RIVAROXABAN

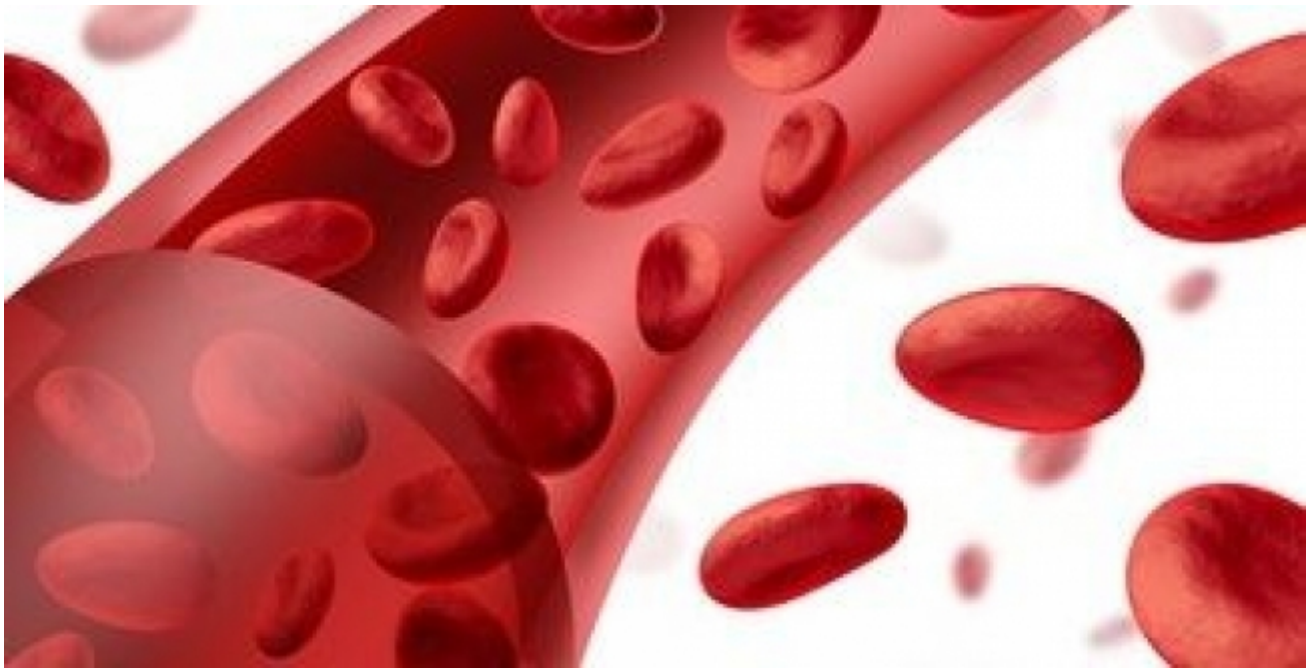
TROMBOSI - ANTICOAGULANTI ORALI DIRETTI

Ultimo aggiornamento: 15 Marzo 2016

Revisione letteratura: Marzo 2016

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Abstract

Rivaroxaban is an oral direct reversibile and competitive inhibitor of activated factor X (Factor Xa). It binds to both free and clot-bound factor Xa. Rivaroxaban was studied in 4 clinical trials (RECORD trials) for thromboprophylaxis in patients who have undergone a total knee or a total hip arthroplasty and the results in the rivaroxaban group were favorable.
Rivaroxaban was also studied in one trial,ROCKET-AF trial,**(1) (NEJM 2011 vol. 365 pp. 883-891)** for the prevention of stroke or systemic embolism in patients with non valvular atrial fibrillation, in 2 trials, EINSTEIN-DVT **(2) (NEJM 2010 vol. 363 pp. 2499-2510)** and EINSTEIN-EXTENSION **(2) (NEJM 2010 vol. 363 pp. 2499-2510)** trials,for treatment and secondary prevention of symptomatic deep vein thrombosis (DVT) and for prevention of recurrent venous thromboembolism in patients who had already completed 6 to 12 months of treatment for venous thromboembolism respectively, and in one trial, EINSTEIN-PE trial, **(3) (NEJM 2012 vol. 366 pp. 1287-1297)** was studied for treatment of symptomatic pulmonary embolism and for prevention of recurrent venous thromboembolism. In another clinical trial, ATLAS ACS 2-TIMI 51,**(4) (NEJM 2012 vol. 366 pp. 9-19)** rivaroxaban was compared to placebo in patients with a recent acute coronary syndrome. (For the results of these trials, and for diseases in which the therapeutic use of rivaroxaban has been approved by regulatory agencies, see section on "Indications") All these trials were funded by rivaroxaban manufacturer. As for dabigatran, also for rivaroxaban we do not have a specific antidote to neutralize its anticoagulant effect but, differently from dabigatran,in case of rivaroxaban bleedings,we can use Prothrombin Complex Concentrates (PCC) with a certain efficacy. Although there are less drug interactions than vitamin k antagonists such as warfarin,some important drug interactions are present with rivaroxaban.
This drug is both a CYP3A4 and P-glycoprotein (P-gp) substrate and its elimination is partially dependent on normal renal function. Concomitant use of rivaroxaban with strong inhibitors of CYP3A4 and P-glycoprotein (P-gp) as ketoconazol, ritonavir,chloramphenicol etc. must be avoided because AUC (area under the curve) that is a method of measurement of the bioavailability of a drug based on a plot of blood concentrations sampled at frequent intervals, and the Cmax,that is the maximum peak concentration that a drug achieves, are increased.
Also use with strong inducers of CYP3A4 and P-gp as carbamazepine, phenytoin, dexamethasone, rifampicin etc. must be avoided because in this case the average rivaroxaban AUC and Cmax are reduced. In this review, in the section “indications”, we will examine the results of the numerous clinical trials in which rivaroxaban was studied. Comments on these studies will be discussed at the end, in the section “ Conclusions “.
At the moment rivaroxaban has been approved by the European Medical Agency (EMA) for a) venous thromboprophylaxis in patients undergoing hip or knee replacement surgery, b) to prevent stroke or systemic embolism in patients with Nonvalvular Atrial Fibrillation, c) to treat Deep Vein Thrombosis (DVT) and Pulmonary Embolism (PE), d) to prevent recurrent DVT and PE, e) to prevent atherothrombotic events in patients who have had an Acute Coronary Syndrome (ACS) with elevated

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biomarkers. It has been approved for the same first four indications by the Food and Drug Administration (FDA) and in Canada, but not to prevent atherothrombotic events in patients with an Acute Coronary Syndrome (ACS). In fact on february 14 2014, the U.S. FDA has rejected rivaroxaban as a treatment for patients with acute coronary syndrome (ACS). This is the third time the agency has denied the supplemental new drug application (sNDA) based on data from the ATLAS-ACS 2 TIMI-51 trial for the rivaroxaban ACS indication. In January, the Cardiovascular and Renal Drugs Advisory Committee voted almost unanimously against approving rivaroxaban as a treatment in ACS patients. In addition to denying the sNDA for rivaroxaban in ACS to reduce the risk of MI, stroke, or death, the FDA also denied an expanded indication for rivaroxaban in ACS patients to reduce the risk of stent thrombosis. **(5) (www.medscape.com/viewarticle/820651)** Just recently, in November 2014 the New England Journal of Medicine published a letter. The authors write that PER977 (Aripazine), developed by Perosphere, a small synthetic, water-soluble, cationic molecule that is designed to bind specifically to unfractioned heparin (UF) and low molecular weight heparin (LMWH) through non-covalent hydrogen bonding and charge-charge interactions, binds in a similar way to the new oral factor Xa inhibitors, edoxaban, rivaroxaban and apixaban, and to the oral thrombin inhibitor dabigatran. **(6) (New England Journal of Medicine 2014 vol. 371 pp. 2141-2142)** Andexanet alfa, a modified recombinant protein derived from human coagulation factor X, is a new agent which can be used in antagonizing the anticoagulant effect of direct factor Xa inhibitors such as rivaroxaban, apixaban and edoxaban. However at the moment is not commercially available. **(7) (Nature Medicine 2013 vol. 19 pp. 446-451)** (for details, see section on "adverse reactions") In January 2014,Turpie and collegues published a study of 17,701 patients enrolled from 252 centres in 37 countries, emphasizing the favourable benefit-risk profile of rivaroxaban compared with standard-of-care for thromboprophylaxis after major orthopaedic surgery. Also this study as all the large studies involving DOAs was sponsored by the drug manufacturer, in this case Bayer Heathcare Pharmaceuticals with support from Janssen Research and Development. Primary hip and knee replacement surgery accounted for more than 90% of all surgical operations. It is important to note that standard-of-care in this study included, LMWHs, Unfractioned Heparin (UF), fondaparinux, dabigatran etexilate, acetylsalicylic acid and vitamin K antagonists. The type, duration and dose of pharmacological agents were determined by the attending physician before the patients enrollement into the study. it is clear that considering as standard-of-care all these agents, the results of the study might have a relevant bias because in Europe and North America the most used drugs for thromboprophylaxis in case of hip or knee replacement surgery are LMWHs. In any case also if we analyze the published results of this study is evident that there is not any important advantage of rivaroxaban compared with the standard-of- care treatment. In fact, the results (Table 2, page 98) showed only a slight reduced incidence of thromboembolic events in the rivaroxaban group, balanced by an increased incidence of major and minor bleeding events in the rivaroxaban group compared with the standard-of-care group. The number of deaths was exactly the same in the two groups (7 vs 7). Five authors of the study have been consultants for Bayer HeathCare, the rivaroxaban manufacturer, and other pharmaceutical companies, one author has been paid for educational presentation from Bayer HeathCare, the other four authors are employees of Bayer HealthCare. **(8) (Thrombosis and Haemostasis 2014 vol. 111 (1) pp. 94-102)** I do not see any

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reason to use rivaroxaban in these cases when we can use LMWH that we know very well and that we have been using since many years, although the dosage used in Europe, Enoxaparin 40 mg once daily, (the most used LMWH) is different from the dosage used in the US, Enoxaparin 30 mg twice daily. As many drugs, about 1/3 of rivaroxaban is metabolized by the cytochrome P 450 enzymes CYP3A4/5 and CYP2J2. Rivaroxaban is also a substrate of the efflux transporter proteins P-glycoprotein (P-gp) and breast cancer resistance protein (BCRP).
For this it should not be administered with strong inhibitors of P-gp/CYP3A4 such as azoles and protease inhibitors and coadministration with moderate inhibitors such as erythromycin should be exercised with caution to avoid a dangerous increased concentration of the active drug. Rivaroxaban should also not be administered with strong inducers of CYP3A4/P-gp such as rifampicin to avoid a dangerous decrease of its active concentration. (for details see sections on "Absorption and metabolism" and on "Dosage and drug interactions"). In addition, because clinically relevant polymorphisms exist for genes encoding CYP3A4/5, P-gp, and BCRP, these genetic variations play an important role in determinig rivaroxaban exposure. (for details see section on "Absorption and metabolism") At this point I report exactly the words used by Gong and collegues as conclusions of their interesting paper because any attempt to change these words would result in a loss of their efficacy. "As the clinical use of NOACs increases, surveillance using therapeutic monitoring (measurement of plasma drug concentration or anticoagulation response) throughout the treatment period might be evaluable in minimizing the risk of bleeding and lack of efficacy. Finally, because of the extent of interindividual variation in the metabolism and clearance of NOACs, it is likely that a greater range of NOACs doses will be needed to more precisely treat our patients". **(9) (Canadian Journal of Cardiology 2013 vol. 29 pp. S24-S33)** For other details, see abstracts of reviews on Dabigatran and Apixaban. In the X-VERT study Cappato and collegues used rivaroxaban for the prevention of cardiovascular events in patients with nonvalvular atrial fibrillation scheduled for cardioversion and oral rivaroxaban appears to be an effective and safe alternative to VKA and may allow prompter cardioversion. see section on "Indications" . **(10) (European Heart Journal 2014 vol. 35 pp. 3346-3355)** The most statistically efficient randomization ratio is 1:1 because it maximizes statistical power for a given total sample size. On the contrary, in this study,randomization of patients in a 2:1 ratio causes in any case a loss of statistical power, although modest.This randomization is acceptable when may be more economically efficient to randomize fewer patients to the expensive treatment and more to the cheaper one, or when for ethical reasons as for example in the oncology trials, it is necessary to allocate more patients in the arm of the treatment which probably will prolong the survival time and less patients in the placebo/medical care that will not prolong much their survival time. On the contrary in this study, the authors randomized more patients in the rivaroxaban arm, and this drug is much more expensive than warfarin, and in addition rivaroxaban was never used in this indication and for this, for ethical reasons, would have been more reasonable to allocate more patients in the warfarin group than in the rivaroxaban group. This study was supported by Bayer HealthCare Pharmaceuticals and Janssen Scientific Affairs LLC and the long list of conflicts of interests of the authors at the end of the paper is really impressive. See section on "Indications". **(10) (European Heart Journal 2014 vol. 35 pp. 3346-3355)** The authors caution that the trial was "underpowered to provide statistically rigorous results and was thus exploratory in nature", but in the same time Dr. Cappato, the principal

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author of the study, said to "Heartwire" that X-VERT provides a high level of "solid, methodologically sound evidence" for those clinicians who are already using NOACs in this setting instead of VKA. **(11) (Medscape September 02, 2014)** Safety and efficacy of well managed warfarin compared with DOACs is demonstrated in a recent paper published in 2015, in the June number of Thrombosis and Haemostasis.The study was a retrospective, registry-based study, including 77423 patients treated with warfarin in the Swedish national anticoagulation register Auricula from January 1, 2006 to December 31, 2011. Atrial fibrillation was the most common indication (68%). The mean time in therapeutic range of INR was 76.5%. The annual incidence of severe bleeding was 2.24% and of thromboembolism was 2.65%. The incidence of intracranial bleeding was 0.37% per treatment year in the whole population, and 0.38% among patients with atrial fibrillation. The authors affirm that limiting their analysis to patients with atrial fibrillation as indication for warfarin treatment, and not including the other types of patients, did not change their conclusions. This study is the demonstration that is possible to achieve efficient warfarin therapy with a mean TTR of 76.5% in routine clinical care, in the so called "real word", without exclusion of any patient groups and with very few serious bleeding complications. In fact, bleeding complications were fewer than what reported in the large randomised trials where warfarin was compared with DOACs because the TTR in this study (76.5%) was far higher than the mean TTR levels of 55-64% in the pivotal DOACs trials. In addition, a very important characteristic which strengthens the results of this study is that all warfarin treated patients were included, which means that there were more elderly patients and patients with multiple concomitant diseases than in DOACs clinical trials with inclusion and exclusion criteria. Intracranial bleeding, the most severe adverse event, associated with high mortality, occurred at an annual rate of 0.37% per treatment year in the whole group, and of 0.38% in patients with AF. This was far lower than in the DOACs trials where the warfarin treated patients had intracranial bleeds at a rate of 0.70 to 0.80% annually. It was even lower than with rivaroxaban (0.50%), and not much higher than with apixaban (0.33%), dabigatran 150 mg (0.30%) and dabigatran 110 mg (0.23%). In addition, in patients with atrial fibrillation, stroke, TIA or systemic emboli occurred at an annual rate of 1.54% per treatment year which is considerably lower than the 1.74% and 2.42% found in the warfarin arms in the pivotal studies for dabigatran and rivaroxaban respectively, despite of an unselected patient population with no inclusion or exclusion criteria. Patients with heart valve disease had more bleeding complications than other patients, probably because many of these patients had treatment with higher therapeutic range of INR 2.5-3.5 instead of the more common INR 2.0-3.0. The inclusion of patients with higher INR goals than 2.0-3.0 means that this study showed a larger risk of bleeding than for the patients with lower goals, and could therefore better reflect clinical reality. The authors conclude that **"efficient warfarin therapy with a mean TTR of 76.5% is possible to achieve in routine clinical care with unselected patients, and should not be ruled out in favour of DOACs". (12) (Thrombosis and Haemostasis 2015 vol. 113 (6) pp. 1370-1377)** Recently has been published ahead of print on May 21, 2015 in the journal Thrombosis and Haemostasis the design of a multicentre, randomised, double-blind, active controlled, event-driven study, the EINSTEIN CHOICE study, in which will be evaluated the efficacy and safety of two once-daily doses of rivaroxaban (20 and 10 mg) with aspirin (100 mg daily) for the prevention of recurrent VTE in patients who completed 6-12 months of anticoagulant therapy for their index acute VTE event. All treatments will be given for 12 months.

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(13) (Thrombosis and Haemostasis 2015, vol. 114 (3) pp.645-650) In this study the enrollement criterion of patients is unacceptable because in daily clinical practice, clinicians must decide to continue or not to continue the oral anticoagulant treatment on a case by case basis, evaluating the bleeding risk and the thrombotic risk of every patient and must not to switch to aspirin treatment just because they or their patients have "concerns about bleeding and frequent laboratory monitoring". In case the patient refuses the continuation of the oral anticoagulant treatment considered necessary by the clinician expert in thrombosis and haemostasis, the patient should be told to be treated elsewhere. Aspirin must be used only in patients with a high bleeding risk and consequently cannot continue the oral anticoagulant treatment, and cannot be used just because the "treating physician is uncertain about the need for continued anticoagulant therapy". In addition to affirm that rivaroxaban does not need laboratory monitoring is not correct. **(9) (Canadian Journal of Cardiology 2013 vol. 29 pp. S24-S33);(14) (Blood Coagulation and Fibrinolysis 2015 vol. 26 pp. 925-933); (15) (Thrombosis Research 2016 vol. 137 pp. 178-183)** (see above, section on "Conclusions", and review on "Dabigatran") and let the enrolled patients believe this, is simply unacceptable. At the end of the EINSTEIN-CHOICE study paper **(13) (Thrombosis and Haemostasis 2015 vol. 114 (3) pp.645-650),** the list of conflict of interests of the authors is so long that is really impressive. In addition two authors of the study are employees of Bayer Heathcare, the rivaroxaban manufacturer. The health and the life of patients cannot be considered secondary to the economic interests of pharmaceutical companies, of healthcare institutions and of "key opinion leaders" physicians.

