APIXABAN

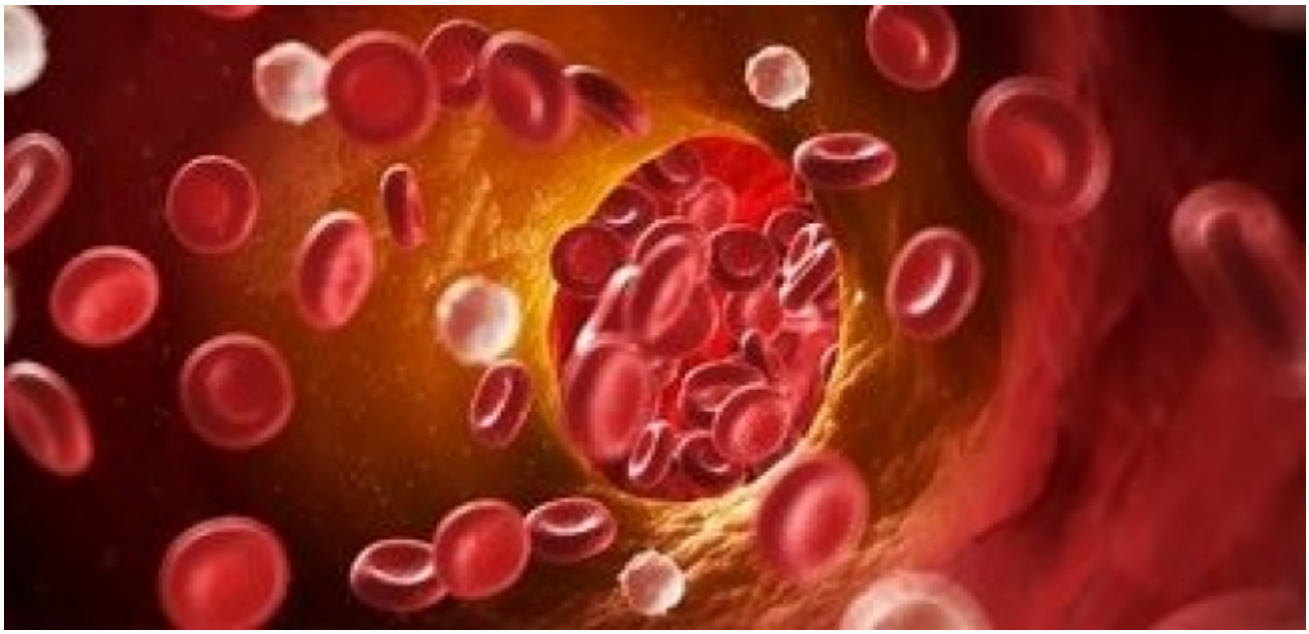
TROMBOSI - ANTICOAGULANTI ORALI DIRETTI

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Abstract

Apixaban is an oral highly selective, reversible direct inhibitor of activated factor X (Fxa) with a half-life of 9-14 hours and an oral bioavailability of approximately 50%. It binds to both free and clot bound Factor Xa. It has been approved in Europe, Canada and United States for thromboprophylaxis in patients undergoing total knee or total hip replacement surgery, for prevention of stroke and systemic embolism in patients with non valvular atrial fibrillation, with one or more risk factors as a previous stroke, a previous transient ischemic attack (TIA), age =/ > 75 years, hypertension, diabetes mellitus, symptomatic heart failure (Class NYHA =/ > 2). (For New York Heart Association Classification see section on "Indications") for treatment of Deep Vein Thrombosis (DVT) and Pulmonary Embolism (PE) and also for prevention of recurrent DVT and PE. Apixaban has been compared to enoxaparin for the prevention of venous thromboembolism in patients undergoing a knee or a hip replacement surgery in the ADVANCE trials **(1) (NEJM 2009 vol. 361 pp. 594-604) (2) (The Lancet 2010 vol. 375 pp. 807-815) (3) (NEJM 2010 vol. 363 pp. 2487-2498)** and the results were favorable to the use of apixaban.
In the ARISTOTLE trial, **(4) (NEJM 2011 vol. 365 pp. 981-992)** apixaban has been compared to warfarin for prevention of stroke and systemic thromboembolism in patients with non valvular atrial fibrillation.
In the AMPLIFY trial, **(5) (NEJM 2013 vol. 369 pp. 799-808)** apixaban has been compared to standard therapy with enoxaparin and warfarin in the treatment of acute venous thromboembolism.
In the AMPLIFY-EXTENSION trial, **(6) (NEJM 2013 vol. 368 pp. 699-708)** apixaban was compared to placebo in patients with venous thromboembolism who had already completed 6 to 12 months of anticoagulation therapy and the study was continued for 12 months.
In the ADOPT trial, **(7) (NEJM 2011 vol. 365 pp. 2167-2177)** the use of an extended thromboprophylaxis with apixaban for 30 days in patients with acute medical illness has been investigated.
In the APPRAISE-2 study, **(8) (NEJM, 2011 vol. 365 pp. 699-708)** apixaban has been compared to placebo in patients on standard antiplatelet therapy, with a recent acute coronary syndrome (ACS)
All these trials and their results with a critical review, will be discussed in the sections "Indications" and "Conclusions" . Use of apixaban must be avoided with concomitant use of potent inhibitors of CYP3A4 or P-glicoprotein (P-gp) as azole antimicotics and protease HIV inhibitors,and with strong inducers of CYP3A4 and P-glicoprotein(P-gp) such as carbamazepine, phenytoin, phenobarbital, dexamethasone, rifampicine etc. (see section on "Contraindications"). At the moment a phase 3 study designed to test an antidote to the factor Xa inhibitor met its primary efficacy end point, according to an announcement from Portola Pharmaceuticals. An intravenous bolus of andexanet alfa, "immediately and significantly" reversed the anticoagulation of apixaban in the ANNEXA-A study, the company reported. In total, 33 healthy volunteers in the study were treated with apixaban 5 mg twice daily for four days and then randomized to andexanet alfa 400 mg. or placebo. Given the

