AOC are globally contraindicated
- Blood count should also be checked occasionally (anemia due to chronic GI bleeding)
- Avoid dabigatran in patients with recurrent dyspepsia and with a previous myocardial infarction

Gastrointestinal bleeding

- Rocket AF: GI major bleeding from GI site (upper, lower and rectal): rivaroxaban 224 events (3.2%), warfarin 154 events (2.2%), p<0.001

  The majority of bleeding were chronic and became symptomatic as hypochromic anaemia; most of these patients received RBC
- RE-LY: 182 (1.51%/yr) major GI bleeding with dabi 150 mg bid vs 120 (1.02%/yr) with warfarin, p<0.001

Gastrointestinal bleeding

- Hypothesis: direct factor inhibition in the GI lumen
- Question: how often do we have to control Hb?
- "Fecal occult blood testing within the first month of treatment is a reasonable option to detect early signs of bleeding"

Huisman et al. *Thromb Haemost* 2012;epub ahead of print

Dabigatran Association With Higher Risk of Acute Coronary Events

Meta-analysis of Noninferiority Randomized Controlled Trials

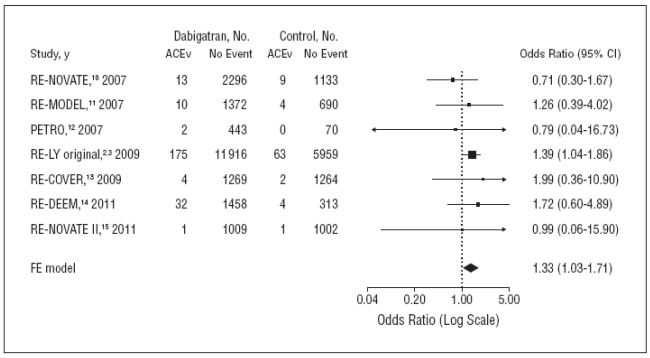


Figure 2. Risk of myocardial infarction and acute coronary syndrome across 7 studies, including original Randomized Evaluation of Long-term Anticoagulant Therapy (RE-LY) results. ACEv indicates acute coronary events; FE, fixed effects; PETRO, Prevention of Embolic and Thrombotic Events in Patients With Persistent AF Study; rectangles, odds ratios; limit lines, 95% CIs; diamond, overall odds ratio and 95% CI; and arrows, 95% CIs that exceed the limits of the graph (0.04-5.00).

Uchino and Hernandez. *Arch Int Med* 2012;172:397

“Uncharted waters and potential harms”

« Physicians considering dabigatran or an oral FXa inhibitor for individual patients should be extraordinarily conservative in considering whether these medications are appropriate replacements for warfarin.

Strict adherence to prescribing guidelines and a vigilant eye on medication safety literature should guide management of individual patients »

Radecki P. *Ann Intern Med* 2012;157:66

Q8) Cost

- Sintrom® about 3 Sfrs/month
- New OAC about 120 Sfrs/month
- LMWH price about 300 Sfrs/month

Net clinical benefit of new oral anticoagulants (dabigatran, rivaroxaban, apixaban) versus no treatment in a 'real world' atrial fibrillation population: A modelling analysis based on a nationwide cohort study

Amitava Banerjee[1]; Deirdre A. Lane[1]; Christian Torp-Pedersen[2]; Gregory Y. H. Lip[1]
[1]University of Birmingham Centre for Cardiovascular Sciences, City Hospital, Birmingham, UK; [2]Department of Cardiology, Copenhagen University Hospital Gentofte, Denmark

In the absence of head-to-head trials for these new OACs, our analysis may help inform decision making processes when all these new OACs become available to clinicians for stroke prevention in AF. Using 'real world' data, our modelling analysis has shown that when the risk of bleeding and stroke are both high, all three new drugs appear to have a greater net clinical benefit compared to warfarin.

Thromb Res 2012;107:584

Q9) How the pneumologist can manage?

- Confusion with the dosages and the frequency of administration:
  - AF dabigatran 110 or 150 mg bid + 2x75 mg FDA, rivaroxaban 20 mg od, apixaban 5 mg or 2.5 bid
  - DVT dabigatran 2x150 mg after 10 d heparinS, rivaroxaban 2x15 mg 3 weeks, then 20 mg/d and apixaban 2x10 mg 7 d, then 2x5 mg/d…..
- Dosages vary according to weight < 60 kgs, age > 80 : dabi 2x110 (AFSSAPS) or 2x75 (USA); API 2x2.5mg and creatinine clearance

« Il nous faut une machette acérée pour tailler notre chemin dans les jungle des anticoagulants »

Jean-Luc Magnenat

Nvx OAC: indications in December 2012

Approved in Switzerland

Major orthopedic surgery prophylaxis

Atrial fibrillation

DVT treatment

Not validated = CI

Prophylaxis in non orthopedic surgery

Prophylaxis or treatment during pregnancy

Medical prophylaxis

Cancer

Heart mechanic valve

Children

Conclusions

- New OAC: a major progress
- End of heparins and VKA: not for tomorrow
- Careful patients selection (see exclusion criteria and follow-up studies) and dosage according to the recommendations
- Although regular monitoring (dose-adjustment) is not required, the laboratory may help for measuring NOAC in selected cases
- Renal function should be assessed regularly in elderly (and caution GI bleed and anemia, particularly when long tem NOAC is required)

Old and new cars….

« Perhaps an analogy is that warfarin is like our old car. It is prone to breakdowns but when it breaks down we usually know the problem and how to fix it.

The new oral agents are analogous to the new sport cars of our dreams. However before we start off down the highway, it is best to make sure we know where the emergency brake is.

And let's hope we continue to smile when we look in the rearview mirror ».

Soff G et al. *ATVB* 2012;32:569

Quand faut-il suspecter après une EP que le patient va développer une MTEV chronique?

- Pas de réponse claire
- Prévalence faible de HTAP : 1 à 4%
- Proposition, envisager un écho à 3 mois chez
  - ceux qui ont déjà fait 1 ou des EP
  - ceux qui ont des EP multilobaires

Traitement ambulatoire d'une EP?

- Score de PESI < 86 points
  (seuls score validé dans une étude randomisée mais d'autres scores existent)

Aujesky et al. *Lancet* 2011;378:41

A garder à l'hôpital

- Score de PESI > 86 points
- Co-morbidités
- Douleurs difficiles à contrôler, …

PE Severity Index

Predictors	Points Assigned
Age, per year	Age, in years
Male sex	+10
Cancer	+30
Heart failure	+10
Chronic lung disease	+10
Temperature <36°C	+20
Pulse ≥110/minute	+20
Systolic BP <100 mm Hg	+30
Respiratory rate ≥30/minute	+20
Altered mental status	+60
Arterial oxygen saturation <90%	+20

Patients with <86 points are at low risk

Aujesky et al. *Am J Resp Crit Care Med* 2005

Medical Outcomes

Outcomes	Outpatient (N=171)	Inpatient (N=168)	1-sided P-Value*
	n (%)		
Recurrent VTE at 90 days	1 (0.6)	0	0.011
Major bleeding			
at 14 days	2 (1.2)	0	0.031
at 90 days	3 (1.8)	0	0.086
Overall mortality at 90 days	1 (0.6)	1 (0.6)	0.005

Non-inferiority margin= 4%

Aujesky et al. *Lancet* 2011;378:41