Just recently, the British Medical Journal found that in the ROCKET AF trial a defective point of care device was used to measure INR in its comparator arm of patients taking warfarin. For this reason, may be that warfarin results looked worse than they otherwise would seem. This point of care device was subject to a recall. In December 2014 a recall notice said that certain INRatio devices could deliver INR results that were clinically significantly lower than a laboratory INR method. It said that Alere, the manufacturer of the device, had received 18924 reports of malfunctions, including 14 serious injuries. **(16) (British Medical Journal 2015 vol. 351 pp. h6431)** In a letter submitted to the New England Journal of Medicine (as yet unpublished) and shown to the BMJ, former FDA cardiovascular and renal drug reviewer, Thomas Marcinicak, says : "The care for the warfarin control arm patients in the ROCKET AF trial appears to have been compromised". **(17) (British Medical Journal 2016 vol. 352 pp. i575)** The authors of this trial made another analysis of 5294 (37%) patients who had a recall condition and now affirm that the results obtained by this analysis, indicate that possible malfunction of the point-of-care device used for INR measurement that potentially led to lower INR values than would be obtained by laboratory testing, did not have any significant clinical effect on the primary efficacy and safety outcomes in the ROCKET AF trial. **(18) (New England Journal of Medicine 2016 vol. 374 pp. 785-788)** However, a recent article published in The New England Journal of Medicine of March 1, 2016 has revealed that lawyers for patients suing Johnson & Johnson and Bayer over the safety of the drug Xarelto claimed that the letter published in the NEJM left out critical laboratory data. In fact investigators in the ROCKET AF trial compared the device readings with test results that were done at a central laboratory at two points in the trial, drawing blood from more than 5,000 of the patients who took warfarin and sending the samples for testing. The blood was taken 12 and 24 weeks after patients enrolled in the

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trial. But the Duke researchers made no mention of these lab data in their letter. Dr. Steve Nissen, a cardiologist at the Cleveland Clinic, who served on the FDA advisoty panel that voted to approve Xarelto in 2011, and who was one of the two members who voted against the drug said : "Given the fact that the device was inaccurate, there is no way anybody can tell you what would have happened in the trial ". **(19) (The New York Times March 1, 2016)** (for details see section on "Conclusions") Siegal and collegues recently reported the results of two randomized, double-blind, placebo-controlled studies of adexanet alfa, a novel antidote to Factor Xa inhibitors, to antagonize the anticoagulant effects of apixaban (ANNEXA-A) and of rivaroxaban (ANNEXA-R). The study was performed in healthy volunteers with an age range of 50 to 75 years and although andexanet alfa seems to effectively neutralize the anticoagulant effect of apixaban and rivaroxaban without adverse events and thrombotic complications, it is unknown whether andexanet use would improve outcomes for patients with major bleeding. For this reason, the ongoing ANNEXA-4 phase 3b-4 study (ClinicalTrials.gov.number, NCT02329327) is evaluating the efficacy and safety of andexanet in patients with factor Xa inhibitor-associated acute major bleeding. Interestingly the dosage used to antagonize rivaroxaban was twice of that used to neutralize the anticoagulant effect of apixaban. **(20) (New England Journal of Medicine 2015 vol. 373 pp. 2413-2424); (21) (New England Journal of Medicine 2015 vol. 373 pp. 2471-2472)** For details, see the last section on "Conclusions".

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Mechanism of action

Rivaroxaban is a direct, selective, reversible and competitive inhibitor of activated factor X (factor Xa) in both the intrinsic and extrinsic coagulation pathways. It binds directly to the catalytic site of factor Xa, independently of antithrombin, and inhibits both free and prothrombinase-bound Xa that is more efficient than free Xa at activating prothrombin to thrombin, increasing the reaction of about 300,000 folds. **(1) (Thrombosis Haemostasis 2010 vol. 103 pp. 815-825)** Factor Xa, as part of the prothrombinase complex that consists also of factor Va, calcium ions, prothrombin and phospholipid, catalyzes the conversion of prothrombin to thrombin. (see figure 2) Thrombin activates platelets, catalyzes the conversion of fibrinogen to fibrin, activates factor V and factor VIII, activates Protein C in presence of thrombomodulin and Protein S as cofactor, and inhibits fibrinolysis by thrombin activated fibrinolysis inhibitor (TAFI) (see “mechanism of action” of "Dabigatran Etexilate")

(Enzyme)(cofactor)
FXa+FVa+calcium ions+phosholipids
Prothrombin ----------Thrombin
(figure 1)

Rivaroxaban does not require cofactors for its anticoagulant effect.
The onset of inhibition of Factor Xa activity is rapid and the inhibition is reversible.

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Simplified Coagulation Cascade - zoom

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Indications

Rivaroxaban has been approved by the European Medical Agency (EMA) for the following indications :
1) to prevent venous thromboembolism in patients undergoing hip or knee replacement surgery. In this case the recommended dosage is 10 mg. once daily. Treatment with rivaroxaban should start about 6-10 hours after surgery, provided that the patient is no longer bleeding from the site of surgery. Normally treatment is continued for 5 weeks in patients who had a hip replacement surgery, and for two weeks in patients who had a knee replacement surgery.
2) to prevent stroke or systemic embolism in patients with non-valvular atrial fibrillation with one or more risk factors such as heart failure, hypertension, age >/= 75, diabetes mellitus, previous stroke or a transient ischemic attack (TIA). The recommended dose is 20 mg. once daily, and treatment is continued indefinitely.
3) to treat Deep Vein Thrombosis (DVT) and Pulmonary Embolism (PE). The recommended dose for the initial treatment of acute DVT is 15 mg. twice daily for the first three weeks followed by 20 mg. once daily for 3, 6 or 12 months.
4) to prevent recurent deep vein thrombosis (DVT) and pulmonary embolism (PE) after an acute deep vein thrombosis (DVT) at the dosage of 20 mg. daily for additional 6 or 12 months in patients who had completed 6 to 12 months of treatment for venous thromboembolism.
5) to prevent atherothrombotic events in patients who have had an acute coronary syndrome (ACS) with elevated biomarkers. The recommended dose is 2.5 mg. twice daily. Rivaroxaban must be taken in combination with aspirin alone or together with aspirin plus clopidogrel or ticlopidine.Treatment should start as soon as possible after the acute coronary syndrome has stabilised. The benefits of the treatment should be regularly evaluated by a specialist against the risk of bleeding.
At the moment, in april 2015, rivaroxaban has been approved by the Food and Drug Administration (FDA) and in Canada only for the first four indications described above, and not to prevent atherothrombotic events in patients who have had an acute coronary syndrome.
In the RECORD-1 trial, a double blind randomized trial, **(1) (NEJM 2008 vol. 358 pp. 2765-2775)** 4541 patients undergoing total hip arthroplasty were assigned to receive either an oral dose of 10 mg. of rivaroxaban once daily, beginning after surgery, or 40 mg. of enoxaparin subcutaneously once daily, beginning the evening before surgery, plus placebo tablet or injection for 31-39 days. The safety profile was similar for the two drugs. In this study 1.1% of patients (18 out of 1,595) who completed treatment with rivaroxaban had deep vein thrombosis (either symptomatic or detected by bilateral venography if the patient was asymptomatic), nonfatal pulmonary embolism, or death from any cause at 36 days (range, 30 to 42) compared with 3.7% of the patients receiving enoxaparin (58 out of 1,558). Another 0.2% of the patients (4 out of 1686) treated with rivaroxaban had major venous thromboembolism events compared with 2% of patients (33 out of 1678) treated

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with enoxaparin. Major bleeding occurred in 6 of 2209 patients (0.3%) in the rivaroxaban group and in 2 of 2224 patients (0.1%) in the enoxaparin group. The investigators concluded that a once-daily, 10 mg. oral dose of rivaroxaban was significantly more effective for extended thromboprophylaxis than a once-daily, 40 mg subcutaneous dose of enoxaparin in patients undergoing elective total hip arthroplasty. In the RECORD-2 trial, a double blind randomised trial, **(2) (The Lancet 2008 vol.372 pp. 31-39)** 2509 patients scheduled to undergo elective total hip arthroplasty were randomly assigned to receive rivaroxaban 10 mg. once daily for 31-39 days (with placebo injection for 10-14 days; n = 1252), or enoxaparin 40 mg. once daily subcutaneously for 10-14 days (with placebo tablet for 31-39 days; n = 1257) In this second study, 2% of the patients taking rivaroxaban (17 out of 864) had deep vein thrombosis (symptomatic or asymptomatic detected by mandatory, bilateral venography), non-fatal pulmonary embolism, and death from any cause to day 30-42, compared with 9.3% of the patients receiving enoxaparin (81 out of 869). Analyses were done in the modified intention-to-treat population, which consisted of all patients who had received at least one dose of study modification, had undergone planned surgery, and had adequate assessment of thromboembolism. The incidence of any on-treatment bleeding was much the same in both groups, 81 events (6-6%) in 1228 patients in the rivaroxaban safety population versus 68 events (5.5%) of 1229 patients in the enoxaparin safety population. Extended thromboprophylaxis with rivaroxaban was significantly more effective than short term enoxaparin plus placebo. In the RECORD-3 trial, a double blind randomized trial, **(3) (NEJM 2008 vol.358 pp. 2776-2786)** in 2531 patients who were to undergo total knee arthroplasty, rivaroxaban 10mg. once daily, beginning 6-8 hours after surgery, was compared with enoxaparin 40 mg. once daily, beginning 12 hours before surgery for 10-14 days. Deep vein thrombosis, nonfatal pulmonary embolism, or death from any cause within 13 to 17 days after surgery occurred in 79 of 824 patients (9.6%) who received rivaroxaban and in 166 of 878 (18.9%) of patients who received enoxaparin. Major venous thromboembolism occurred in 9 of 908 patients (1%) who were treated with rivaroxaban and in 24 of 925 (2.6%) who were treated with enoxaparin. Major bleeding occurred in 0.6% of patients in the rivaroxaban group and 0.5% of patients in the enoxaparin group. The incidence of drug-related events, mainly gastrointestinal, was 12.0% in the rivaroxaban group and 13.0% in the enoxaparin group. Rivaroxaban was superior to enoxaparin for thromboprophylaxis after total knee arthroplasty and the rates of bleeding were similar. In RECORD-4 trial, a double-blind randomized trial, **(4) (The Lancet 2009 vol. 373 pp. 1673-1680)** 3148 patients undergoing knee arthroplasty received either oral rivaroxaban, 10 mg. daily, beginning 6-8 hours after knee arthroplasty surgery, or subcutaneous enoxaparin 30 mg. twice daily starting 12-24 hours after surgery according to U.S. guidelines recommendations, and not 40 mg. daily according to European guidelines, for 10-14 days. Patients had mandatory bilateral venography between days 11 and 15. Deep vein thrombosis, non-fatal thrombosis or death from any cause up to day 17 after surgery occurred in 67 (6.9%) of 965 patients who received rivaroxaban, compared with 97 (10.1%) of 959 patients who received enoxaparin. Ten (0.7%) of 1526 patients treated with rivaroxaban and four (0.3%) of 1508 patients treated with enoxaparin had major bleeding. Also in this trial was found a significantly superiority of rivaroxaban compared to subcutaneous enoxaparin for prevention of venous thromboembolism after total knee arthroplasty.

Rivaroxaban was compared to warfarin in non valvular atrial fibrillation for prevention of

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stroke or systemic embolism in the ROCKET AF trial, a double blind trial, **(5) (NEJM 2011 vol. 365 pp. 883-891).**
In this trial, 14,264 patients with nonvalvular atrial fibrillation were randomly assigned to receive rivaroxaban at a dosage of 20 mg. once daily was compared to adjusted-dose warfarin. Rivaroxaban was found noninferior to warfarin for the primary end point of stroke or systemic embolism. In the primary analysis, stroke or systemic embolism occurred in 188 patients in the rivaroxaban group (1.7% per year) and in 241 in the warfarin group (2.2% per year). In the intention-to-treat-analysis, the primary end point (stroke or systemic embolism) occured in 269 patients in the rivaroxaban group (2.1% per year) and in 306 patients in the warfarin group (2.4% per year). Major and nonmajor clinically relevant bleeding occurred in 1475 patients in the rivaroxaban group (14.9% per year) and in 1449 in the warfarin group (14.5% per year), with reductions in intracranial hemorrhage (0.5% versus 0.7%, P=0.02) and fatal bleeding (0.2% versus 0.5%, P=0.003) in the rivaroxaban group. The authors conclude that in patients with atrial fibrillation, rivaroxaban was noninferior to warfarin for the prevention of stroke or systemic embolism. There was not significant between-group difference in the risk of major bleeding, although intracranial and fatal bleeding occurred less frequently in the rivaroxaban group.
In the EINSTEINT-DVT trial, an open label randomized, event-driven, noninferiority trial, **(6) (NEJM 2010 vol. 363 pp. 2499-2510)** 3449 patients who had acute deep-vein thrombosis (DVT), were randomized to receive rivaroxaban at a dosage of 15 mg. twice daily for 3 weeks, followed by 20 mg.once daily (1731 patients), or subcutaneous enoxaparin at a dosage of 1.0 mg/kg of body weight twice daily, followed by an adjusted-dose vitamin K antagonists (warfarin or acenocoumarol) for 3, 6, or 12 months (1718 patients). Enoxaparin was discontinued when the International Normalized Ratio (INR) was =/> 2.0 for two consecutive days and the patient had received at least 5 days of enoxaparin treatment. The therapeutic INR range was between 2.0 and 3.0. Rivaroxaban had noninferior efficacy compared with the standard therapy and similar rates of clinically non major bleedings and similar rates of major bleedings. In parallel (EINSTEIN-EXTENSION trial), was carried out a double-blind, randomized, event-driven superiority study that compared 602 patients treated with rivaroxaban alone,at the dosage of 20 mg.daily with 594 patients treated with placebo for additional 6 or 12 months in patients who had completed 6 to 12 months of treatment for venous thromboembolism.The primary efficacy outcome for both studies was recurrent venous thromboembolism. The principal safety outcome was major bleeding or clinically relevant nonmajor bleeding in the initial-treatment study and major bleeding in the continued-treatment study. Rivaroxaban had non inferior efficacy for the primary outcome, 36 events (2.1%), versus 51 events (3.0%) with enoxaparin and vitamin K antagonists. The principal safety outcome occurred in 8.1% of the patients in each group. In the continued-treatment study, (EINSTEIN-EXTENSION trial) rivaroxaban had superiority efficacy, 8 events (1.3%) versus 42 with placebo (7.1%).Four patients in the rivaroxaban group had nonfatal bleeding (0.7%), versus none in the placebo group.
In the EINSTEIN-PE trial **(7) (NEJM 2012 vol. 366 pp. 1287-1297)** a randomized, open-label, event-driven, noninferiority trial including 4832 patients who had acute symptomatic pulmonary embolism with or without deep-vein thrombosis, rivaroxaban 15 mg. twice daily for 3 weeks, followed by 20 mg. once daily (2419 patients) was compared with standard therapy with enoxaparin

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at the dosage of 1.0 mg/kg of body weight twice daily followed by an adjusted-dose vitamin K antagonist (warfarin or acenocumarol) for 3, 6, or 12 months (2413 patients). Enoxaparin was discontinued when the International Normalized Ratio (INR) was =/> 2.0 for 2 consecutive days and the patient had received at least 5 days of enoxaparin treatment. The primary efficacy outcome was symptomatic recurrent venous thromboembolism. The principal safety outcome was major or clinically relevant nonmajor bleeding. Rivaroxaban was not inferior to standard therapy for the primary efficacy outcome, with 50 events in the rivaroxaban group (2.1%) versus 44 events in the standard-therapy group (1.8%). The principal safety outcome occurred in 10.3% of patients in the rivaroxaban group and in 11.4% of those in the standard-therapy group. Major bleeding occurred in 26 patients (1.1%) in the rivaroxaban group and in 52 patients (2.2%) in the standard-therapy group. (initial and long term treatment of pulmonary embolism. The bleeding rates were similar but, in the rivaroxaban group there were less major bleedings as intracranial and retroperitoneal bleedings. The investigators conclude that a fixed-dose regimen of rivaroxaban was noninferior to standard therapy for the initial and long-term treatment of pulmonary embolism and had a potentially improved benefit-risk profile. In another trial, a double-blind, placebo controlled trial, ATLAS ACS2-TIMI 51 trial, **(8) (NEJM 2012, vol.366 pp. 9-19)** 15,526 patients with a recent acute coronary syndrome received twice daily doses of either 2,5 mg. (5174 patients) or 5 mg. of rivaroxaban (5176 patients) or placebo (5176 patients) for a mean of 13 months and up to 31 months. The primary efficacy end point was a composite of death from cardiovascular causes, myocardial infarction, or stroke. It was co-administered with aspirin alone or with aspirin plus a thienopyridine, clopidogrel or ticlopidine. Patients were seen at 4 weeks, at 12 weeks and thereafter every 12 weeks. Patients who had an important gastrointestinal bleeding within 12 months before randomization, with a hemoglobin level of less than 10 gr. per deciliter or with a creatinine clearance of less than 30 ml. per minute at screening, with a previous intracranial hemorrhage, with a platelet count < 90000/mm3, with a previous ischemic stroke or a previous transient ischemic attack who were taking a double antiplatelet therapy, both aspirin and a thienopyridine were excluded. The study included patients with an ST-segment elevation myocardial infarction (STEMI) a non-ST-segment elevation myocardial infarction (NSTEMI), or unstable angina. Patients who were under the age of 55 years of age had either diabetes mellitus or a previous myocardial infarction in addition to the index event were also included. Rivaroxaban significantly reduced the primary efficacy end point, as compared with placebo, with rates of 8.9% and 10.7% respectively. With the twice-daily 2.5 mg. dose, compared with placebo the rates were 9.1% and 10.7% respectively and with the twice-daily 5 mg. dose, 8.8% and 10.7% respectively. The twice-daily 2.5 mg. dose of rivaroxaban reduced the rates of death from cardiovascular causes (2.7% versus 4.1%) and from any cause (2.9% versus 4.5%), a survival benefit that was not observed with the twice-daily 5 mg. dose. As compared with placebo, rivaroxaban increased the rates of major bleeding not related to coronary-artery bypass grafting (2.1% versus 0.6%) and intracranial hemorrhage (0.6% versus 0.2%) without a significant increase in fatal bleeding (0.3% versus 0.2%) or other adverse events. The twice-daily 2.5 mg. dose caused fewer fatal bleeding events than the twice-daily 5 mg. dose (0.1% versus 0.4%). In patients with a recent acute coronary syndrome, rivaroxaban reduced death from cardiovascular causes,myocardial infarction or stroke and increased major bleedings and intracranial hemorrhages, but not the risk of fatal bleedings. In the MAGELLAN study **(9) (NEJM**