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positive results, Portola plans to file an application with the US Food and Drug Administration (FDA) for accelerated approval. (see section on "Adverse reactions") Recently in November 2014, The New England Journal of Medicine published a letter in which a new small synthetic, water-soluble, cationic molecule, PER977 (Arizapine) 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, also 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. **(9) (New England Journal of Medicine 2014 vol. 371 pp. 2141-2142)** For details, see review on Dabigatran, section on "Adverse reactions".
The time in therapeutic range (TTR) in all the studies which involved the DOACs was quite low (55-64%) and far below the 80% achieved, using the INR self-testing with online remote monitoring and management ($STORM_2$) **(10) (Journal of Thrombosis and Thrombolysis 2011 vol. 31 (3) pp. 265-274).** In the EAA study **(11) (Journal of Thrombosis and Haemostasis 2014 vol. 12 pp.1193-1195)** using warfarin, the incidence of overall events (% per year) for stroke, major bleedings, minor bleedings and death were 0.30, 0.86, 2.70 and 0.75 per year respectively, that is much less compared with the incidence observed in patients treated with warfarin in DOACs trials. In addition, the annualized incidence of intracranial hemorrhage (ICH) was much lower in atrial fibrillation patients taking warfarin, in the SPORTIF III trial (0.53%) **(12) (Lancet 2003 vol. 362 pp. 1691-1698),** in the SPORTIF V trial (0.28%) **(13) (JAMA 2005 vol. 293 pp. 690-698),** in a Cochrane review 0.30% **(14) (Cochrane Database of Systematic Reviews 2005 Issue 3 Art. No. CD001927),** in another Cochrane Review 0.45% **(15) (Cochrane Darabase Review 2007 Issue 3 Art. No. CD006186)** than the incidence of ICH in patients taking warfarin in DOACs trials. For this reason, also the statement that DOACs cause less intracranial hemorrhages than warfarin must be taken with caution. As demonstrated in the recent EAA study **(11) (Journal of Thrombosis and Haemostasis 2014 vol. 12 pp. 1193-1195),** a state of the art laboratory control of warfarin reduces in an impressive manner all the bleeding and thrombotic adverse events. In the so called "real world", at least in western european countries and north america, it is not anymore possible to accept a not optimal laboratory control of vitamin K antagonists treatment, because of the great number of specialized anticoagulation clinics. All the clinicians involved in the oral anticoagulant therapy should refer their patients to these anticoagulation clinics. Only in this manner it is possible to obtain an optimal laboratory control of vitamin K antagonists treatment and consequently to use DOACs in selected cases only. In addition, differently from vitamin K antagonists with the use of DOACs we do not have a laboratory value that will be able to let we know if the patient can receive a surgical procedure without any bleeding. On the contrary, with the use of INR we certainly can say that with a value < 1.4 the patient can receive a major surgery too. **(16) (Journal Watch, September 30, 2014 Reader Comments, Vincenzo Marottoli)**
The health and the life of our patients is so an important issue that cannot be prevaricated by our personal career and economic interests.