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2013 vol.368 pp.513-523) a double blind trial, 8101 patients of 40 years of age or older who were hospitalized for an acute medical illness were randomized to receive as thromboprophylaxis rivaroxaban administered for an estended period, or subcutaneous heparin administered for a standard period, followed by placebo. Patients were randomized to receive enoxaparin at the dosage of 40 mg. once daily, for 10+/-4 days and oral placebo for about 35+/-4 days or to receive subcutaneous placebo for 10+/-4 days and oral rivaroxaban, 10 mg. once daily for about 35+/-4 days. The primary efficacy outcomes were the composite of asymptomatic proximal or symptomatic venous thromboembolism up to day 10 (noninferiority test) and up to day 35 (superiority test). The principal safety outcome was the composite of major or clinically relevant nonmajor bleeding. A primary efficacy outcome event occurred in 78 of 2938 patients (2.7%) in the rivaroxaban group and in 82 of 2993 patients(2.7%) in the enoxaparin group at day 10 and in 131 of 2967 patients (4.4%) who received rivaroxaban and in 175 of 3057 patients (5.7%) who received enoxaparin followed by placebo at day 35. A principal safety outcome event occurred in 111 of 3997 patients (2.8%) in the rivaroxaban group and in 49 of 4001 patients (1.2%) in the enoxaparin group at day 10 and in 164 patients (4.1%) and 67 patients (1.7%) in the respective groups at day 35.For the standard duration of therapy 10+/-4 days,rivaroxaban was noninferior to enoxaparin. Rivaroxaban administered for an extended duration 35+/-4 days was superior to enoxaparin administered for the standard standard duration 10+/-4 days followed by placebo. However the incidence of clinically relevant bleedings, and the incidence of major bleeding events,was significantly higher in the rivaroxaban group than in the enoxaparin group. For other details and critical review of these trials, see section on "Conclusions". In the X-VERT study, a prospective randomized trial **(10) European Heart Journal 2014 vol. 35 pp. 3346-3355),** Cappato and collegues used rivaroxaban in patients with atrial fibrillation undergoing elective cardioversion. They assigned 1504 patients to rivaroxaban (20 mg once daily, 15 mg if creatinine clearance was between 30 and 49 mL/min) or dose-adjusted vitamin K antagonists (VKAs) in a 2:1 ratio. They selected either an early (target period of 1-5 days after randomization) or delayed (3-8 weeks) cardioversion strategy. The primary efficacy outcome was the composite of stroke, transient ischaemic attack, peripheral embolism, myocardial infarction, and cardiovascular death. The primary efficacy outcome was major bleeding. The primary efficacy outcome occurred in 5 (two strokes) of 978 patients (0.51%) in the rivaroxaban group and in 5 (two strokes) of 492 (1.02%) in the VKA group. In the rivaroxaban group, four patients experienced primary efficacy events following early cardioversion (0.71%) and one following delayed cardioversion (0.24%). In the VKA group, three patients had primary efficacy events following early cardioversion (1.08%) and two following delayed cardioversion (0.93%). Major bleeding occurred in six patients (0.6%) in the rivaroxaban group and in four patients (0.8%) in the VKA group. About this trial there are some considerations that we are obliged to make. First of all, the most statistically efficient randomization ratio is 1:1 because it maximizes statistical power for a given total sample size. In this case, randomization of patients in a 2:1 ratio causes in any case a loss of the statistical power, although modest. This randomization is acceptable when may be more economically efficient to randomize fewer patients to the expensive treatment and more to the cheaper one, or when for ethical reasons as for example it happens in the oncology trials, it is necessary to allocate more patients in the arm of the treatment which probably will prolong the survival time and less patients in the

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placebo/medical care that will not prolong much their survival time. In this case, the authors randomized more patients in the rivaroxaban arm and this drug is much more expensive than warfarin. In addition rivaroxaban was never used in this indication and for this, for ethical reasons, was more reasonable to allocate more patients in the warfarin group than in the rivaroxaban group. If we look at the results of the primary efficacy outcomes expressed in percentage, the difference between the rivaroxaban group and the warfarin group may seem impressive because in the warfarin arm this percentage is exactly the double compared with that in the rivaroxaban group, but if we look at the number of the events, there were the same number of events (5 vs. 5) in the two groups, and considering that the number of patients in the rivaroxaban group was about the double of those included in the warfarin group, we can presume that probably we could find only 5 events less in the rivaroxaban arm. **(10) (European Heart Journal 2014 vol. 35 pp. 3346-3355)** On the other hand the same authors of the study caution that the trial was "underpowered to provide statistically rigorous results and was thus exploratory in nature" but in the same time, Dr. Cappato, the principal author of the study, said to "Heartwire" that X-VERT provides a high level of "solid, methodologically sound evidence" for clinicians who are already using NOACs in this setting instead of VKA. **(11) (Medscape, September 02, 2014)**

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Absorption and metabolism

Rivaroxaban is rapidly absorbed after oral administration and reaches maximum concentrations (Cmax) in about 2-4 hours after tablet intake. The oral bioavailability after a 2,5 or 10 mg. dose is high (80-100%), independently if the capsules are swallowed with or without food and for the 15 mg and 20 mg tablets when taken with food. The intake with food does not modify the AUC, (area under the curve) that is a method of measurement of the bioavailability of a drug based on a plot of blood concentrations sampled at frequent intervals, or the Cmax (maximum concentration) that is the maximum concentration that a drug achieves. For this, the patient can swallow rivaroxaban capsules of 2,5 and 10 mg. with or without food. The oral bioavailability after a dose of 20 mg. is about 66% in fasting conditions. In case of intake with food of a capsule of 20 mg. is described an increase of 39% of the AUC (area under the curve) in comparison with fasting intake. This means a complete absorption and an high oral availability. The rivaroxaban capsules of 15 and 20 mg. must be taken with food. The elimination of rivaroxaban from plasma occurs with a mean terminal half-life of 5-9 hours in young people and of 11-13 hours in old people. Its intra-individual variability is low, and its interindividual variability is moderate and is between 30-40%. Maximum inhibition of Factor Xa activity is achieved 1-4 hours after oral administration and the prolongation of the PT has a similar profile. Approximately one-third (36%) of the dose is eliminated as unchanged active drug in the urine. Of the 36% of the rivaroxaban dose eliminated in urine, active renal secretion accounts for 30% and glomerular filtration for 6%. Transporters involved in active renal secretion of rivaroxaban are P-glycoprotein (P-gp) and breast cancer resistance protein [BCRP (ABCG2)].
About 2/3 of the administered dose of rivaroxaban are metabolized mainly via oxidative degradation in the liver. Rivaroxaban is metabolized by several cytochrome P450 enzymes (CYP 3A4/5, CYP2J2) and CYP-independent mechanism. CYP3A4 accounts for approximately 18% and CYP2J2 for approximately 14% of total rivaroxaban elimination. In addition to this oxidative biotransformation, non-CYP-mediated hydrolysis of the amide bonds accounts for 14% of total rivaroxaban elimination. The resulting metabolites are eliminated both renally and via hepatobiliary route. In summary, about 90% of rivaroxaban dose is circulating in plasma as unchanged drug; no major or active metabolites are present. About 50% of rivaroxaban oral dose is cleared via hepatic biotransformation; CYP3A4 (18%), CYP2J2 (14%), CYP independent hydrolytic cleavage (14%). Rivaroxaban is excreted via feces and urine. In feces it is possible to found 28% of dose, 7% unchanged (potentially not absorbed) and 21% as metabolites. In urine is excreted about 66% of dose, 36% unchanged and 30% as metabolites. Elimination of rivaroxaban from plasma occurs with a terminal half-life of 5-9 hours in healthy subjects and 11-13 hours in elderly subjects. Investigations in healthy elderly subjects aged > 75 years showed that there was an increase in rivaroxaban exposure in this age group compared with younger subjects (aged 18-45 years). Elderly subjects exhibited higher plasma concentrations, with mean AUC (area under the curve) values being 41% higher in elderly than in younger subjects. These changes were mainly attributed to the reduced rivaroxaban clearance in the elderly subjects, arising from reduced renal and non-renal clearance. Because approximately one-third of the administered rivaroxaban dose is excreted renally as unchanged drug, renal insufficiency is expected to affect drug elimination. The AUC (area under the curve) increases by 44% with mild

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impairment (creatinine clearance 50-79 ml/mn), by 52% with moderate impairment (creatinine clearance 30-49 ml/mn) and 64% with severe impairment (creatinine clearance < 30 ml/mn). **(1) (Thrombosis Research 2011 vol.127 pp.497-504) (2) (Clinical Pharmacokinetics 2014 vol. 53 pp. 1-16)** In elderly people, because there is a decrease of creatinine clearance of about 7,5-8 ml/mn every decade after an age of thirty years, rivaroxaban plasma concentrations increase, causing an inhibition of Factor Xa activity increasing from 68% after a dose of 30 mg to 75% after 40 mg.and no further increase with a dose of 50 mg. **(1) (Thrombosis Research 2011 vol. 127 pp. 497-504)** In subjects with moderately impaired liver function (i.e. Child-Pugh classification B), the area under the plasma concentration-time curve (AUC) of rivaroxaban (10 mg single dose) is increased by 2.27 fold, causing an increase in FXa inhibition. **(3) (Clinical Pharmacokinetics 2013 vol. 52 (4) pp. 243-254)**

In patients in treatment with 20 mg. of rivaroxaban once daily the mean concentration of the drug after 2-4 hours is 215 ng/ml (22-535) and after 24 hours is 32 ng/ml (6-239). Rivaroxaban is a substrate of the efflux transporters P-glycoprotein (P-gp). It is bound to plasma proteins for about 92-95% and for this high binding, cannot be removed from plasma by dialysis. Volume of distribution at steady state is approximately 50 L (0.62 L/kg), indicating its low-to moderate affinity to peripheral tissues.

The pharmacogenetic impact on rivaroxaban is not well understood; however, its metabolism may provide some insight into potential interests for future studies. Rivaroxaban is metabolized by CYP3A4 and CYP2J2 enzymes as cited above, and is also a substrate for P-Glycoprotein systems. **(3) (Clinical Pharmacokinetics 2013 vol. 52 (4) pp. 243-254)** Because rivaroxaban is a P-glycoprotein substrate, it may be inferred that as with dabigatran, the ABCB1 gene which encodes for P-glycoprotein may have a role in rivaroxaban availability. A clinical trial, "New Oral Anticoagulant Drugs Dabigatran Etexilate and Rivaroxaban : Influence of Genetic Factors in Healthy Volunteers" is currently underway. **(https://clinicaltrials.gov/ct2/show/NCT01627665)** Another gene, the ABCG2 gene, which encodes for another efflux transport protein, the breast cancer resistance protein (BCRP) that belongs to the ATP-binding cassette family of efflux transporters may also have a role in rivaroxaban availability. Although drug interactions with BCRP are less likely as a large fraction of BCRP substrates and inhibitors are chemotherapeutic agents, unlike P-gp, there are common reduced function polymorphisms in BCRP (c.34 G > A, c.421 C > T) recognized for affecting the PK of its substrates. The authors postulate that homozygous carriers of BCRP variants concomitantly taking P-gp/CYP3A4 inhibitors likely possess the greatest risk for hemorrhage. This must be considered especially for patients with atrial fibrillation, the principal disease of the elderly with declining renal function, whereby comorbidities and concomitant use of P-gp/CYP3A4-inhibiting medications may be difficult to avoid. The highest at-risk subset of such patients would be those who carry loss-of-function polymorphisms in BCRP. Similar to other new anticoagulants agents, there is a need for post-marketing surveillance of adverse events, including analysis of bleeding events within the context of drug transporter pharmacogenetics, to exactly delineate rivaroxaban safety and efficacy. Future clinical studies are required to evaluate the combined effect of P-gp and BCRP in modulating rivaroxaban exposure in plasma, bleeding complications and anticoagulation efficacy. **(4) (Basic & Clinical Pharmacology & Toxicology 2013 vol. 112 pp. 164-170)** The interindividual variability in exposure/response of NOACs and bleeding risk associated with

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anticoagulation is a very important issue. In fact, also in a clinical trial setting with stringent enrolling criteria, the 1-dose-fits-all dosing regimen strategy did not appear successful for NOACs, likely due to the various clinical covariates that significantly affected extent of drug exposure and response. **(5) (Canadian Journal of Cardiology 2013 vol. 29 pp. S24-S33)** In addition,it has been demonstrated that dabigatran and rivaroxaban use outside of the clinical trial setting present large interindividual variability in concentration and response. **(6) Thrombosis and Haemostasis 2012 vol. 107 pp. 985-997) (7) (Journal of Thrombosis and Thrombolysis 2013 vol. 35 pp. 140-146)** For these considerations, dose-lowering adjustments in conjunction with anticoagulation monitoring should be used to ensure efficacy and safety of rivaroxaban.

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Dosage and drug interactions

The daily dosage of rivaroxaban depends from which patients we want to treat.
A dosage of 2,5 mg. twice daily co-administered with acetylsalicylic acid (ASA)75-100 mg. once daily, alone or with ASA plus clopidogrel 75 mg. once daily is indicated for the prevention of atherothrombotic events in adult patients after an acute coronary syndrome (ACS) with elevated cardiac biomarkers. Treatment should be evaluated in every patients weighing the risk for ischaemic events against the bleeding risk.
Normally the treatment is continuated for 12 months because there are not clinical trials in which was used for more time. Treatment should be started as soon as possible after stabilization of the acute coronary event, including revascularization procedures, at the time when parenteral anticoagulation therapy is normally discontinued.
A dosage of 10 mg. once daily is used as thromboprophylaxis in adult patients who have undergone a total knee or a total hip replacement surgery. The treatment must be started 6-10 hours after surgery, provided that haemostasis has been established. The duration of treatment is 10-14 days in case of knee replacement surgery and 28-35 days in case of hip replacement surgery. In these cases, initial dose should be taken at least 6 to 10 hours after surgery once hemostasis has been established.
A dosage of 15 mg. twice daily for the first 3 weeks and after a dosage of 20 mg. once daily for 3, 6, or 12 months is used in the treatment of patients with acute, symptomatic deep vein thrombosis (DVT) and in patients with acute symptomatic pulmonary embolism (PE) with or without deep-vein thrombosis. The duration of therapy must be individualized after assessment of the treatment benefit against risk of bleeding. The duration of 3 months is normally used when DVT or PE are a consequence of a known cause as recent surgery, trauma or immobilization. Longer durations are normally used when are present permanent risk factors or in case of idiopathic DVT or PE.
A dosage of 20 mg. once daily is used in the treatment of patients with non valvular atrial fibrillation who are at high risk score for stroke. Normally the drug is taken with the evening meal. Patients with elevated risk were those with a history of stroke, transient ischemic attacks, (TIA) or systemic embolism or at least two of the following risk factors : heart failure or a left ventricular ejection fraction of 35% or less, hypertension, an age of 75 years or more, or the presence of diabetes mellitus. (CHADS score of 2 or more) The mean CHADS score in the ROCKET-AF trial where rivaroxaban at 20 mg once daily was used in this category of patients was 3,5 **(1) (NEJM 2011 vol.365 pp. 883-891)**

CHADS SCORE

Congestive heart failure (any history) Points 1
Hypertension (prior history) Points 1
Age =/> 75 years Points 1
Diabetes Mellitus Points 1
Secondary prevention in patients with a prior ischemic stroke, a transient ischemic attack or a prior

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systemic embolism Points 2

Use in patients with a moderate risk for stroke was limited to just 10% of patients in the only clinical trial, the Rocket-AF trial, a double-blind trial, that tested 20 mg. of rivaroxaban in these patients.
This category was formed by patients with non valvular atrial fibrillation whithout a previous ischemic stroke, a transient ischemic attack, or a systemic embolism with no more than two risk factors.

Dosage modifications in case of renal insufficiency

In patients with deep vein thrombosis (DVT), pulmonary embolism (PE) and for reduction of the risk of recurrent DVT or PE , in case of creatinine clearance = / > 30 ml/mn, no dosage adjustment is provided in U.S. labeling, Canadian and European labeling.
With a creatinine clearance < 30 ml/mn must be avoided use of rivaroxaban

In patients with non valvular atrial fibrillation in the U.S., Canadian and European labeling, in case of creatinine clearance > 50 ml/mn no dosage adjustment is necessary.In the U.S. labeling, with a creatinine clearance of 15-50 ml/mn is recommended a dosage of 15 mg. once daily, and is recommended to avoid use of rivaroxaban with a creatinine clearance less than 15 ml/mn. On the contrary, in the Canadian and European labeling is recommended to use 15 mg. once daily with a creatinine clearance of 30-49 ml/mn and is recommended to avoid use of rivaroxaban already with a creatinine clearance less than 30 ml/mn.

For post-operative thromboprophylaxis, in case of creatinine clearance > 50 ml/mn and also for creatinine clearance between 30-50 ml/mn no dosage adjustment is necessary. In case of creatinine clearance less than 30 ml/mn, use of rivaroxaban must be avoided.

Dosage modifications in case of hepatic impairment

In patients with mild hepatic impairment no dosage adjustment is provided in manifacturer's labeling.
In patients with moderate or severe hepatic impairment and in patients with any hepatic disorders associated with coagulopathy, use of rivaroxaban must be avoided.

Also if it seems that body weight does not significantly influence rivaroxaban exposure, **(2) (Journal of Clinical Pharmacology 2007 vol. 47 pp. 218-226)** I recommend to use a determination of anti-FXa activity 3 and 24 hours after the oral administration of rivaroxaban by a calibrated chromogenic assay, or a rivaroxaban modified PT when we treat very thin (< 60 kg of weight) or very fat (> 110 kg of weight) patients.
I recommend also to use the same tests in elderly patients > 75 years and in patients with moderate renal insufficiency (creatinine clearance 30-50 ml/mn).

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Drug interactions

Rivaroxaban is a substrate of CYP3A4 and P-glycoprotein (P-gp) and its elimination is partially dependent on normal renal function. For this reason, the interaction with inhibitors and inducers of CYP3A4 and P-gp is of greater severity and significance in patients with renal impairment.
Rivaroxaban must not be used in patients in treatment with strong CYP3A4 and P-glycoprotein inhibitors as azole antimycotics (Systemic Ketoconazole, Itraconazole, Voriconazole, Posaconazole) that are associated with a 160% increase in rivaroxaban AUC (area under the curve) and a 70% increase in rivaroxaban Cmax, (maximum concentration) and HIV protease inhibitors (ritonavir, Indinavir, telaprevir) that are associated with a 150 % increase in rivaroxaban AUC and a 60% increase in rivaroxaban Cmax.
The association of rivaroxaban with clarithromycin is associated with only a 50% increase in rivaroxaban AUC because clarithromycin is a strong inhibitor of CYP3A4 but a less potent inhibitor of P-glycoprotein.
The administration of rivaroxaban with less potent inhibitors of CYP3A4 and P-gp, as systemic erythromycin, with a moderate CYP3A4 inhibitor as fluconazole must be done carefully only in case of renal impairment, because in patients with normal renal function the increase in Cmax is only 1.3 fold.
Caution must be used also when we use rivaroxaban with P-glycoprotein inhibitors as amiodarone, dronedarone, verapamil and quinidine because they increase the plasma concentration of rivaroxaban. If we consider that amiodarone, dronedarone and verapamil are the most important drugs that can be used in patients with non valvular atrial fibrillation, it easy to understand that also in these patients, we need to measure the anti-Factor Xa activity with a calibrated chromogenic assay or to avoid to use rivaroxaban considered also that the dosage of amiodarone can be different from one patient to another.
The administration of rivaroxaban with strong CYP3A4 and P-glycoprotein (P-gp) inducers as carbamazepine, phenytoin, systemic dexamethasone, phenobarbital, rifampicine, aminoglutethimide must be avoided because they decrease rivaroxaban AUC and Cmax. In fact, for example, when a single dose of 20 mg. of rivaroxaban was administered to patients taking 600 mg a day of rifampicin, there was a 50% decrease of rivaroxaban AUC and a 22% reduction of Cmax. With the concomitant administration of digoxin, omeprazol and atorvastatin were not observed clinically significant interactions.
Because of increased risk of bleeding, rivaroxaban must be used very carefully with drugs that inhibit platelet aggregation as aspirin, non steroidal anti-inflammatory drugs (NSAIDs) and thienopyridines as clopidogrel and ticlopidine.

For all these considerations we can only say that rivaroxaban presents less interactions than vitamin k antagonists, but in the same time, these interactions are clinically very important.

For conversion from warfarin to rivaroxaban, warfarin must be discontinued and must be initiated rivaroxaban as soon as INR falls to < 3.0 (U.S. labeling) or to = / < 2.5 (Canadian labeling)

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For conversion from rivaroxaban to vitamin K antagonists, because rivaroxaban affects INR, this test cannot be used during co-administration with warfarin for determining the appropriate dose of warfarin.If continuos anticoagulation is necessary, rivaroxaban must be discontinued, and begin both a parenteral anticoagulant and warfarin at the next scheduled dose of rivaroxaban,discontinuing the parenteral anticoagulant when INR reaches an acceptable therapeutic range.

For conversion from continuos infusion of unfractioned heparin, rivaroxaban must be initiated at the time of heparin discontinuation.

For conversion from rivaroxaban to continuos infusion of unfractioned heparin, the infusion must be initiated 24 hours after discontinuation of rivaroxaban.

For conversion from other anticoagulants as low molecular weight heparins,(LMWH) to rivaroxaban, the current anticoagulant must be discontinued and must be initiated rivaroxaban = / < 2 hours prior to the next scheduled dose of the discontinued anticoagulant.

For conversion from rivaroxaban to other anticoagulants, different from warfarin, the anticoagulant can be initiated 24 hours after discontinuation of rivaroxaban.
In any case, before initiating another anticoagulant drug, it is useful to evaluate rivaroxaban concentration by a calibrated chromogenic assay after 24 hours of the last administration of rivaroxaban.

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Adverse reactions

The most important adverse reaction as for all anticoagulants is bleeding. Major hemorrhages as intracranial, gastrointestinal, retinal hemorrhages ,epidural hematoma and minor hemorrhages have been described. Risk factors that increase possibility of important bleeding are congenital and acquired bleeding diseases, thrombocytopenia, (platelets < 90000 per cubic millimeter) a recent stroke, severe uncontrolled hypertension, severe renal impairment, recent major surgery, recent major bleeding as intracranial, gastrointestinal, pulmonary or intraocular bleeding, concomitant use of drugs that increase rivaroxaban Cmax (maximum concentration) (see section on dosage and drugs interactions) and concomitant use of drugs that inhibit platelet aggregation as aspirin, non steroidal anti-inflammatory drugs (NSAIDs), and thienopyridines, as clopidogrel and ticlopidine. At the moment, does not exist an antidote commercially available to neutralize the anticoagulant effect of rivaroxaban. It is not possible to use dialysis because of the strong binding of rivaroxaban with plasmatic proteins. Just recently on November 5, 2014, New England Journal of Medicine, published a letter on line in which a new small synthetic, water-soluble, cationic molecule PER977 (Arizapine) binds specifically to unfractioned heparin (UF) and to low molecular weight heparin (LMWH) through non-covalent hydrogen bonding and charge-charge interactions and binds in a similar way to the new oral factor Xa inhibitors, edoxaban, rivaroxaban and apixaban, and to the oral thrombin inhibitor dabigatran antagonizing their anticoagulant effect. **(1) (New England Journal of Medicine 2014, vol. 371 pp. 2141-2142)** For details, see review on Dabigatran, section on "Adverse reactions". Andexanet alpha, PRT064445, Annexa, (Portola Pharmaceuticals inc., San Francisco) is a modified recombinant protein derived from human coagulation factor X which can be used to antagonize the anticoagulant effect of direct inhibitors of factor Xa. The protein lacks a membrane-binding γ-carboxylic acid (GLA) domain and this is not catalytically active due to a serine---> alanine residue mutation (S419A) in the protease catalytic triad, which is typically composed of histidine, aspartic acid, and serine. Andexanet alpha was expressed in its functional or activated form in mammalian cell (Chinese Hamster Ovary culture). Andexanet alpha did not require any activation steps by factors VIIa from the extrinsic pathway or by factor IXa from the intrinsic pathway. In contrast to human anticoagulation factor Xa, andexanet alfa is unable to assemble into a prothrombinase complex to cleave prothrombin to thrombin and prothrombin fragments F1 and F2. The protein acts as a decoy for direct inhibitors of factor Xa, binding to these drugs in a dose-dependent manner and preventing the antidote-direct-FXa-inhibitor complex from acting on the coagulation cascade. Andexanet alpha could also bind to, and modulate the activity of the complex formed by ATIII and indirect FXa-inhibitors such as LMWH and fondaparinux. A study of rivaroxaban 0.23 micromoles in human and rat plasma found that at least 0.5 micromoles of andexanet alfa reversed most of the anticoagulant's anti-Xa activity. In addition researchers also tested the effects of andexanet alfa on LMWH and the pentasaccharide fondaparinux, both of which increase the activity of ATIII. They found that anti-Xa activity decreased dose-dependently and higher doses of andexanet alfa reduced blood loss to baseline. **(2) (Nature Medicine 2013 vol. 19 pp. 446-451)** A phase 3 study to evaluate the effect of andexanet in bleeding patients receiving FXa inhibitors just started (NCT02329327, status March 2015). The currently available data suggest that different

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doses of andexanet alpha seem to be required for the two direct FXa inhibitors apixaban and rivaroxaban. For the indirect FXa inhibitors, fondaparinux and the LMWHs likely again different doses are needed. This make it challenging to apply the appropriate dose under emergency conditions clinically. An important issue is that as with all modified proteins, immunogenicity might become a problem because although no anti-andexanet alpha antibodies have been reported yet, a modified human protein always bear the risk to induce antibodies. These antibodies do not cause any problem if they are directed against the modified protein, but if they cross react with the native endogenous protein, in this case they could lead to autoimmune FX deficiency. **(3) (Thrombosis and Haemostasis 2015 vol. 113 (5) pp. 931-942)** Therapy for severe hemorrhage include supportive therapies as mechanical compression, surgical hemostasis procedures, and transfusional support. Four factors prothrombin complex concentrates (PCC) and activated recombinant factor VII (rVIIa) did not reverse the rivaroxaban bleeding in a rabbit hemorrhagic model **(4) (Anesthesiology 2012 vol. 116 pp.1-9).** Four factors (PCC) in 12 normal non bleeding volunteers were able to reverse the prolongation of Prothrombin Time (PT) and the inhibition of endogenous thrombin potential caused by rivaroxaban. **(5) (Circulation 2011 vol. 124 pp. 1573-1579)** In another study, in 10 normal non bleeding volunteers 4 factor PCC and FEIBA were able to correct impaired thrombin generation caused by rivaroxaban in a dose dependent manner. **(6) (Thrombosis Haemostasis 2012 vol. 108 pp. 217-224)**

Other minor adverse reactions are gastrointestinal disturbs as diarrhea (5%), nausea (3%), dyspepsia (2%) and abdominal pain (2%). Dermatologic reactions are bruising (3%), pruritus (2%) and rash (2%).

Midterm analysis of a large prospective registry regarding use of Direct Oral Anticoagulants (DOACs) has shown that real-life hemorrhagic complications are similar to those seen in phase 3 drug trials. Pernod and collegues presented preliminary results regarding characteristics and care of major bleeding through a French prospective observational registry, the GIHP (French Working Group on Perioperatice Hemostasis) - NACO registry that started in 2013 in 32 emergency centres in France and Belgium. Although the rate of intracranial hemorrhage is lower, the risk for major bleeding is similar as for warfarin. Patients treated with DOACs and hospitalized for major bleeding or urgent surgery were registered. In a midterm analysis in June 2014, 339 patients were included, among which 219 for major bleeding.

Seventy-five patients were treated by dabigatran (150 mg. bid : 81%), and 142 by rivaroxaban (20 mg. od : 54%), and 2 patients were treated by Apixaban. Mean patient age was was 76.4 +/- 11 years and mean BMI was 26.3. Creatinine clearance was lower than 60 ml/min in 65% of patients. Eighty percent of patients were treated for AF, 20% for VTE. Among patients with AF, 67.2% hyad CHADS2 at 2 or less, 61.6% received concomitant administration of at least one drug interfering with cytochrome P (CYP) or P-glycoprotein (Pgp), and 26.9% received another antithrombotic drug at the time of bleeding. Major hemorrhagic sites were gastrointestinal (25%) and intracranial, either spontaneous (20%) or post trauma (15%). DOAC concentrations were determined in 46% of patients. Twenty percent of patients with major bleeding had a plasma concentration < 50 ng/ml. As expected, there was no relationship between drug concentrations and standard hemostatic tests such as prothrombin time and activated partial thromboplastin time. A total of 38.4% patients received Prothrombin Complex Concentrates (PCC) or activated Prothrombin Complex Concentrates

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(aPCC), and 25.7% benefited from additional procedures such as surgery, endoscopy, and embolization. A total of 42.2% of bleeding stopped completely after administration of clotting factors. At 30 days of follow-up, 9.1% of patients had suffered a cardiovascular event, and all-cause mortality was 14.2%. Pernod concluded that results of this midterm analysis of the GIHP NACO registry are consistent with phase III studies, with some particularities compared to clinical trials, especially in the use of PCC. The registry allows the analysis of specific population such as trauma patients and highlights the care of such major hemorrhages. **(7) (56th ASH Annual Meeting, San Francisco, December 6-9, 2014)**

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Characterization and care of major bleeding in patients treated by direct oral anticoagulants. https://ash.confex.com/ash/2014/webprogram/Paper68844.html

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Contraindications

a) Use of rivaroxaban is contraindicated in patients with significant hepatic disease, including moderate and severe hepatic impairment associated with coagulopathy and clinically relevant bleeding risk including cirrhotic patients with Child Pugh B and C .

Child-Pugh score

Total bilirubin (mg/dl)	< 2 mg/dl (1 point)	2-3 mg/dl (2 points)	> 3 mg/dl (3 points)
Serum albumin (g/dl)	> 3,5 g/dl (1 point)	2,8-3,5 g/dl (2 points)	< 2,8 g/dl (3 points)
PT INR	< 1,7 (1 point)	1,71-2,30 (2 points)	> 2,30 (3 points)
Ascites	None (1 point)	Mild (2 points)	Moderate to severe (3 points)
Hepatic encephalopathy	None (1 point)	Grade I-II (2 points)	Grade III-IV (3 points)

Points 5-6	Class A	One year survival 100%	two years survival 85%
Points 7-9	Class B	One year survival 81%	two years survival 57%
Points 10-15	Class C	One year survival 45%	two years survival 35%

b) Use is contraindicated in patients at increased risk of bleeding as patients with congenital or acquired bleeding disorders, with current or recent gastrointestinal ulceration, with vascular retinopathy, recent puncture of large vessels or organ biopsy, recent major hemorrhages, (intracranial, gastrointestinal, intraocular, pulmonary)recent major surgery, recent stroke, known or suspected oesophageal varices, arteriovenous malformations, vascular aneurysms, concomitant use of drugs that affects hemostasis (Unfractioned heparin, (UHF) low molecular weight heparins, (LMWH) Heparin derivatives, (fondaparinux)
other oral anticoagulants) except when we switch therapy to or from rivaroxaban.

c) In patients with severe renal insufficiency (creatinine clearance < 30 ml/mn) use of rivaroxaban is contraindicated.

d) In case of invasive procedures or surgical interventions, rivaroxaban must be discontinued at least 24 hours before the intervention if possible. We must also consider longer duration of treatment cessation with patients at higher risk of bleeding, or in case of major surgery where is required a better hemostasis.

e) Use of rivaroxaban is contraindicated in patients who are receiving concomitant systemic treatment with azole-antimycotics as ketoconazole or HIV protease inhibitors as ritonavir, because these drugs are strong inhibitors of CYP3A4 and P-glycoprotein (P-gp) and because rivaroxaban is a substrate of CYP3A4 and (P-gp). (see section on dosage and drug interactions) In these cases rivaroxaban plasma concentrations increase and can eventually cause an important bleeding.
Use in patients who are in treatment with strong inducers of CYP3A4 and P-gp as carbamazepine,

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phenytoin and rifampicin must be avoided because rivaroxaban plasma concentrations can decrease to a clinically relevant degree causing an increase of thrombotic risk.

f) Rivaroxaban use in patients with severe hypertension not well controlled must be avoided.

g) Use of rivaroxaban is contraindicated in women who are pregnant, and therefore, in women in fertile age, before starting its use, a pregnancy must be excluded.

h) I do not recommend use of rivaroxaban in patients = / > 80 years because the higher risk of bleeding in these patients, especially in those with low body weight and moderate renal impairment, and because at the moment we do not have clinical trials in which rivaroxaban has been used in very elderly people.

i) Also if in some papers, sponsored by rivaroxaban manufacturer, **(1) (The Journal of Clinical Pharmacology 2007 vol. 47 pp. 218-226)** is described that extreme body weight (=/ < 50 kg. and =/ > 120 kg.) does not affect in a relevant clinical manner the rivaroxaban Cmax, (maximum concentration) I do not recommend its use in these patients until we will not gain more clinical experience treating them in the next years.

l) Use of rivaroxaban is contraindicated in patients with thrombocytopenia (platelets < 90000 per cubic millimeter)

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1) Kubitza Dagmar, Becka Michael, Zuehlsdorf Michael et al. : Body weight has limited influence on the safety, tolerability, pharmacokinetics, or pharmacodynamics of rivaroxaban (BAY 59-7939) in healthy subjects. The Journal of Clinical Pharmacology 2007; 47, issue 2 : 218-226

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Laboratory tests

Measurements of the anticoagulant effect of rivaroxaban is indicated in many clinical situations :

a) Suspected overdosage due to excessive drug intake or decreased drug clearance

b) Unexplained bleeding in patients taking the drug

c) Thrombotic events during the treatment, to assess patients compliance

d) In patients with moderate renal insufficiency, (creatinine clearance 30-50 ml/mn) because they have an increase in rivaroxaban plasma concentration

e) In patients with liver impairment because rivaroxaban is metabolized by the liver

f) Before emergency surgery

g) Before non urgent surgery or invasive procedure when the patient has taken rivaroxaban in the previous 24-48 hours, or longer, if the patient has moderate renal or liver impairment

h) In patients taking the drug presenting at the emergency room with thrombotic or hemorrhagic events

i) In patients requiring anticoagulation reversal because of life-threatening hemorrhages

l) In patients taking P-glycoprotein inhibitors (P-gp) as verapamil, amiodarone, dronedarone, quinidine to identify a supratherapeutic level of rivaroxaban. Measurement of rivaroxaban anticoagulant effect is also indicated in patients taking moderate inhibitors of CYP3A4 and P-gp as systemic erythromycin, fluconazol but with moderate renal insufficiency. Use of rivaroxaban with strong inhibitors of CYP3A4 and P-gp as azole antimycotics (ketoconazole) and HIV protease inhibitors as ritonavir must be avoided. Also use with strong CYP3A4 and P-gp inducers as carbamazepine, phenytoin anf systemic dexamethasone is contraindicated. (see section on dosage and drug interactions)

m) In patients with a stroke taking rivaroxaban, we cannot perform thrombolysis if we do not know if they are or they are not anticoagulated.

n) Identification of supratherapeutic or sub-therapeutic level in very thin or very fat patients respectively, also if some papers describe that body weight does not significantly influence rivaroxaban exposure **(1) (Journal of Clinical Pharmacology 2007 vol. 47 pp. 218-226)** (see section on dosage and drug interactions)

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o) In elderly patients, because they have more bleeding episodes, are more prone to fall, and normally have more renal impairment than younger people.