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Mechanism of action

Apixaban is an oral, reversible, and selective active site inhibitor of activated factor X (FXa). It does not require antithrombin III for its anticoagulative activity. Apixaban inhibits free and clot-bound FXa, and prothrombinase activity. By inhibiting FXa, apixaban decreases thrombin generation and thrombus development.

(Enzyme) (Cofactor)
Factor Xa+Factor Va+calcium ions,+phospholipids
Prothrombin----------Thrombin
(figure 1)

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)

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Indications

Apixaban has been approved in Europe, Canada and United States for thromboprophylaxis in patients undergoing total knee or total hip replacement surgery (apixaban should be started 12 to 24 hours after the operation at a dosage of 2.5 mg. twice a day for 32-38 days after a hip replacement or for 10-14 days after a knee replacement), for prevention of stroke and systemic embolism in patients with nonvalvular atrial fibrillation, with one or more risk factors such as a previous stroke, a previous transient ischemic attack (TIA), age =/ > 75 years, hypertension, diabetes mellitus, symptomatic heart failure (Class NYHA =/ > 2) at a dosage of 5 mg. twice a day, for treatment of Deep Vein Thrombosis (DVT) and Pulmonary Embolism (PE) at a dosage of 10 mg. twice daily for the first 7 days followed by 5 mg. twice daily and for prevention of recurrent DVT and PE following completion of 6 months of treatment for DVT or PE, at a dosage of 2.5 mg. twice daily. The recommended dosage of apixaban is 2.5 mg. twice daily in patients with NVAF and at least two of the following characteristics : age >/= 80 years, body weight < / = 60 kg, or serum creatinine > / = 1.5 mg/dl. In patients with creatinine clearance < 15 ml/min, or in patients undergoing dialysis, the use of apixaban is not recommended. In the ADVANCE-1 trial, a double-blind, double-dummy study,**(1) (NEJM 2009 vol. 361 pp. 594-604)** 3195 patients undergoing total knee replacement surgery were randomized to apixaban 2.5 mg. twice daily or enoxaparin 30 mg. twice daily. In a double dummy trial, there are usually two placebos. This is necessary when the drugs are administered by different routes (for example by injection as enoxaparin or by pill as apixaban) or by different protocol (once a day versus weekly dosing). To keep participants from knowing in which treatment arm they are, they usually take one active drug and one of placebo. Both medications, apixaban and enoxaparin were started 12 to 24 hours after surgery and continued for 10 to 14 days. Bilateral venography was then performed, and patients were followed for 60 days after anticoagulation was stopped. Asymptomatic and symptomatic deep vein thrombosis (DVT), non fatal pulmonary embolism, and all-cause death during treatment were found in 9% of patients in the apixaban group, and in 8,8% of patients in the enoxaparin group. Major and clinically relevant non-major bleedings were significantly lower in the apixaban group than in the enoxaparin group, 2,9% versus 4,3% respectively.
In the ADVANCE-2 trial, a randomised , double blind phase 3 study, **(2) (The Lancet 2010 vol. 375, issue 9717, pp. 807-815)** 3057 patients undergoing total knee replacement surgery were randomized to receive oral apixaban 2.5 mg. twice daily, or enoxaparin 40 mg. once daily. Apixaban was started 12-24 hours after wound closure and enoxaparin 12 hours before surgery. Both drugs were continued for 10-14 days and bilateral venography was then performed. Asymptomatic and symptomatic deep vein thrombosis, non fatal pulmonary embolism, and all-cause death during treatment occurred in 15% of patients in the apixaban treated group and in 24% of patients in the enoxaparin treated group. Major and clinically relevant non-major bleedings occurred in 4% of patients receiving apixaban, and in 5% of patients receiving enoxaparin.
In the ADVANCE-3 trial, a double-blind, double-dummy study, **(3) (NEJM 2010 vol. 363 pp. 2487-2498)** 5407 patients undergoing total hip replacement surgery were randomized to receive apixaban at a dose of 2.5 mg. orally twice daily, or enoxaparin at a dose of 40 mg. subcutaneously

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once daily. Apixaban was initiated 12 to 24 hours after closure of the surgical wound , enoxaparin was initiated 12 hours before surgery and prophylaxis was continued for 35 days after surgery and bilateral venography was then performed. Asymptomatic and symptomatic deep vein thrombosis (DVT), nonfatal pulmonary embolism, and death from any cause occurred in 1.4% of patients in the apixaban group and in 3.9% of patients in the enoxaparin group. Major and clinically relevant nonmajor bleedings occurred in 4.8% of patients in the apixaban treated group and in 5.0% of patients in the enoxaparin group.
In the AVERROES trial,a double blind study, **(4) (NEJM 2011 vol. 364 pp.806-817)** 5999 patients with atrial fibrillation who were at increased risk for stroke and for whom vitamin K antagonist therapy was unsuitable, or patients who were unwilling to receive therapy with vitamin K antagonists, were randomized to receive apixaban at a dose of 5 mg. twice daily or aspirin (81 to 324 mg. per day) to determine if apixaban was superior. Patients were eligible if they were 50 years of age or older, if they had atrial fibrillation with at least one of the following risk factors for stroke : previous stroke or previous transient ischemic attack (TIA), an age of 75 years or older, hypertension, diabetes mellitus, heart failure (NYHA class 2 or higher), a left ventricular ejection fraction of 35% or less, or documented peripheral-artery disease.

New York Heart Association (NYHA)

Class I (Mild) No limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, or dyspnea (shortness of breath).

Class II (Mild) Slight limitation of physical activity. Comfortable at rest, but ordinary physical activity results in fatigue, palpitation, or dyspnea.

Class III (Moderate) Marked limitation of physical activity. Comfortable at rest but less than ordinary activity causes fatigue, palpitation, or dyspnea.

Class IV (Severe) Unable to carry out any physical activity without discomfort. Symptoms of cardiac insufficiency at rest. If any physical activity is undertaken, discomfort is increased.

There were stroke or systemic embolism in 1,6% patients per year in the apixaban group and in 3,7% patients per year in the aspirin group. The rates of death were 3,5% patients per year in the apixaban group and 4,4% patients per year in the aspirin group. Major bleedings were 1,4% patients per year in the group treated with apixaban and 1,2% patients per year in the group treated with aspirin.
In the ARISTOTLE trial, a double-blind trial, **(5) (NEJM 2011 vol. 365 pp. 981-992)** 18201 patients with atrial fibrillation and at least one additional risk for stroke, were randomized to receive apixaban at a dose of 5 mg. twice daily or warfarin (target INR 2.0-3.0). The risk factors for stroke were an age of 75 years or more, a previous stroke or a previous transient ischemic attack (TIA), or a systemic embolism, symptomatic heart failure within the previous three months or a left