Laboratory results are dependent on when the last dose of drug was taken. Peak plasma levels of rivaroxaban are reached in about 3 hours after ingestion. At the dose of 20 mg. daily, used in atrial fibrillation for stroke prevention, the Cmax of rivaroxaban after 2-4 hours is about 290 ng/ml with a range of 177-409 ng/ml, and the Ctrough (lowest concentration) after 24 hours is about 32 ng/ml with a range of 5-155 ng/ml. In patients receiving rivaroxaban 20 mg. once daily for treatment of Deep Vein Thrombosis (DVT), geometric mean concentrations after 2-4 hours were 215 ng/ml (22-535 ng/ml) and after 24 hours were 32 ng/ml (6-239 ng/ml). **(2) (Journal of Thrombosis and Haemostasis 2013 vol. 11 suppl. 1 pp. 122-128) (3) (Journal of Thrombosis and Haemostasis 2013 vol. 11 pp.756-760)**
The PT and APTT tests are the most used tests to study coagulation in many laboratories. In patients who are taking rivaroxaban, the PT is more suitable than APTT for assessing the intensity of anticoagulation because of its higher sensitivity and its linearity to different concentrations of rivaroxaban. **(2) (Journal of Thrombosis and Haemostasis 2013 vol. 11 suppl. 1 pp. 122-128)** In the same time, there is marked variability between PT reagents and for this, each laboratory must determine the sensitivity of its own PT assay to rivaroxaban concentrations using commercially available calibrants. The commercial PT reagent that is more sensitive than others to rivaroxaban is Neoplastin Plus and the results must be expressed in seconds, not converted to International Normalized Ratio Values, (INR) because INR increases the discrepancy between PT results. The APTT is sensitive to rivaroxaban with a curvilinear concentration-response relationship and its results are influenced by coagulometers and reagents that some time are completely insensitive with no prolongation of APTT also at rivaroxaban Cmax. **(3) (Journal of Thrombosis and Haemostasis 2013 vol. 11 pp. 756-760)**
Also if we can use the PT expressed in seconds to measure rivaroxaban concentration, we must consider that there will be important differences in responsiveness using different thromboplastins .
The calibration of a thromboplastin test must be done against an international reference thromboplastin.
The PT results are plotted on a double-log paper with the reference samples on the perpendicular axis,Y axis, and the plasma tests on the horizontal axis, X axis. The use of the double-log paper removes the necessity to derive the log for each PT result. A line of best fit (by orthogonal regression analysis) is drawn and the slope of this line is the ISI (International Sensitivity Index).The slope is measured as the tangent of the angle that the line forms with the horizontal axis. In case of the line at 45 degrees the tangent is 1 and therefore ISI is 1 (same sensitivity). ISI more than 1 have less sensitivity than the standard and vice versa. **(4) (Guida alla terapia con anticoagulanti orali 2013 pp. 113-119)** The International Normalized Ratio (INR) is the PT ratio of a test sample compared to a normal PT, corrected for the ISI of the thromboplastin used in the test.

$$INR = \left(\frac{PT\ patient\ plasma}{PT\ normal\ plasma}\right)^{ISI}$$

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An international sensitivity index (ISI), valid for rivaroxaban (ISI Rivaroxaban) can be determined by plotting on a double-log paper the PT results for a normal plasma spiked with increasing concentrations of rivaroxaban obtained with the working thromboplastin (horizontal axis, X axis) versus a standard thromboplastin (perpendicular axis, Y axis). The Rivaroxaban ISI is the slope of the orthogonal regression line. The between thromboplastin variability according to the results expression in INRrivaroxaban is low, with a CV (coefficient of variation) of 2,1% only. The INRrivaroxaban is calculated in the same manner as we have seen before.

ISI Rivaroxaban

INRriv.=(PT rivaroxaban plasma/PT normal plasma)

The PT values increase increasing dosage of rivaroxaban and the linearity is excellent for many thromboplastins. The responsiveness to rivaroxaban is highest for Neoplastin-Plus. **(5) (Journal of Thrombosis and Haemostasis 2011 vol. 9 pp. 226-228)** This modified PT is a readily available method for determining the relative degree of anticoagulation in patients taking rivaroxaban.

The thrombin time (TT), the diluted thrombin time (dTT) , the Ecarin clotting time (ECT), the reptilase time, and the Clauss fibrinogen assay, are not affected by rivaroxaban. Rivaroxaban has no effect on D-dimer assay, but false low levels of D-dimer can be found because of inhibition of thrombin generation in patients treated with rivaroxaban. **(2)(Journal of Thrombosis and Haemostasis 2013 vol.11 suppl. 1 pp. 122-128)** Determination of antithrombin (AT) results higher than the expected value, if we use activated factor X (FXa) as target enzyme. Also measurements of activated protein C resistance (APCR), of protein C (PC) and of protein S (PS) should be affected by rivaroxaban. **(6)(Seminars in Thrombosis and Hemostasis 2012 vol. 38 pp. 586-592)** Increasing rivaroxaban concentrations increases the dilute russel's viper venom time (dRVVT) ratio and a linear response is obtained over a broad range of concentrations. Similar results were obtained with the confirmation test. Other clotting tests as the one-step heparin clotting assay kit (Hep Test) and the prothrombinase-induced clotting time (PiCT) with shortened incubation times, can be also used to measure the anticoagulant effect of rivaroxaban. These last two methods do not require rivaroxaban calibrators differently from anti-Fxa chromogenic assays. **(7) (Thrombosis and Haemostasis 2010 vol. 103 pp. 815-825)** The responsiveness to rivaroxaban (ability to increase the baseline clotting time increasing rivaroxaban concentrations) is high for HepTest, dRVVT, **(6) (Seminars in Thrombosis and Hemostasis 2012 vol. 38 pp. 586-592)** and also for PiCT.
A concentration of rivaroxaban of 0,2 microg./mL which corresponds to one single dose of 10 mg., prolongs about 3 times the basal shortened incubation time HepTest, about 2,5 times the dRVVT and also about 2,5 times the shortened incubation time PiCT.

Rivaroxaban concentrations can be determined by a calibrated anti FXa assay by the use of chromogenic substrates. This assay must be calibrated with rivaroxaban calibrators and controls, and the strong correlation between rivaroxaban levels and anti-FXA activity in a chromogenic assay, make this test, when available, the most suitable test for quantitation of rivaroxaban and other FXa

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inhibitors as apixaban. **(2) (Journal of Thrombosis and Haemostasis 2013 vol. 11 suppl. 1 pp. 122-128)** The inter-laboratory precision of the measurement was tested in 24 centres in Europe and North America and when were used Rotachrom reagents, (modified STA Rotachrom assay) there was a lower inter-laboratory variation of the measurement, mainly at the lowest concentrations. **(8) (Thrombosis and Haemostasis 2012 vol. 107 pp.379-387)** Other specific and calibrated chromogenic assays with rivaroxaban calibration and control plasmas, commercially available, are COAMATIC Heparin and Technochrom anti-Xa.

At the moment there is a debate on which test to use to evaluate rivaroxaban concentrations, if to use an anti-factor Xa assay or a rivaroxaban standardized PT test. In favour of an anti-factor Xa assay has been recently published a paper **(9) (Journal of Thrombosis and Haemostasis 2013 vol.11 pp.579-580)** in which the author remarked the fact that the presence of anti-Xa activity is very rare in untreated patients, whereas several morbidities can influence the PT, which is a non specific test and, also if a modification of the International Sensitivity Index of different thromboplastin reagents has been proposed, further studies with plasma patients are required, and a therapeutic range expressed in INR rivaroxaban has to be determined. Another observation made by the author in favour an anti-Xa assay,was the fact that in case of patients switching from warfarin to rivaroxaban, the interpretation of the INR can be difficult, because both drugs affect the PT/INR. Moreover, rivaroxaban plasma concentrations measured by anti-FXa activity when rivaroxaban calibrators and controls are used, were comparable to rivaroxaban concentrations measured by HPLC.

On the contrary,in another paper **(10) (Journal of Thrombosis and Haemostasis 2013 vol. 11 pp. 576-578)** the author is in favour of a rivaroxaban standardized PT test to evaluate rivaroxaban plasma concentrations. The major advantages compared to an anti-Xa assay are its possible availability to emergency departments of large and small hospitals 24 hours a day and 7 days a week, and the fact that can be performed even by unskilled medical technologists. There is a linearity of dose response, and an adequate responsiveness especially at high rivaroxaban concentrations that are the concentrations we normally can have when the patient in treatment with rivaroxaban is bleeding, and therefore the test is required. In this paper the author hypothesized that the between thromboplastin variability of the PT for rivaroxaban could be minimized by a new scale of values called the rivaroxaban-standardized PT ratio (Riva-PT-ratio) by using the equation :

$$\text{Riva - PT - ratio} = [\text{PT patient} / \text{PT normal}]^{\text{Riva-SI}}$$

where Riva-SI is determined by orthogonal regression analysis as the slope of the calibration curve constructed by plotting, on a double-log scale, PT results for a normal plasma spiked with increasing concentrations of rivaroxaban obtained with the working thromboplastin (horizontal axis, X axis) versus a standard thromboplastin (perpendicular axis, y axis). **(10) (Journal of Thrombosis and Haemostasis 2013 vol. 11 pp. 576-578)**. The Riva-SI value could be determined by the manifacturers by testing with their thromboplastins and with the international standard for thromboplastin a set of rivaroxaban-spiked plasmas and could be reported in the package inserts of their thromboplastins.

The author concludes that the Rivaroxaban PT should be the preferred test by which to assess the anticoagulant effect of rivaroxaban because it can be readily available also in small hospitals,

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because is cheap, is adequately responsive to rivaroxaban and can be easily standardized.
In my opinion I agree with this last author especially if we consider the easy availability in every laboratory.
Herrmann et al. studied 17 patients receiving dabigatran 150 mg mg. twice daily for non-valvular atrial fibrillation and 15 patients receiving rivaroxaban 10 mg daily for the prevention of deep venous thrombosis after hip or knee replacement surgery. The effects of Prothrombin Complex Concentrate (PCC), Factor VIII Inhibitor By-passing Activity (FEIBA) and recombinant activated factor VII (rVIIa) were tested by reversal of abnormal thrombin generation using the CAT. Concentrations added ex vivo were chosen to reflect doses normally given in vivo. Dabigatran significantly increased the dynamic parameters of the TEG and ROTEM and the lag time of the CAT. It significantly reduced the endogenous thrombin potential (ETP) and reduced the peak height of the CAT. Rivaroxaban did not affect the TEG and ROTEM parameters but did increase the lag time and reduce ETP and peak height of the CAT. For both drugs, these parameters were significantly and meaningfully corrected by PCC and FEIBA and to a lesser but still significant extent by rVIIa. However we cannot be certain if this in vitro effect corresponds to a clinical in vivo effect. In fact for example, PCC reversed rivaroxaban in vitro in a rabbit model but did not reverse bleeding. **(11) (Thrombosis and Haemostasis 2014 vol. 111 pp. 989-995)** From their results PCC and FEIBA seem to be the most effective nonspecific haemostatic agents in vitro based on the CAT parameters to measure effect and may be helpful in designing a reversal strategy.
Gosselin and collegues evaluated commercial drug-specific calibrators for determining PT and APTT reagent sensitivity to dabigatran and rivaroxaban. The dabigatran and rivaroxaban calibrator material over-estimated drug sensitivity for all PT reagents when compared to sensitivity data calculated based on drug levels obtained by LC-MS/MS from patient samples. The authors conclude that drug-specific calibrators overestimated reagent sensitivity which may understimate in vivo drug concentration in a given patient. Further studies are required to assess whether this method of determining relative sensitivity of DOAC on routine coagulation assays should be recommended. **(12) (Thrombosis and Haemostasis 2015 vol. 113 pp. 77-84)** In a nationwide Belgian survey Van Blerk Marjan et al. showed the influence of dabigatran and rivaroxaban on routine coagulation assays and the results of this study indicate that the sensitivity to dabigatran and rivaroxaban does not only depend on the reagent but also on the instrument used. Their data demonstrate that there is a wide variation in responsiveness between reagent/instrument combinations but that the agreement between laboratories using the same reagent/instrument combination is good. **(13) (Thrombosis Haemostasis 2015 vol. 113 pp. 154-164)**

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Conclusions

Rivaroxaban has been approved for prevention of thromboembolism (VTE) in patients who have undergone a total knee or a total hip arthroplasty, in prevention of stroke and systemic embolism in patients with non valvular atrial fibrillation with one or more risk factors (see section on "indications"), for treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE),and for prevention of recurrent deep vein thrombosis and pulmonary embolism after an acute deep vein thrombosis. Recently rivaroxaban has also been approved by the European Medical Agency (EMA) but not by the FDA and in Canada for the prevention of atherothrombotic events in patients after an acute coronary syndrome (ACS) with elevated biomarkers. In acutely ill medical patients rivaroxaban 10 mg. once daily, was compared to enoxaparin 40 mg. once daily for thromboprophylaxis, but if rivaroxaban was not inferior to enoxaparin for standard duration therapy of 10+/-4 days and if was superior to enoxaparin for a prolonged therapy of 35+/-4 days , in the rivaroxaban group there was a significant increased number of major bleeding episodes, so we cannot consider to use rivaroxaban in this indication.
The results of the 4 RECORD trials (see section on "indications") in which rivaroxaban was compared to enoxaparin for thromboprophylaxis in patients who have undergone a total hip replacement surgery, (RECORD 1 and RECORD 2 trials) and in patients who have undergone a total knee surgery, (RECORD 3 and RECORD 4 trials) demonstrated a superiority of rivaroxaban over enoxaparin for the prevention of deep vein thrombosis, nonfatal pulmonary embolism and death from any cause. The rates of major and minor bleedings were similar in the rivaroxaban group and in the enoxaparin group. Considering these results, we could use rivaroxaban in this particular group of patients, but in any case, I recommend the use of a calibrated chromogenic anti-Xa assay (see section on "laboratory tests") at the beginning of therapy, after 3 hours and after 24 hours the administration of rivaroxaban. In case the patient is taking some drugs that interfere with rivaroxaban concentration, we must repeat the chromogenic assay after some days to evaluate possible supra-therapeutic or sub-therapeutic levels. Clearly we can use rivaroxaban in these patients only in the hospitals that have a laboratory that can evaluate rivaroxaban concentrations using a calibrated chromogenic assay that is the most reliable test or, alternatively, a modified rivaroxaban PT.
In the EINSTEIN-DVT trial **(1) (NEJM 2010 vol. 363 pp. 2499-2510)**,for treatment of acute deep vein thrombosis, (DVT) rivaroxaban at a dosage of 15 mg. twice daily for 3 weeks, followed by 20 mg. once daily, was compared to subcutaneous enoxaparin at a dosage of 1.0 mg/kg of body weight twice daily, and warfarin or acenocumarol for 3, 6, or 12 months. Enoxaparin was discontinued when the International Normalized Ratio (INR) was = / > 2.0 for 2 consecutive days and the patient had received at least 5 days of enoxaparin treatment. The therapeutic INR range was from 2.0 to 3.0. In this study, rivaroxaban had non-inferior efficacy with respect to the recurrent venous thromboembolism and similar rates of clinically relevant non major bleedings, and similar rates of major bleedings.
In the EINSTEIN-EXTENSION trial **(1) (NEJM 2010 vol. 363 pp. 2499-2510)** rivaroxaban at a dosage of 20 mg. once daily, was compared to placebo for an additional 6 or 12 months in patients

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who had completed 6 to 12 months of treatment for venous thromboembolism. In this study rivaroxaban had superior efficacy with respect to the recurrent venous thromboembolism, 1.3% compared to 7.1% in the placebo group, but more clinically relevant nonmajor bleedings, 5.4% compared to 1.2% in the placebo group, and four patients in the rivaroxaban group had non fatal major bleedings.
For what concerns the EINSTEIN-DVT trial,in the vitamin K antagonists group,the INR was in the therapeutic range (2.0 to 3.0) just for 57.7% of the Time (TTR), above 3.0 for 16.2% of the time, and below 2.0 for 24.4% of the time. The percentage of time within the therapeutic range varied from 54.1% in the first month to 66.4% in the tenth month.
If we consider that in Italy in the Thrombosis and Haemostasis Centers of the **FCSA (Federation for the diagnosis of thrombosis and the surveillance of antithrombotic therapies)**, in many Thrombosis and Haemostasis Centers in many west european countries, the majority of patients have the INR in the Therapeutic Range (TTR) for about 70% of the time, we understand that to decide if rivaroxaban is non inferior to enoxaparin followed by a vitamin K antagonist in the treatment of deep vein thrombosis to prevent recurrent venous thromboembolism, we need more clinical trials not sponsored by the drug manufacturer in which, however, the INR must have a TTR >/= 70%. Again, we must consider that in the EINSTEIN-DVT trial, patients treated with vitamin K antagonists had the INR below 2.0, for 24.4% of the time, that is a high percentage of time below the therapeutic range. For these reasons, at the moment we are not able to know if really rivaroxaban compared to enoxaparin followed by a vitamin K antagonist is non inferior in treating these patients in many west countries where we have a good clinical and laboratory control of the anticoagulant therapy with vitamin K antagonists. On the other hand, at the moment we do not have an antidote commercially available, although a 4 factor unactivated prothrombin complex concentrates can be used to reverse the anticoagulant effect of rivaroxaban. **(2)(Circulation 2011 vol. 124 (14) pp. 1573-1579) (3) (Thrombosis and Haemostasis 2012 vol. 108 (2) pp. 217-224)** Just recently, Siegal and collegues reported the results of two randomized, double blind, placebo-controlled studies of Andexanet Alfa, a novel antidote to direct factor Xa inhibitors, to neutralize the anticoagulant effect of apixaban (ANNEXA-A) and of rivaroxaban (ANNEXA-R). Andexanet alfa is a factor Xa protein modified by elimination of the gla residues and inactivation of its catalytic site by amino acid substitution. The studies were performed in healthy volunteers between 50 and 75 years of age who received the standard dose of apixaban or rivaroxaban to achieve steady-state concentrations, followed by treatment with andexanet. Healthy volunteers were given 5 mg of apixaban twice daily or 20 mg of rivaroxaban daily. For each factor Xa inhibitor, a two-part randomized placebo controlled study was conducted to evaluate andexanet administered as a bolus or as a bolus plus a 2-hour infusion. The primary outcome was the mean percent change in anti-factor Xa activity, which is a measure of factor Xa inhibition by the anticoagulant. After 2-5 minutes the andexanet intravenous administration, was obtained a significant reduction of anti-factor Xa activity and of mean plasma concentrations of unbound apixaban and rivaroxaban. However an increase in both measures was observed within 15 minutes after the completion of the bolus. For this reason was necessary a bolus plus a 2-hour infusion to achieve sustained suppression of anti-factor Xa activity and of concentration of the anticoagulants in plasma. In the rivaroxaban group was used twice the dose that was given in the apixaban study and this choice was based on

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pharmacokinetic and pharmacodynamic models that incorporated preclinical data from animal models and phase 2 dose-ranging studies. Adverse events and thrombotic complications were not observed in healthy volunteers (n=101) who received andexanet alfa. Nonneutralizing antibodies appeared in 17% of volunteers. The effect of these antibodies on the pharmacology of andexanet if subsequent events require readministration is unknown. Although the concentration of apixaban or rivaroxaban could be measured immediately and the dose of andexanet could be calculated for each anticoagulant, it is unknown whether andexanet use would improve outcomes for patients with major bleeding. For this reason, at the moment, the ANNEXA-4 phase 3b-4 study (ClinicalTrials.gov.number, NCT02329327) is evaluating the efficacy and safety of andexanet in patients with factor Xa inhibitor-associated acute major bleeding. In these studies were also observed transient increases in D-dimer amd prothrombin fragments 1 and 2, with no clinical thrombotic events and without high levels of thrombin generation. These increases may be related to the binding of andexanet to tissue factor pathway inhibitor (an endogenous inhibitor of factor Xa) in a manner analogous to its binding to factor Xa. The fact that a tissue factor pathway inhibitor-binding antibody, concizumab, showed elevations in prothrombin fragments 1 and 2 and D-dimer without evidence of thrombotic events support the hypothesis that the elevations of these markers are not necessarily associated with thrombotic events. **(4) (New England Journal of Medicine 2015 vol. 373 pp. 2413-2424); (5) (New England Journal of Medicine 2015 vol. 373 pp. 2471-2472)** Cirapantag (PER977) is a synthetic water-soluble compund that binds directly to unfractioned and low molecular weight heparin by charge-charge interaction (non-covalent) preventing the anticoagulants from binding to their endogenous targets. Cirapantag also binds to the target-specific IIa and Xa inhibitors such as dabigatran, rivaroxaban, apixaban, and edoxaban removing them or preventing them from binding to their respective targets. In animal studies, a single dose of ciraparantag reversed anticoagulation and reversed anticoagulation and reduced bleeding with all the above cited anticoagulants. **(6) Journal of Thrombosis and Thrombolysis 2016 vol. 41 pp. 248-252)** In a phase I trial of 180 healthy volunteers, ciraparantag immediately reversed anticoagulation induced by a 60 mg dose of edoxaban
following a 100 or 300 mg dose. reversal was sustained over the next 24 hours without further treatment. The drug was
well tolerated with mild side effects. **(7) (New England Journal of Medicine 2014 vol. 339 pp. 2141-2142)**
For what concerns the EINSTEIN-EXTENSION trial, there was a significant reduction of venous thromboembolic events, but there was also a significant increase of bleeding episodes also if these episodes did not cause any death. The most important limitations of this study are the small number of patients, 602 in the rivaroxaban group, and 594 in the placebo group, and the fact that some particular populations of patients as the elderly, patients with cancer, patients with renal insufficiency and morbidly obese patients, are scarcely represented in this trial. **(8) (Expert Revue of Cardiovascular Therapy 2011 vol.9 pp. 841-844)** For these reasons, also in this case, until we will not have other larger clinical trials possibly not sponsored by the drug manufacturer, we are not able to decide if rivaroxaban is really superior to placebo for an additional 6 or 12 months in patients who had completed 6 to 12 months of treatment for venous thromboembolism.
In the EINSTEIN-PE trial **(9) (NEJM 2012 vol. 366 pp. 1287-1297)** rivaroxaban at a dosage of 15

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mg. twice daily for 3 weeks, followed by 20 mg. once daily, was compared to enoxaparin at a dosage of 1.0 mg/kg of body weight twice daily, with warfarin or acenocumarol for 3, 6, or 12 months. Enoxaparin was discontinued when the International Normalized Ratio (INR) was = / > 2.0 for 2 consecutive days and the patient had received at least 5 days of enoxaparin treatment. In this study rivaroxaban had non inferior efficacy with respect to the recurrent venous thromboembolism, similar clinically relevant nonmajor bleeding episodes and less major bleeding episodes, 1.1% with rivaroxaban and 2.2% with standard therapy. The INR was in the therapeutic range (2.0 to 3.0) for 62.7% of the time, was above 3.0 for 15.5% of the time, and below 2.0 for the 21.8% of the time. The percentage of time within the therapeutic range, ranged from 57.8% in the first month to 72.7% in the eleventh month. Again in this trial, patients treated with a vitamin K antagonist, had the INR below 2.0 for 21.8% of the time, that is a high percentage of time below the therapeutic range.
Also in this case, as for the EINSTEIN-DVT trial, to decide if rivaroxaban is non inferior to standard therapy for the treatment of pulmonary embolism in many anticoagulation clinics of many west countries, we need more clinical trials not sponsored by the drug manufacturer, in which patients treated with enoxaparin and vitamin K antagonist must have the INR in the therapeutic range for > / = 70% of the time also during the first months of treatment and considering that at the moment we do not have an antidote commercially available.
In many developing countries that do not have a good clinical and laboratory control of the oral anticoagulant therapy, with many patients with the INR in the therapeutic range for a low percentage of the time, rivaroxaban can be useful in treating these patients. For Anticoagulation Clinics with a TTR < 60%, we must try to ameliorate their controls of the anticoagulation therapy of vitamin K antagonists by periodic laboratory control tests and by self monitoring, or we can refer patients to centres with a better TTR when possible. The use of rivaroxaban may be restricted to particular situations when for example the patient is not able to arrive to the centre for many reasons, when he refuses blood drawings to perform laboratory controls, in patients at high risk of intracerebral hemorrhage (ICH) or in patients who during treatment with a vitamin K antagonist had an ICH and after need to restart an anticoagulation therapy, due to the high risk of recurrence or demonstrated by the CHIRONE study (see at the end of the section).
Another important consideration is that in these trials in which a fixed-dose regimen of rivaroxaban was used, was never executed a laboratory monitoring. In my opinion, although in some papers was stated that rivaroxaban has predictable pharmacokinetics and pharmacodynamics profiles in healthy individuals **(10) (European Journal of Clinical Pharmacology 2005 vol. 61 pp. 873-880)** and in patients undergoing total hip or total knee arthroplasty, **(11) (Clinical Pharmacokinetics 2008 vol.47 pp.203-216)** we need to execute a laboratory control using a calibrated chromogenic anti-Xa assay at the beginning of therapy, after 1 week, 3 hours and 24 hours after the administration of rivaroxaban, just to know if in that patient we will obtain the optimal therapeutic level . On the other hand, recent evidences showed a high intra and inter-individual variability of Direct Oral Anticoagulants plasma concentrations **(12) (Canadian Journal of Cardiology 2013 vol. 29 pp. S24-S33)** (see review on "Dabigatran") In a recent paper apixaban and rivaroxaban plasma concentrations and their anticoagulant effects were evaluated in 102 patients undergoing total hip or knee replacement. Half of them received rivaroxaban and the other half received apixaban. Drug-circulating concentrations were functionally measured by an

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anti-Xa test and compared with the results obtained on the same blood samples,using liquid chromatography tandem mass spectometry (LC-MS/MS) validated according to the FDA. The correlation of the functional anti-Xa results with the mass spectometry measurements was very satisfactory, but the rivaroxaban and apixaban results in this study in patients at T0, and in 50 other untreated patients were spread over a 0-30 ng/ml range. In this study, although anti-Xa rivaroxaban and apixaban determinations were very reliable in the 30-600 ng/ml range, they cannot be trusted to recognize a physiological versus a therapeutic anti-Xa effect in the 0-30 ng/ml zone, in which case LC-MS/MS is more reliable. Blood samples were taken the day before surgery (T0) then about 2 hours after drug ingestion on the day after surgery (T1), on day 4 (T2), and day 7 (T3) after surgery. To obtain a residual concentration (Ctrough) after a treatment period of about a week, day 8 (T4), withdrawl was performed just before the morning drug ingestion. T0 - T4 are referred as "times of withdrawls". Residual concentrations were very low in all patients receiving rivaroxaban. On the contrary, residual apixaban concentrations were closer to the peak concentrations than those of rivaroxaban and were also higher than those of rivaroxaban. The authors observe that an altered postoperative drug absorption may partecipate in the very high inter-individual variation in the Cmax, which culminates at time T1 with a coefficient of variation of about 100%, but remains high at T2 and T3 with a coefficient of variation around 50%. Moreover, the Standard Deviations from T1 to T3 were 30-50% higher in the rivaroxaban group than in the apixaban group. Interestingly, rivaroxaban and apixaban affected the Thrombin Generation Test (TGT) very differently. In particular ex-vivo apixaban induced alterations of the TGT look more likely dabigatran induced alterations than rivaroxaban induced alterations. The thrombin maximum concentration was markedly decreased from T2 to T3 with rivaroxaban treatment (112 ng/ml and 76 ng/ml respectively) while it remained almost unchanged in patients receiving apixaban (124 ng/ml and 117 ng/ml respectively). On the contrary, both drugs delayed thrombin generation, although to a lesser extent for apixaban. Very surprisingly, the TGT observed in the ex-vivo samples from patients receiving apixaban did not reflect the in-vitro alterations observed in plasmas spiked with increasing concentrations of apixaban (from zero=control to 1000 ng/ml), differently from TGT observed in the ex-vivo samples from patients receiving rivaroxaban which were similar to those observed in the ex-vitro samples spiked with increasing concentrations of rivaroxaban. The major target for the DOCAs is the Xa embedded in the prothrombinase complex. **(13) (Blood Coagulation and Fibrinolysis 2015 vol. 26 pp. 925-933)** Sinha and collegues showed that anti-Xa drugs with similar
inhibitory constant (Ki) towards free factor Xa can differ significantly for prothrombinase complex inhibition. **(14) (Atherosclerosis Thrombosis and Vascular Biology 2003 vol. 23 pp. 1098-1104)** but results obtained by others authors (Perzborn et al.) suggest a high similarity in the rate constants for prothrombinase-bound factor Xa. Freyburger and collegues point out that although the mistery of mechanisms underlying the highly different pharmacodynamics results in response to drugs that have comparable constant rates remains, their ex-vivo results confim the difference in the effect of both drugs on coagulation. **(13) (Blood Coagulation and Fibrinolysis 2015 vol. 26 pp. 925-933)** A recent interesting article by Brunner-Ziegler and collegues assessed the anticoagulant effect of single daily doses of rivaroxaban therapy after administration at different times of the day in 16 volunteers. In particular all subjects were given three morning and three evening single doses of 10 mg rivaroxaban.The rivaroxaban concentrations evaluated by Liquid Chromatography-Mass

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Spectometry (LC-MS) were higher 12 hours after evening intake of rivaroxaban, (53.3 ng/ml) compared with concentrations obtained 12 hours after morning intake (23.3 ng/ml). In accordance, the anti-FXa activity of rivaroxaban evaluated by BIOPHEN Factor X (Hyphen BioMed, Lower Austria, Austria) was detectable for a period of 12 hours after the evening intake of the drug but only for at least 8 hours after the morning intake. In addition, evening intake of rivaroxaban better suppressed in vivo thrombin formation in the morning than did drug intake in the morning. The reasons for these time-dependent effects are not clear, but might be due to biologic rhythmic variations of the enzymatic activity of cytochromes, which are responsible for the metabolism of anti-Xa inhibitors and/or the pharmacologic profile of the drug. The authors conclude that evening intake of rivaroxaban leads to prolonged exposure to rivaroxaban concentrations and may better neutralize the morning hypofibrinolysis. **(15) (Journal of Thrombosis and Haemostasis 2016 vol. 14 (2) pp. 316-323)** An important clinical concern is that the relationship between DOACs plasma concentrations and bleeding risk is unclear. In addition, as antidotes for direct Xa inhibitors are still not commercially available, patients using these DOACs who are at risk of bleeding or present with a major bleeding event cannot be effectively treated. **(16) (Journal of Thrombosis and Haemostasis 2014 vol. 12 pp. 1636-1646)** In a recent study were measured trough and peak DOAK concentrations with UPLC-MS/MS and routine coagulation tests in a prospective study including 40 patients receiving thromboprophylactic treatment with dabigatran 220 mg once daily (od) and 40 patients receiving rivaroxaban 10 mg od after major orthopaedic surgery. For rivaroxaban, the median trough concentration with UPLC-MS/MS was 17.1 ng/ml, and mediam peak concentration was 149 ng/ml. The anti-Xa assay displayed a good correlation, but trough levels were mostly below the Lower Liit Of Detection (LOD) of the anti-Xa assay. For dabigatran, the median trough concentration with UPLC-MS/MS was 12.1 ng/ml, and median peak level was 80.8 ng/ml. In this case was found a positive bias when results obtained by coagulation assays were compared with results obtained by UPLC-MS/MS. This bias was resolved when glucuronidated metabolites were added to dabigatran concentrations measured by UPLC-MS/MS (total dabigatran). The authors found a large heterogeneity in both peak and trough concentrations of dabigatran and rivaroxaban and their data suggest that age and gender might have effects on DOACs concentrations. Although current coagulation assays are a good option to exclude high concentrations of DOACs, they cannot be used to accurately measure low (trough) concentrations. The UPLC-MS/MS is the method of choice to measure trough levels of DOACs in patients after orthopaedic surgery. Whether patients with high or low trough concentrations are at increased risk for bleeding or thrombotic events respectively, remains to be established, since the association between concentration and bleeding risk has not been established **(17) (Thrombosis Research 2016 vol. 139 pp. 128-134)** although a concentration < 30 ng/ml seems to be compatible with surgical management, without increasing the risk of bleeding, especially in an emergency. **(18) (Archives of Cardiovascular Medicine 2013 vol. 106 pp. 382-393)**. The inter- and intra-individual variability in real-world atrial fibrillation patients on dabigatran, rivaroxaban or apixaban was evaluated in four Italian anticoagulation clinics. In addition was assessed the correlation between DOAC plasma concentration and creatinine-clearance. In this study were included 330 patients, of which 160 were on dabigatran (70 and 90 taking 150 mg or 110 mg twice-daily, respectively), 71 on rivaroxaban (37 and 34 taking 20 mg or 15 mg once-daily) and 99 on apixaban (73 and 26 taking 5 g or 2.5 mg twice daily). Blood samples were

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taken at trough and peak within the first month of treatment. The trough samples were obtained at 12 hours from the last dose intake for dabigatran and apixaban, and at 24 hours for rivaroxaban. The peak sample was obtained at 2 hours from ingestion for all drugs and 2 hours after trough sample. Patients on rivaroxaban treatment ingested concomitant food. Diluted thrombin time (dTT) calibrated for dabigatran, and anti-Xa assays calibrated for rivaroxaban or apixaban were performed locally in each clinic. The lower limit of detection for dTT and for the anti-Xa was 20 ng/ml and 15 ng/ml, respectively. Results below the lower limits were interpolated on the calibration curve from the clotting time for dTT and from the optical density for the anti-Xa assay. The inter-individual variability was expressed as coefficient of variation (CV) for each drug and each dosage. For dabigatran 110 mg, CV values ranged from 56% to 71% at peak and from 36% to 72% at trough. For dabigatran 150 mg, CV values ranged from 45% to 56% at peak and from 42% to 92% at trough. For apixaban 5 mg, CV values ranged from 31% to 33% at peak and from 29% to 49% at trough. For apixaban 2.5 mg, CV values ranged from 21% to 42% at peak and from 44% to 68% at trough. For rivaroxaban 20 mg, CV values ranged from 32% to 49% at peak and from 40% to 103% at trough. For rivaroxaban 15 mg, CV values ranged from 46% to 52% at peak and from 30% to 79% at trough. There were no major differences among the different clinics. For dabigatran 110 mg, overall CV value was 69% at trough and 67% at peak. For dabigatran 150 mg, overall CV value was 78% at trough and 51% at peak. For rivaroxaban 20 mg, overall CV value was 61% at trough and 43% at peak. For rivaroxaban 15 mg overall CV value was 60% at trough and 43% at peak. For apixaban 5 mg, overall CV value was 49% at trough and 35% at peak. For apixaban 2.5 mg, overall CV value was 59% at trough and 39% at peak. Overall CV values for all drugs were lower at peak than at trough. Dabigatran showed the highest overall CV value. Interestingly, the authors also calculated the percentage of patients outside the 10° and 90° percentile to assess the eventual under- or over-anticoagulation. The percentage of patients outside the 10-90° percentile was 26% and 22% at trough and at peak, respectively. The intra-individual variability, expressed as the CV value calculated for the three DOACs measured over time on 120 patients, was assessed from the data provided by one of the clinics, at trough and peak. Dabigatran showed the greatest variability with a CV of 59% at trough and 60% at peak for the 110 mg dose and 49% at trough and 51% at peak for the 150 mg dose. Rivaroxaban variability was intermediate with a CV of 39% at trough and of 27% at peak for the 20 mg dosage, and 35% at trough and 31% at peak for the 15 mg dosage. Apixaban had the smallest variability with a CV of 23% at trough and 22% at peak for the 5 mg dosage, and 15% at trough and 14% at peak for the 2.5 mg dosage. The results of this study show that while rivaroxaban or apixaban plasma concentrations are not correlated with creatinine clearance at trough, the high inter-individual dabigatran variability can only in part be accounted for by a degree of inverse correlation between its plasma concentrations and creatinine clearance suggesting that prescribing dabigatran to patients at the lower end of normal range for creatinine clearance may prompt excessive residual plasma concentrations. This study showed a high inter-individual variability for the three DOACs in patients treated with different dosages. On average, the drug concentration levels varied more than 20-times among the patients for dabigatran, about 15-times for rivaroxaban and 7-times for apixaban. The authors point out that this variability was similarly high if assessed within each clinic or evaluated as a whole, suggesting that it cannot be accounted for by the variability of the different laboratory assays. Variability was considerably higher in patients treated

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with the lowest dose of DOAC. Interestingly, patients taking the same oral dose of single DOAC may present with highly variable plasma concentrations. A different DOAC metabolism patterns in individual patients may be the explanation for this variability. The data of this study show a greater variability at trough than at peak levels. Correctly the authors point out that there is an urgent need to establish drug-specific cut-off levels for the eventual occurrence of hemorrhagic and thrombotic events in treated patients. However, as demonstrated by this study, due to the relatively high inter-individual variability, it will be difficult to set precise cut off values. In addition there is also an urgent need to establish cut off values for patients receiving treatment after stopping anticoagulation in the event of surgery or invasive procedures. At the moment, current recommendations for these patients suggest to stop DOAC administration two days before surgery, provided that renal function is normal. The assessment of renal function is recommended by measuring serum creatinine and calculating clearance by means of the Cockroft Gault formula. These recommendations are based on the assumption that DOAC plasma concentrations are correlated with creatinine clearance. The results of this study on the contrary, show that this assumption is not true, in particular for rivaroxaban and apixaban. For this reason, to avoid a bleeding risk during surgery, it is much more useful to perform a direct measurement of plasma drug level just before surgery or other invasive procedures. The high intra-individual variability observed for dabigatran (55%) and to a lesser extent for rivaroxaban (33%) and apixaban (19%), suggests that a single DOAC measurement cannot provide an estimation of the level of anticoagulation achieved at the steady state in treated patients. In addition, this study showed that the relatively high inter-individual variability cannot be explained by the rate of renal clearance of the three DOACs since the correlation of their plasma concentrations and creatinine clearance was poor. The values of rivaroxaban levels determined with the anti-factor Xa assay obtained in this study at peak, Mean 247 ng/ml (61-449) at Clinic A, Mean 229 ng/ml (65-370) at Clinic B, Mean 231 ng/ml (138-341) at Clinic C, and at trough, Mean 39 ng/ml (16-74) at Clinic A, Mean 41 ng/ml (16-106) at Clinic B, Mean 43 ng/ml (3-119) at Clinic C, **(19) (Thrombosis Research 2016 vol. 137 pp. 178-183)** were different from those showed on the EMA website. (rivaroxaban concentration at peak, Mean 215 ng/ml (22-535) and at trough, Mean 32 ng/ml (6-239). **(20) (www.ema.europa.eu)**
In the ROCKET-AF trial, **(21) (NEJM 2011 vol. 365 pp. 883-891)** a large double-blind trial, patients with non valvular atrial fibrillation were randomized to receive rivaroxaban at a dosage of 20 mg. once daily or 15 mg. once daily in patients with a creatinine clearance 30-49 ml/mn, or a dose-adjusted warfarin.
In this study rivaroxaban was found non inferior to warfarin for the prevention of stroke or systemic embolism, with similar rates of major and minor bleedings. Also in this study, in patients taking warfarin, the INR was in the therapeutic range for a low percentage of time, (mean, 55%) and in my opinion, to decide if rivaroxaban is really non inferior to warfarin for the prevention of stroke or systemic embolism in our patients with non valvular atrial fibrillation, treated in the west countries, we need more clinical trials not sponsored by the drug manufacturer, in which the INR must be in the therapeutic range >/= 70% of the time. Again, many patients with non valvular atrial fibrillation are taking drugs as amiodarone, verapamil or dronedarone that are inhibitors of P-glycoprotein (P-gp) and can increase rivaroxaban concentration. If we can detect drug interactions with vitamin K antagonists very easily by unexplained INR changes, the assessment of drug