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ventricular ejection fraction of no more than 40%, diabetes mellitus, hypertension requiring pharmacologic treatment. A dosage of 2,5 mg. twice daily was used in patients with two or more of the following criteria : an age of at least 80 years, a body weight of no more than 60 kg., or a serum creatinine level of 1,5 mg. per deciliter or more. Stroke or systemic embolism occurred in 1,27% patients per year in the apixaban group and in 1,60% patients per year in the warfarin group. The rate of major bleeding was 2,13% patients per year in the apixaban group and 3,09% patients per year in the warfarin group, and the rates of death from any cause were 3,52% and 3,94% patients per year respectively. The rate of hemorrhagic stroke was 0,24% patients per year in the group of patients treated with apixaban and 0,47% patients per year in the warfarin treated group.
In the ADOPT trial, a double-blind, double-dummy, placebo controlled trial, **(6) (NEJM 2011 vol. 365 pp. 2167-2177)** 6528 acutely ill patients with heart failure or respiratory failure or other medical disorders and who were hospitalized with an expected stay of at least 3 days, were randomized to receive apixaban at a dose of 2.5 mg. twice daily for 30 days, or enoxaparin administered subcutaneously at a dose of 40 mg. once daily for 6 to 14 days. On day 30, total venous thromboembolism (VTE), including fatal or non fatal pulmonary embolism, symptomatic deep-vein thrombosis, and asymptomatic proximal-leg deep vein thrombosis as detected with the use of systematic bilateral compression ultrasonography was 2.71% in the apixaban group and 3.06% in the enoxaparin group. Major bleeding was 0.47% the apixaban group and 0.19% in the enoxaparin group.
In the AMPLIFY trial, a randomised, double blind trial, **(7) (NEJM 2013 vol. 369 pp. 799-808)** 5395 patients with acute venous thromboembolism were randomized to receive apixaban at a dose of 10 mg. twice daily for 7 days, followed by 5 mg. twice daily for 6 months or to receive standard therapy, subcutaneous enoxaparin followed by warfarin. In the study were included patients of 18 years of age or older and with a confirmed symptomatic proximal deep vein thrombosis or pulmonary embolism with or without deep vein thrombosis. Patients were excluded if they had a high risk of bleeding, if they had cancer, if their deep vein thrombosis or pulmonary embolism was provoked in the absence of a persistent risk factor for recurrence, if an anticoagulant treatment was planned for less than 6 months, if they were treated with dual antiplatelet therapy or potent inhibitors of cytochrome CYP3A4, if they had a platelet count less than 100000 per cubic millimeter, or a serum creatinine level of more than 2.5 mg. per deciliter, or an alanine aminotransferase or aspartate aminotransferase level more than 2 times the upper limit of the normal range. Symptomatic venous thromboembolism or death related to venous thromboembolism occurred in 2.3% of patients in the apixaban group and in 2.7% of patients in the standard therapy group. Major bleeding occurred in 0,6% of patients who received apixaban and in 1,8% of patients who received standard therapy. Major bleeding and clinically relevant non major bleeding occurred in 4.3% of patients treated with apixaban and in 9.7% of patients treated with standard therapy.
In the AMPLIFY-EXTENSION trial, a randomized, double blind study, **(8) (NEJM 2013 vol. 368 pp. 699-708)** apixaban at doses of 2.5 mg. and 5 mg. twice daily, was compared with placebo in patients with venous thromboembolism who had completed 6 to 12 months of anticoagulation therapy and for whom we were not clinically obliged to continue the anticoagulation therapy. The study drugs were administered for 12 months. In the study were included patients who were 18 years of age or older , if they had confirmed, symptomatic deep vein thrombosis or pulmonary

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embolism, with or without deep vein thrombosis, if they had been treated for 6 to 12 months with standard anticoagulant therapy, or had completed treatment with apixaban or enoxaparin as participants in the AMPLIFY trial. Symptomatic recurrent venous thromboembolism or death from venous thromboembolism occurred in 8,8% of patients in the placebo group, compared with 1,7% of patients in the apixaban group at a dosage of 2,5 mg. twice daily and with 1,7% of patients in the other apixaban group at a dosage of 5 mg. twice daily. The rates of major bleeding were 0,5% in the placebo group, 0,2% in the 2,5 mg. apixaban group, and 0,1% in the 5 mg. apixaban group. The rates of clinically relevant nonmajor bleeding were 2,3% in the placebo group, 3,0% in the group treated with 2,5 mg. of apixaban twice daily and 4,2% in the other group treated with 5 mg. twice daily.
In the phase II APPRAISE trial, a double blind, placebo controlled, dose ranging study, **(9) (Circulation 2009 vol. 119 pp. 2877-2885)** 1715 patients with recent ST-elevation or non ST-elevation acute coronary syndrome were randomized to 6 months of placebo or 1 of 4 doses of apixaban : 2.5 mg. twice daily, 10 mg. once daily, 10 mg. twice daily, or 20 mg. once daily, but the last two higher-dose apixaban arms were discontinued because of excess total bleeding. All patients received aspirin and 76% received clopidogrel. Major or clinically relevant nonmajor bleeding occurred in 3,0% of patients in the placebo group, in 5.7% of patients in the 2.5 mg. twice daily apixaban group and in 7.9% of patients in the 10 mg. once daily group. Cardiovascular death, myocardial infarction, severe recurrent ischemia, or ischemic stroke occurred in 8.7% of patients in the placebo group, in 7.6% of patients in the 2.5 mg. twice daily apixaban group, and in 6.0% of patients in the 10 mg. once daily group.
In the plase III APPRAISE-2 trial, a randomized, double-blind, placebo-controlled trial, **(10) (NEJM 2011 vol. 365 pp. 699-708)** 7392 patients were randomized to receive apixaban at a dose of 5 mg. twice daily or placebo, in addition to standard antiplatelet therapy, in patients with a recent acute coronary syndrome and at least two additional risk factors for recurrent ischemic events as an age of at least 65 years, diabetes mellitus, myocardial infarction within the previous 5 years, cerebrovascular disease, peripheral vascular disease, clinical heart failure or a left ventricular ejection fraction less than 40% . The trial was terminated prematurely after enrolment of 7392 patients because an increase in major bleeding events without a reduction in recurrent ischemic events. Cardiovascular death, myocardial infarction, or ischemic stroke occurred in 7,5% of patients in the apixaban group and in 7,9% of patients in the placebo group.
Major bleeding occurred in 1,3% of patients in the apixaban group and in 0,5% in the placebo group. A greater number of intracranial and fatal bleeding events occurred with apixaban than with placebo.