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interactions with rivaroxaban is more difficult because we must use a calibrated chromogenic anti-Xa assay that at the moment is available only in few laboratories. For these considerations, I do not see at the moment a noninferiority of rivaroxaban over warfarin, when the latter is used carefully by skilled physicians and the laboratory tests are executed by skilled technicians too. Can we rely the use of a drug in a certain disease in our daily clinical practice based only on one trial, also if large ? Certainly not. We need to understand if the results of the trial can be applied to our particular category of patients, in our hospital or in our private practice and in our country. In addition, can non-inferiority trials be used to assess with real efficacy the utility of a drug compared with another drug ? Certainly not. Superiority trials are the only "Gold Standard" to effectively compare a new drug with an older one. In a published editorial some authors state : " We believe that non-inferiority trials have no ethical justification, since they do not offer any possible advantage to present and future patients, and they disregard patients' interest in favour of commercial ones. Non-inferiority trials claim minor advantages for the test drugs, but do not prove their efficacy compared with older products. Few patients would agree to participate if this message were clear in the informed consent form : as we said before, why should patients accept a treatment that, at best, is not worse, but could actually be less effective or less safe than available treatment ?. In conclusion we believe that non-inferiority trials fail to meet the commitments of good clinical research : Ask an important question, and aswer it reliably". **(22) (The Lancet 2007 vol. 370 pp. 1875-1877)**
In the ROCKET AF trial was used the INRdevice, made by Alere, to determine whether, and by how much, patients' doses of warfarin should be adjusted to keep the drug in the right therapeutic range. An investigation conducted by the British Medical Journal has uncovered that in December 2014 this device received a recall notice which said that some INR results obtained with it could be "clinically significantly lower" than a laboratory INR method. This means that patients in the warfarin arm could have received unnecessarily adjusted warfarin treatment. Too much warfarin could be given and this could have led to an increased risk of bleeding in patients included in the warfarin arm of the trial. The recall notice also said that Alere had received 18924 reports of malfunctions, including 14 serious injury. As it is point out by the BMJ " In terms of the trial results, it could make rivaroxaban seem better than it was at reducing the risk of bleeding". The US independent watchdog Project on Government Oversight reported that the 2014 recall notice did not require that Alere retrieve its devices from patients but said that patients with particular medical conditions should stop using the recalled devices. Others patients should have their INR values verified by laboratory tests. When the FDA approved rivaroxaban, one of the advisory committee members, the cardiologist Steven Nissen of the Cleveland Clinic, Cleveland, Ohio, said that the approach to warfarin therapy in the ROCKET AF trial " was a fatal flaw in the study design". In addition, an FDA reviewer also said in a memo to the FDA that the "poor warfarin control" in this trial "biased the study in favor of rivaroxaban". On the contrary, other FDA advisory committee members stated that in the ROCKET AF trial warfarin was used as it would be used in the real word. Robert Califf, recently appointed by President Barack Obama as head of the FDA, who co-chaired the executive committee of the trial, said that the researchers "gave warfarin not only in an acceptable way, we gave it in a commendable way during this trial". **(23) (British Medical Journal 2015 vol. 351 pp. h6431)** However, we should do some considerations. First of all,in a posthoc analysis, the TTRs of patients on OAC in a randomized trial of OAC versus clopidogrel plus aspirin (Atrial

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Fibrillation Clopidogrel Trial With Ibersartan for Prevention of Vascular Events (ACTIVE W) were used to calculate the mean TTR for each of 526 centers and 15 countries. The primary study outcome was the first occurrence of stroke, non-central nervous system systemic embolism, myocardial infarction, or vascular death. Major bleeding was defined as any bleeding requiring transfusion of at least 2 units of red blood cells or the equivalent of whole blood or any bleed associated with death. Stroke included ischemic and hemorrhagic stroke. Of the 6706 enrolled in this study, 3371 were randomized to OAC and 3335 to clopidogrel plus aspirin. The mean TTR of each patient randomized to and receiving OAC was calculated, and each clinical center was characterized by the mean TTR of all its patients on OAC. The mean TTR for all patients in ACTIVE W was 63.4% and the median TTR was 65%. For patients at centers with mean TTRs below the median, no reduction in events occurs with OAC, but for patients at centers with TTRs above the median value, OAC reduced vascular events > 2-fold. A population-average model was used to account for the clustering of TTR at sites.The outcome of stroke,myocardial infarction,non-central nervous system embolism, vascular death,or major hemorrhage was used to have sufficient numbers of events to perform the analysis. This model showed that the relationship between relative risk and TTR is positive with increasing benefit from OAC with increasing TTR and that the relationship is non linear. The population-average model also showed that at TTR values < 58%, it was not possible to expect any benefit from being on OAC. The authors of the study point out that medical practice is an important determinant of TTR. Although clearly patient-specific factors exist such as genetic polymorphisms, age, and compliance with medications, physician- and medical system-related factors are important determinants because the dosing of OAC is variable for every patient and often requires dosage adjustments. The use of anticoagulation clinics and computer assisted decision support tools improve the TTR. A TTR > 70% is associated with even greater benefit from OAC and was achieved in some countries. The authors conclude the article stating that : " Practices, centers, and regions need to assess the TTR achieved in their own patients and to set a minimum target TTR of 60% to 65%. Medical systems that cannot achieve this goal for biological, systematic, economic, or social reasons should consider not preferring OAC in AF patients". **(24) (Circulation 2008 vol. 118 pp. 2029-2037)** The conclusions of these authors clearly establish that in their study, below a certain value of TTR (< 58% in their study) it is better to treat AF patients with Dual Antiplatelet therapy than with Warfarin. If we consider that the TTR of the ROCKET AF trial is 55%, it is clear that the results obtained with rivaroxaban were compared with a poor laboratory monitoring of warfarin. As a consequence, we do not know if rivaroxaban is non inferior to a good laboratory monitoring of warfarin with a TTR >/ = 65%. Another consideration is that unstable anticoagulation is associated with hemorrhagic and thrombotic complications, and although the TTR is used to assess the control and intensity of oral anticoagulation, it does not measure variation in the INR. No study on DOACs evaluated the INR variability. Patients with unstable coagulation have a significantly increased risk of clinical events at 3 and 6 months before an event. In addition the TTR alone does not assess the fluctuations in the INR, even when the patient is within the therapeutic target range. In a multicenter study, based on a large number of patients on long-term oral anticoagulation, INR control and variability measured with the Variance Growth Rate (VGR) and TTR were analyzed in the conventional target of 2.0-3.0, with a small number up to 3.5. The findings of this study demonstrate the predictive ability and the possible increased safety of using the VGR, and

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show that unstable patients definied by a high VGR have an increased risk of clinical events while receiving warfarin or alternative oral anticoagulants. Three different methods of VGR determination (A, B1, and B2) together with the TTR were studied. Method A measures both INR variability and control, but methods B1 and B2 measure variability only. The VGR and TTR were determined over three time periods : overall follow-up to an event, and 6 months and 3 months before an event. Six hundred and sixty-one control patients were matched to 158 cases (bleeding, thromboembolism, or death). With all VGR methods, the risk of an event was greater in unstable patients at 6 months before an event than in stable patients. The predictive ability of the VGR methods was shown to be as effective as that of the reported percentage TTR, especially for INR monitoring in the short term. Patients with unstable anticoagulation have a significantly increased risk of clinical events at 3 and 6 months before an event. Among the three different methods, method A, which takes both INR control and variability into consideration, demonstrated the greatest association with clinical events (bleeding or thrombotic) at 3 months before an event.The VGR can be incorporated into computer-dosage programs, and may offer additional safety when oral anticoagulation is monitored. **(25) (Journal of Thrombosis and Haemostasis 2013 vol. 11 pp. 1540-1546)** For more clear explanation about the three different types of VGR and about its calculation, see the following website : **www.4s-dawn.com/wp-content/uploads/2014/01/Introduction-to-Variance-Growth-Rate-VGR-4S-Dawn-Clinical Software.pdf** In a retrospective, registry-based swedish study, was evaluated the safety and efficacy of well managed warfarin in 77423 unselected patients since January 1, 2006 to December 31, 2011. Atrial fibrillation was the most common indication (68%) but patients with other indications for OAC were also included. The therapeutic range is defined by prothrombin time expressed as international normalised ratio (INR) between 2.0 and 3.0. The ESC Working Group on Thrombosis Anticoagulation Task Force recommends that a TTR of > 70% is needed, whenever a vitamin K antagonists such as warfarin is used. The mean time in therapeutic range of the International Normalized Ratio (INR) 2.0-3.0 was 76.5%. The annual incidence of severe bleeding was 2.24% and of thromboembolism 2.65%. The incidence of intracranial bleeding was 0.37% per treatment year in the whole population, and 0.38% among patients with atrial fibrillation. In particular bleeding complications were fewer than what reported in the large randomised trials where warfarin was used as a comparator to NOACs. In this study, major bleedings from any cause in the AF population occurred at an annual rate of 2.18%, which is to be compared to 3.57% in the RE-LY trial, to 3.4% in the ROCKET AF trial and to 3.09% in the ARISTOTLE trial. These less severe major bleedings may have been more thorough in the prospective clinical trials than in this study, which may explain some of the difference in bleeding rate. On the other hand, the TTR in this study (76.5%) was higher than the mean TTR levels of 55-64% in the pivotal NOAC trials. In addition, in this study as cited above, were included all warfarin treated patients and consequently there were more elderly patients and patients with multiple concomitant diseases than in randomised trial with inclusion and exclusion criteria. The rate of intracranial bleeding in AF patients (38%) was lower than with rivaroxaban (0.50%), and not much higher than with apixaban (0.33%), with dabigatran 150 mg. (0.30%) and dabigatran 110 mg. (0.23%). In addition, this rate was much lower than in warfarin-treated control patients in NOAC trials where they had intracranial bleeds at a rate of 0.70 to 0.80% annually. The authors of the study point out that is very unlikely that there was any

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significant underreporting of intracranial bleeds in the all-inclusive national Swedish Patient register that could have accounted for the low bleeding rate. In addition in AF patients, the incidence of stroke, TIA or systemic emboli per year was 1.54% that is considerably lower than the 1.74% and 2.42% found in the warfarin arms in the pivotal studies for dabigatran and rivaroxaban, respectively. This despite of an unselected patient population with no inclusion or exclusion criteria. Patients with heart valves disease had more bleeding complications than other patients. Many of these patients had treatment with a higher therapeutic range of INR 2.5-3.5 instead of 2.0-3.0. The bias of including patients with higher INR goals than 2-3 means that the authors show a larger risk of bleeding than for the patients with lower goals, and could therefore better reflect clinical reality. The authors conclude that "Efficient warfarin therapy with a mean TTR of 76.5% is possible to achieve in routine clinical care with unselected patients. Warfarin treatment with a high TTR performs well, and should not be ruled out in favour of NOACs". **(26) (Thrombosis and Haemostasis 2015 vol. 113 pp. 1370-1377)** Due to the use of a defective device to measure the INR in the ROCKET AF trial, the former FDA cardiovascular and renal drug reviewer, Thomas Marciniak said to the British Medical Journal : "The care for the warfarin control arm patients appears to have been compromised". When the BMJ contacted the European Medicines Agency in April 2015 and the Food and Drug Administration, both said they did not know that the recalled device had been used in ROCKET-AF trial. The author of the article, Deborah Cohen write : "What happens to a pivotal drug trial when a device used is found defective?". In November 2015 the European Medicines Agency (EMA) told journalists : "Due to the defect it is now thought that the INR device may have impacted the clotting results in some patients in the warfarin group". Executive director of EMA, Guido Rasi, also said : "It would be nice to have some independent study carried out to give confidence in the use of this medicine". The FDA also told The BMJ that is "aware of concerns regarding the INR device and its use in the ROCKET AF trial and is reviewing relevant data". Harlan Krumholz, professor of medicine (cardiology) at Yale University and Editor-in-Chief of NEJM Journal Watch Cardiology, said that the NEJM should place an "immediate expression of concern" on the paper to notify the medical community. He said that "The study should be considered of uncertain validity until a more thorough review can be done", adding that there should be "an investigation by an independent group of experts to quickly determine if there are grounds for retraction". Even before rivaroxaban was approved in Europe and the US in 2011 for use in non-valvular atrial fibrillation, two primary clinical FDA reviewers of the drug recommended that it should not be approved for the US market. In an FDA decisional memo they wrote that "ROCKET provides inadequate information to assess the relative safety and efficacy of Xarelto in patients whose warfarin administration can be well-controlled". At the moment there are few information about which diagnostic point of care devices are used in any of the direct oral anticoagulant trials. The BMJ became aware of the faulty device used in the ROCKET AF trial only by reviewing European regulatory documents in April last year. Dr. Marciniak said that the NEJM which published the trials for three of the direct oral anticoagulants, "should require that the devices used in trials are clearly and specifically identified in your publications". In 2005, a warning letter from the FDA to HemoSense, the company that owned the faulty device before Alere bought it, reprimanded the company for failing to investigate "clinically significant erroneous" high and low INR results generated by the point of care device. "Both high and low INR results have the potential to cause or

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contribute to a death or serious injury, because they may result in erroneous dosing and thus improper control of coagulation" the letter said. Despite these warning letters, the FDA cleared subsequent iterations of the device through its regulatory system that requires makers of such device to show only that the new version is "substantially equivalent" or similar, to one already on the market. This system has been criticised for not providing enough evidence that a device is safe and effective. Johnson and Johnson, however has lobbied against tightening up this aspect of device regulation and the need to provide more evidence. Alere has confirmed to The BMJ that the device was already malfunctioning in 2002 and it may occur in all devices and not just one batch. However, neither it nor the FDA responded to questions about why nothing had been done about the problem earlier. The BMJ asked Johnson and Johnson, Bayer, and Duke if they validated the device at any point before or during the trial. None responded to the questions. For Bob Powell, a former FDA clinical pharmacologist, the specificity and reproducibility of a diagnostic test or assay is vital to the performance of a trial. He said that "The fact that this was apparently not previously done nor reported in the primary publication is concerning as this is a basic principle in drug development". Powell also said that "a comparison should be made between the defective point of care readings and the two sets of gold standard central lab readings as this would determine whether this defective device undermined the integrity of the trial results". In December 2015, Duke issued a press release in which said that after a secondary analysis, the findings from the analysis are consistent with the results from the original trial and do not alter the conclusions of ROCKET AF trial, that rivaroxaban is non-inferior to warfarin for the prevention of stroke and systemic embolism with less intracranial hemorrhage and fatal bleeding. However Powell said this statement is misleading because of the lack of information. Dr. Krumholz also thinks that this statement did not give enough information about what Duke found in terms of the major safety end point, major bleeds. Hugo ten Cate, medical director of the Maastricht Thrombosis Anticoagulation Clinic and coeditor in chief of Thrombosis Journal said that " Large bleeds mostly occur in the gastrointestinal tract and can be lethal if substantial blood loss occurs, especially in elderly subjects with comorbidity and this can be a devastating complication". The author of the article, Deborah Cohen correctly writes " given the lack of clarity over the outcomes and the methods used, is a reanalysis by Duke enough?". Marciniak said that he would not rely on any reanalyses done by Duke, Johnson and Johnson, or the FDA. "Because they already missed the problems both in the trial and with the public marketing, I would not trust them to publish anything that is accurate or that provides any details". He also said that datasets need to be released as "the only solution that would lead to unbiased analyses". Dr. Krumholtz asked Johnson and Johnson for access to the trial data. His Yale University Open Data (YODA) project has an agreement with Johnson and Johnson to make all of the clinical trial data available for its approved products. However, although this company wanted allow access to the data, Bayer refused. At the end of 2015, both the EMA and the FDA discussed the need to measure blood levels of direct oral anticoagulants and adjust the dose to maximise benefit and minimise harm despite all the manufacturers affirm that this not necessary. These regulatory agencies decided to discuss this topic after The BMJ revealed that Boerhinger Ingelheim withheld analyses from the regulators that showed how many major bleeds could be prevented by monitoring anticoagulant activity and adjusting the dose. Last year Robert Temple, deputy director for clinical science at the FDA's Center for Drug Evaluation and Research, suggests that the FDA believes there