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Absorption and metabolism

Despite a short clearance half-life of about 6 hours, the apparent half-life during repeat dosing is about 12 hours, and this allows an effective anticoagulation with a twice daily dosing.The absolute bioavailability of apixaban is approximately 50% for doses up to 10 mg. Food does not affect the AUC (area under the curve) and the Cmax of apixaban at a dose of 10 mg. Maximum concentration (Cmax) of apixaban appears 3 to 4 hours after oral administration. It demonstrates linear pharmacokinetics with dose-proportional increases in exposure for oral doses up to 10 mg. Plasma protein binding of apixaban is from 87% to 93% and for this, cannot be removed by dialysis. Apixaban is metabolized mainly via CYP3A4 and unchanged apixaban is the major drug-related component in human plasma with no active circulating metabolites. Apixaban is eliminated in both urine and feces. Renal excretion accounts for about 27% of total clearance and 25% of the administered apixaban was recovered as metabolites, with the majority recovered in feces. Biliary and direct intestinal excretion contributes to elimination of about 50% of apixaban in the feces. Apixaban is a substrate of the P-glicoprotein (P-gp) that is a transport protein. There is an increase in apixaban exposure correlated to decrease in renal function, as assessed by creatinine clearance. In patients with mild (CrCl 51-80), moderate (CrCl 30-50) and severe (CrCl 15-29) renal insufficiency, apixaban plasma concentrations measured as AUC, were increased 16%, 29%, and 44% respectively, compared to individuals with normal renal function. **(1) (Summary of product characteristics, update 30 july 2014)** The oxidative metabolism of apixaban for the formation of all metabolited is predominantly catalyzed by CYP3A4/5, with minor contributions made by CYP1A2 and CYP2J2. The contributions of CYP2C8, CYP2C9, and CYP2C19 to the metabolism of apixaban are less important. As a consequence of these results, pharmacokinetics of apixaban may be altered by other drugs which are inducers or inhibitors of CYP3A4/5. **(2) American Journal Health-System Pharmacy 2012 vol. 69 (13) : 1113-1126)** The pharmacokinetics of apixaban is not substantially changed in patients with mild or moderate hepatic impairment. **(3) (Clinical Pharmacology & Therapeutics 2009 85 (suppl. 1) : S34 Abstracts)** The oxidative metabolism of apixaban by CYP3A4/5 and the fact that apixaban is a substrate for P-glycoprotein (P-gp) create the potential for drug interactions. In fact coadministration of apixaban with ketoconazole 400 mg. orally once a day, a strong inhibitor of both CYP3A4 and P-gp, led to a 2-fold increase in mean apixaban AUC (area under the curve) and a 1.6 fold increase in mean apixaban maximum concentration. For this reason the use of apixaban is not recommended in patients receiving concomitant systemic treatment with strong inhibitors of both CYP3A4 and P-gp such as ketoconazole, itraconazole, voriconazole, posaconazole and protease inhibitors such as ritonavir, saquinavir, indinavir etc. Diltiazepam hydrochloride 360 mg. orally once a day, a moderate CYP3A4 and a weak P-gp inhibitor, led to a 1.4 fold increase in mean apixaban AUC and a 1.3 fold increase in maximum plasma apixaban concentration. **(4) (Journal of Clinical Pharmacology 2009 vol. 49 pp. 1091-1130 Abstract)** Naproxen 500 mg. orally single dose, an inhibitor of P-gp but not an inhibitor of CYP3A4, led to a 1.5 fold and a 1.6 fold inbcrease in mean apixaban AUC and a 1.3 fold increase in maximum plasma apixaban concentration, respectively. The concomitant use of apixaban with strong CYP3A4 and P-gp inducers such as phenytoin, carbamazepine, phenobarbital, St.John's wort etc. may lead to reduced

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plasma apixaban concentrations. **(1) (Summary of product characteristics, update 30 july 2014)** In fact coadministration of apixaban with rifampicin, a strong inducer of both CYP3A4 and P-gp, led to a decrease of 54% in mean apixaban AUC and a decrease of 42% in maximum plasma apixaban concentration. **(5) (Journal of Clinical Pharmacology 2009 vol. 49 pp.1124 Abstracts)**

In nonvalvular atrial fibrillation in patients taking apixaban for the prevention of stroke or systemic embolism, the predicted apixaban steady-state exposure, median (5th, 95th percentile) in case of 5 mg twice daily is 171 ng/ml (91, 321) at Cmax and 103 ng/ml (41, 230) at Cmin. In case of 2.5 mg twice daily is 123 ng/ml (69, 221) at Cmax and 79 ng/ml (34, 162) at Cmin. The results demonstrate a fluctuation in peak-to-trough levels of about 1.7 folds.
In the treatment of DVT, PE and prevention or recurrent DVT and PE, in case of 10 mg twice daily the predicted apixaban steady-state exposure, median (5th, 95th percentile) is 251 ng/ml (111, 572) at Cmax and 120 ng/ml (41, 335) at Cmin. In case of 5 mg twice daily is 132 ng/ml (59, 302) at Cmax and 63 ng/ml (22, 177) at Cmin.
In case of 2.5 twice daily is 67 ng/ml (30, 153) at Cmax and 32 ng/ml (11, 90) at Cmin.The results demonstrate a fluctuation in peak-to-trough levels of about 2.2 folds. **(1) (Summary of product characteristics, updated 30-Jul-2014)** In a recent paper Skeppholm and collegues found that apixaban plasma concentration varied markedly, more than 10-fold in the entire cohort of patients (n=70) studied and varied markedly, about 6-fold also in the two dosage groups between the lowest and the highest plasma concentrations. The range was between 15-83 and 29-186 ng/ml for the 2.5 mg BID and 5 mg. BID respectively, with patients receiving 5 mg. BID having significantly higher apixaban concentrations. The authors write that "Taking into account the pronounced variability of exposure, it may rather be that measurement of plasma concentrations could represent a future way to guide dosage in vulnerable groups of patients with a high risk of both thromboembolism and bleeding". **(6) (Thrombosis Research 2015 vol. 136 pp. 148-153)**