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is a scientific reason for measuring the blood levels of these drugs and adjusting the dose. However once a drug is on the market, regulators cannot act unless there are safety concerns. Powell said that, depending on the outcomes of reanalyses of the ROCKET AF trial, the regulatory agencies might take action. "After a drug is approved, it usually takes a safety signal to prompt significant action on the part of the FDA. It is this lack of safety signal that appears to be hindering the FDA in their desire to pursue tailored dosing for DOACs. If it turns out that the issue with the INR device changes the safety profile of rivaroxaban, this may constitute the safety signal necessary for the FDA to act in this regard". **(27) (British Medical Journal 2016 vol. 352 pp. i575)** In February 2016, the investigators of the ROCKET AF trial, in a letter published by NEJM, write that in December 2014 the FDA issued a recall notice for a medical device correction of the Alere INRatio Monitor System because this point-of-.care device may provide an INR result that is lower than an automated, plasma-based laboratory INR in patients with certain medical conditions. These conditions include abnormal hematocrit levels, conditions associated with raised fibrinogen levels, and bleeding and unusual bruising. In October 2015, the ROCKET AF executive committee was notified that the device used in this trial was included in this FDA recall notice. The investigators, to understand if the malfuctioning of the device had led to lower INR values and to wrong adjustments of warfarin dosage with inappropriately high doses and bleeding, conducted a series of post-hoc analyses of the ROCKET AF trial. Patients with any of the conditions cited in the recall were identified. In particular also patients with hematocrit values of less than 30% or more than 55% were identified. They divided the patients enrolled in the trial in patients included or not included in the recall condition, and then compared efficacy and safety outcomes of patients receiving rivaroxaban with those receiving warfarin in these subgroups. Of the total safety population of 14236 patients, 8942 (63%) had no recall condition and 5294 (37%) had a recall condition. Both types of patients were equally distributed between the warfarin and rivaroxaban groups. The characteristics of the patients were similar in the rivaroxaban group and the warfarin group in the subgroups with and without recall conditions. The results of the primary analysis of efficacy and safety outcomes in the subgroup of patients with no recall conditions are the same obtained in the overall trial population. They show the noninferiority of rivaroxaban versus warfarin for preventing stroke and systemic embolism, with similar rates of overall bleeding and lower rates of fatal and intracranial bleeding among patients treated with rivaroxaban but a higher rate of gastrointestinal bleeding. The primary efficacy and safety findings in patients with any recall condition are also consistent with the results of the overall trial. Among these patients, the bleeding rate was higher in both the rivaroxaban and warfarin groups. In addition, among patients with any recall condition, there was a trend toward a higher relative risk of major bleeding with rivaroxaban than with warfarin, a trend that was not observed among patients with no recall condition and this finding does not support the hypothesis that device malfunction led to an increased risk of bleeding in the warfarin group. The authors conclude that these results indicate that possible malfunction of the point-of-care device used for INR measurement in the ROCKET AF trial that led to lower INR values than would be obtained by laboratory testing did not have any significant clinical effect on the primary efficacy and safety outcomes in the trial. **(28) (New England Journal of Medicine 2016 vol. 374 pp. 785-788)** However, there are some considerations that need to be done. First of all, the conditions in which we can have a significant variability that can affect INRs results are well

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known since many years. Low molecular weight heparin, hematocrit, fibrinogen level, the presence of antiphospholipid antibodies and, potentially, polyglobulia, hypertriglyceredemia, hemolysis, sensitivity to factor V and hyperbilirubinemia have a relatively large impact on the INR result. **(29) (Journal of Thrombosis and Haemostasis 2013 vol. 10 pp. 251-260)** In particular the influence of haematocrit on INR results using a point-of-care device had been well described. Van de Besselaar and collegues in patients on long-term VKA treatment, evaluated the INR results determined by the CoaguChek S system and reference methods for the classic PT. Four different CoaguChek S strip lots were evaluated. They showed that INR differences between the classic PT and the CoaguChek S are significantly correlated to the haematocrit within the range 0.37-0.51. With increasing haematocrit, the INR difference between the classic PT and Coaguchek S decreased from positive to negative values. **(30) (Thrombosis and Haemostasis 2008 vol. 100 pp. 1181-1184)** On the other hand, it is necessary a correction of the citrate amount in case of haematocrit < 25% or > 55% when we use a traditional laboratory PT to determine a correct INR result. Another consideration is that whereas laboratory-based INR measurements have been highly standardized and are subject to international quality control, the same is not true for POCT coagulometer measurements. As internal quality control some devices such as the Coaguchel XS use electronic onboard quality control. The external quality control can be achieved with the following methods : a) Comparing the INR obtained from venous samples analyzed in a laboratory with that of the POCT coagulometer; b) Comparing the INR of a reference certified POCT coagulometer with that of the POCT coagulometer; c) Comparing plasma with a known INR value sent from a central laboratory with the result of the POCT coagulometer (method developed by the UK National External Quality Assessment Scheme for Blood Coagulation (NEQUAS) which provides lyophilized plasma for external quality control to a number of centers using POCT coagulometers); d) Comparing INR measured on a certified, calibrated POCT coagulometer with that of the patient's POCT coagulometer, using five sets of plasma (method endorsed by the European Action on Anticoagulation (EAA) which recommends five samples at each time-setting which can be delivered by the External Quality Control of Diagnostic Assays and Tests Foundation. **(29) (Journal of Thrombosis and Haemostasis 2013 vol. 10 pp. 251-260)** These considerations show the importance of a correct laboratory monitoring of VKA therapy and I wonder as in such important clinical trials in which NOAC treatment is compared with warfarin therapy this aspect had not been evaluated. In fact, we do not know how the INR in the warfarin group of patients, in these trials, was determined. If it was used a POCT or a laboratory test, and in case of a POCT, which kind of device was used or, in case of a laboratory test, which reagents and which instrumentation were used. "Currently, there is little public information about which diagnostic point of care devices are used in any of the direct oral anticoagulant trials. They are not named in the published phase III trials" writes Deborah Cohen, Associate Editor of The BMJ. Dr. Thomas Marciniak, former FDA cardiovascular and renal drug reviewer, said that the New England Journal of Medicine, which published the trials for the three of the direct oral anticoagulants, should rectify that. "You should require that the devices used in trials are clearly and specifically identified in your publication", he wrote in his letter. **(27) (British Medical Journal 2016 vol. 352 pp.i575)** Until the FDA recall notice received by the Alere device, and revealed by The British Medical Journal we did not know that in the ROCKET AF trial had been used a POCT coagulometer to obtain INR results in the warfarin arm of the trial. On the other hand,

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we cannot use the expression "real word" or "real life situations" to justify a poor laboratory control of warfarin treatment such as that obtained in all the NOAC trials (TTR 55%-64%) and in particular in the ROCKET AF trial in which was obtained the worst TTR (55%). As described above, with a so low TTR (< 58%) it is better to use a dual antiplatelet therapy than to use warfarin in patients with nonvalvular atrial fibrillation. **(24) (Circulation 2008 vol. 118 pp. 2029-2037)** As a consequence, it is not correct to state that rivaroxaban is not inferior to warfarin in patients with NVAF. Fortunately, in many west european countries in the "real word" the TTR is > / = 70% and the majority of anticoagulation clinics and laboratories do not use POCT devices to determine INR results. These devices which when function correctly are normally reliable, are used for Patient Self Testing (PST) at home in those west european countries in which there is a remboursement by the National Health System, due to the high cost of the device (about 800 euro in Italy) and of the higher cost of a strip (in Italy about 5 euro for each strip) compared with the cost of a single PT laboratory determination (in Italy about 3 euro for each test). In the so called "real word" at the moment, these devices are underused. As described above, in a recent swedish study which included 77423 unselected patients, the authors state that an "efficient warfarin therapy with a mean TTR of 76.5% is possible to achieve in routine clinical care". **(26) (Thrombosis and Haemostasis 2015 vol. 113 pp. 1370-1377)** On the other hand, already in a systematic review published in 2012, in which was analyzed the comparative effectiveness of warfarin and NOACs for the management of atrial fibrillation and venous thromboembolism, subgroup analyses suggested a higher bleeding risk for persons older than 75 years or those receiving warfarin who had a "poor" laboratory control. The authors concluded that treatment benefits of NOACs compared with warfarin are small and vary depending on the control achieved by warfarin treatment. **(31) (Annals of Internal Medicine 2012 vol. 157 (11) pp. 796-807)** Recently, in an article published in The New York Times of March 1, 2016, lawyers for patients suing Johnson & Johnson and Bayer claimed that the letter published in The New England Journal of Medicine regarding the point-of-care device used in the ROCKET AF trial and cited above, **(28) (New England Journal of Medicine 2016 vol. 374 pp. 385-388)** left out critical laboratory data. They claimed that the companies were complicit staying silent, helping deceive the editors while the companies were planning to provide the very same data to regulators in the United States and Europe. Top editors at The New England Journal of Medicine said they did not know that separate laboratory data existed until a reporter contacted them, but they dismissed its relevance. The failure to include the lab data in the letter "just feels like it's a real ethical breach", said Dr. Lisa Schwartz, a professor of medicine at Dartmouth. "If you know the direct answer to this question, then how can you not provide it to be able to give insight ?". In the ROCKET AF trial investigators compared the device readings with test results done at a central laboratory at two points in the trial, drawing blood from more than 5,000 of the patients who took warfarin and sending the samples for testing. The blood was taken 12 and 24 weeks after patients enrolled in the trial. But the Duke researchers made no mention of the lab data in their letter. Lawyers in the case against Johnson & Johnson and Bayer filed a legal brief in federal court in New Orleans, asking a judge to unseal documents in the case, which involves more than 5,000 lawsuits filed by patients and their families who claim they were harmed by Xarelto. Of those, 500 involve patient deaths. In a previous statement, Duke said it had conducted its research separately from Johnson & Johnson and Bayer. But this fall, Bayer submitted an analysis to the European Medicine

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Agency that was nearly identical to the approach used by the Duke researchers, comparing the outcomes of patients who had specific medical conditions with outcomes of those who did not. Some experts remember when in 2005, The New England Journal of Medicine published a rare Expression of Concern after it learned that researchers had failed to include three heart attacks in a study of Vioxx, made by Merck, which has since been with drawn from the market. In that case, editors learned that data had benn deleted from the trial manuscript two days before it was submitted to the journal. Dr. Rita F. Redberg, a cardiologist who is also editor of the medical journal JAMA Internal Medicine, said : "I think it's always important to make sure that you have all the information to answer the scientific question before publication". Dr. Steve Nissen, a cardiologist at the Cleveland Clinic, who served on the FDA advisory panel that voted against the drug about the letter published in the NEJM said : "Given the fact the device was inaccurate, there is no way anybody can tell you what would have happened in the trial". **(32) (The New York Times March 1, 2016)** Recently, the safety and effectiveness of dabigatran or rivaroxaban, were compared with VKA in anticoagulant-naive patients with nonvalvular atrial fibrillation during the early phase of anticoagulant therapy. This nationwide cohort study which used the french medico-administrative databases, included patients with nonvalvular atrial fibrillation who initiated dabigatran or rivaroxaban between July and November 2012 or VKA between July and November 2011. Dabigatran and rivaroxaban new users were matched to VKA new users by the use of 1:2 matching on the propensity score. Patients were followed for up to 90 days until outcome, death, loss to follow-up, or December 31 of the inclusion year. Hazard ratios of hospitalizations for bleeding and arterial thromboembolic events were estimated in an intent-to-treat analysis using Cox regression models. In the study were included 19713 warfarin new users and 8443 dabigatran and 4651 rivaroxaban new users. In this study, no significant differences were observed between dabigatran or rivaroxaban and VKA in terms of hospitalizations for bleeding or for arterial thromboembolic events during the early phase of anticoagulant therapy among new users with NVAF. Comparing NOAC with VKA, NOACs cannot be considered to be safer than VKA during the early phase of treatment. The authors conclude that the clinical implications of their results are that physicians must be just as cautious when initiating NOACs as when initiating VKAs. No statistically significant difference was observed between dabigatran or rivaroxaban, and VKAs for what concerns the risk of bleeding or arterial thromboembolic events during the early phase of anticoagulant therapy in NVAF. In addition, they affirm that similar considerations should be extended to other NOACs such as apixaban. **(33) (Circulation 2015 vol. 132 pp. 1252-1260)** In the ATLAS ACS2-TIMI trial, a double-blind, placebo-controlled trial, patients with a recent acute coronary syndrome were randomly assigned to receive, in addition to the standard therapy, twice-daily doses of 2.5 mg. or 5 mg. of rivaroxaban or placebo for a mean of 13 months and up to 31 months. In this trial were excluded patients who had an important bleeding within 12 months before randomization, with a previous intracranial hemorrhage, with a platelet count < 90000 per cubic millimeter and were also excluded patients with a previous ischemic stroke or a previous transient ischemic attack who were taking a double antiplatelet therapy, both aspirin and a thienopyridine. Rivaroxaban significantly reduced death from cardiovascular causes, as myocardial infarction or stroke and death from any cause. On the other hand, rivaroxaban significantly increased TIMI (Thrombolysis in Myocardial Infarction) major bleeding not associated with CABG (Coronary Artery Bypass Graft) and TIMI bleeding requiring

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medical attention, compared to placebo. There were 14 intracranial hemorrhages (0.4%) with the twice-daily dose of 2.5 mg., 18 (0.7%) with the twice-daily dose of 5 mg. compared to 5 (0.2%) with placebo. Fatal bleeding were 6 (0.1%) with 2.5 mg., 15 (0.4%) with 5 mg.. and 9 (0.2%) with placebo. As we can see from the results of this trial, if rivaroxaban reduced cardiovascular events and death from any cause compared to placebo, and although the dosage of 2.5 mg. twice daily provoked fewer fatal bleeding events than the twice daily 5 mg. dose, in any case, using rivaroxaban in this category of patients, there is a significant increase of major and minor bleedings. **(34) (NEJM 2012 vol. 366 pp. 9-19)** For these reasons, if we want to use rivaroxaban in this patients population, we need to evaluate cardiovascular risk and bleeding risk very well for every patient, especially for patients already taking a double antiplatelet therapy.
The addition of direct inhibitors of Factor Xa to the standard therapy in the treatment of acute coronary syndromes, (ACS) results in an excessive risk of major bleedings without any clear evidence to obtain major clinical benefits.
(35) (Atherosclerosis 2013 vol. 229 issue 2 pp. 482-488) In conclusion, after these observations, use of rivaroxaban in west countries, if we refer patients to specialized Anticoagulation Clinics is recommended only in selected cases and not on a large scale, especially until we will not have an antidote commercially available to neutralize its anticoagulant effect in case of a serious bleeding or in case of an emergency surgery procedure. Rivaroxaban use must be restricted to some cases, such as restarting anticoagulant therapy in patients with a non valvular atrial fibrillation who had an intracranial hemorrhage (ICH) during anticoagulant therapy with vitamin K antagonists, considered the high probability of recurrence with warfarin as demonstrated by the Italian Collaborative Study **CHIRONE** (**C**erebral **H**emorrhage **I**n patients **R**estarting **O**ral a**N**ticoagulant th**E**rapy) although there are not clinical studies about rivaroxaban use in these patients. **(36) (Neurology 2014 vol. 82 (12) pp. 1020-1026)** We can also use rivaroxaban in patients who cannot arrive to the Anticoagulation Clinic for many reasons, and in the same time are not able to perform a self-monitorinf using a point-of-care instrument, considering that with self- monitoring is possible to obtain a good control of anticoagulant therapy with vitamin K antagonists. Although a drug be approved by regulatory agencies for its use in specific disorders, this does not mean that this drug must be used in all patients with those specific disorders. This is the case of rivaroxaban and of all new oral anticoagulants that in my opinion are useful, but must be used in selected cases only and not on a large scale without any laboratory monitoring as some key opinion leaders in the medical field would have us believe. Until we will not have clinical trials not sponsored by the drug manufacturer, we will always have some bias in these clinical trials. Fortunately, there are some other opinion leaders who consider that these new drugs should be used with caution on a case by case only, and should be monitored by specific laboratory tests too. Despite their emphasized predictable pharmacokinetics and pharmacodynamics in many published studies, in reality their plasma levels have an inter- and intra-individual variability that in many cases may become clinically relevant. For other details, see review on "Dabigatran" and on "Apixaban", section on "Conclusions".

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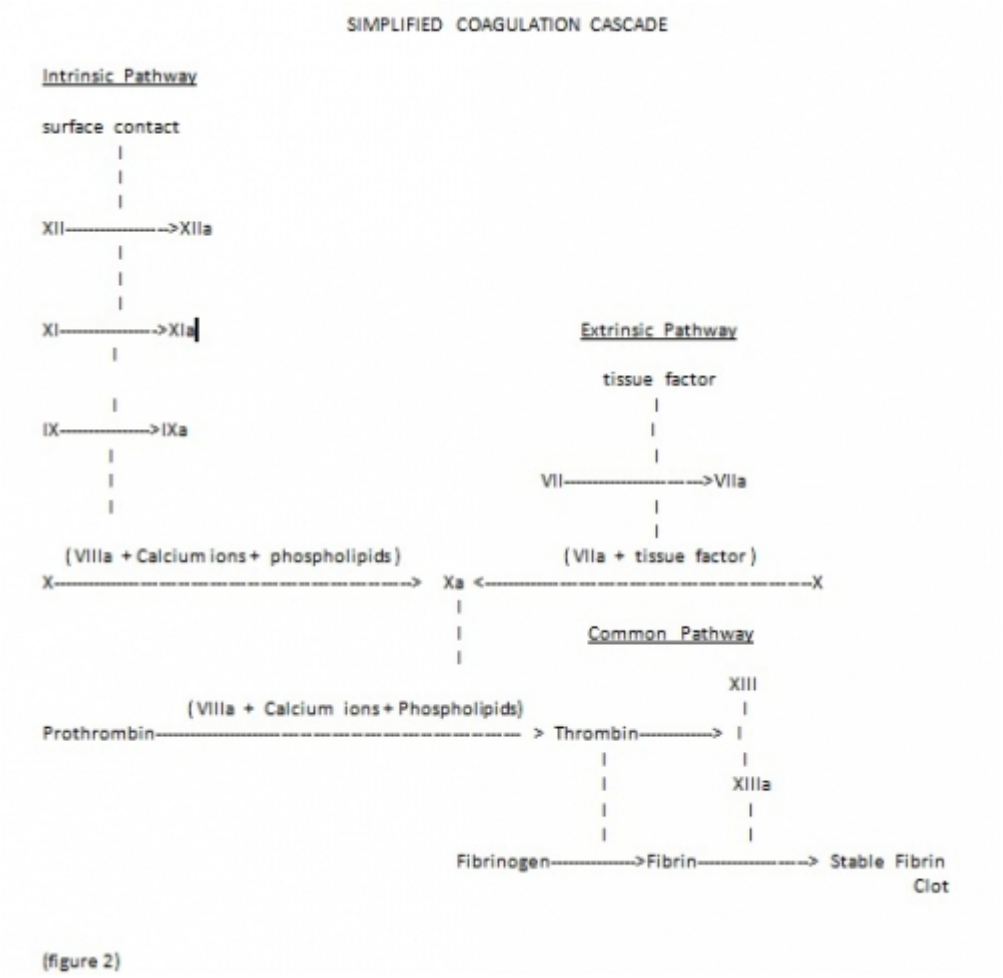
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Appendice delle figure

Mechanism of action - Simplified Coagulation Cascade



(figure 2)

torna al capitolo: Mechanism of action

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