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Dosage and drug interactions

In this section we will consider only the apixaban dosage that is used in the clinical indications approved by regulatory agencies in Europe, Canada and U.S.A. The dosages used in other indications in clinical trials, but not yet approved by regulatory agencies, will not be discussed here, also because they have already been treated in the section “Indications”.
For stroke prevention in patients with non-valvular atrial fibrillation, the recommended dose is 5 mg.twice daily taken with water, with or whithout food. In patients with at least two of the following characteristics : age = / > 80 years, body weight = / < 60 kg. or serum creatinine = / > 1,5 mg./dl (133 micromol/ml) , the recommended dose is 2,5 mg. twice daily. When used to prevent stroke with nonvalvular atrial fibrillation and CrCl < 25 ml/mn, **The American Heart Association/American Stroke Association recommendes to avoid use (Furie, 2012)**

For thromboprophylaxis in patients undergoing a total knee or a total hip replacement surgery, the dosage is 2,5 mg. twice daily. The treatment is started 12 to 24 hours after surgery and continued for 10-14 days or for about 35 days in case of total knee or total hip replacement surgery respectively.

Dosage modification in case of renal impairment

In case of mild (CrCl 51-80 ml/mn) or moderate (CrCl 30-50) renal impairment, in which the apixaban concentration is increased of 16% and of 29% respectively, is not required any dose adjustment, unless the patient fulfils criteria for dose reduction to 2,5 mg. twice daily based on age > / = 80 years, body weight < / = 60 kg, and/or serum creatinine = / > 1,5 mg./dl (133 micromol/ml). In case of severe renal impairment (CrCl < 30 ml/mn) use of apixaban is contraindicated. In this category of patients is useful to perform a calibrated anti-Xa chromogenic assay as we will discuss in the sections “Laboratory tests” and “Conclusions”.

Dosage modification in case of hepatic impairment

In mild or moderate hepatic impairment, Child-Pugh Class A or B, (for Child-Pugh score, see section on “Contraindications” in the Rivaroxaban review) is not recommended a dosage reduction, but only caution with apixaban use.
In severe hepatic impairment the use is not recommended .
In hepatic disease associated with coagulopathy and clinically relevant bleeding, use of apixaban is contraindicated.
Patients with elevated liver enzymes ALT/AST > 2 of normal values,and with a total bilirubin= / > 1,5 were excluded in clinical trials and therefore apixaban must not be used in this category of patients.
Prior to initiating apixaban, liver function testing must be performed.

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Dosage modifications in case of elderly patients

In elderly patients, systemic exposure is increased of about 32% in patients > 65 years of age, however, dose reductions are not required. Dosage reduction is only recommended for patients with non valvular atrial fibrillation who are = / > 80 years of age and either weight = / < 60 kg. or with a serum creatinine = / > 1,5 mg/dl. In any case, in this category of patients as will be discussed in the sections “Laboratory tests “ and “Conclusions”, it is useful to perform a calibrated anti-Xa chromogenic assay.

Drug interactions

Concomitant use of apixaban with strong inhibitors of both CYP3A4 and P-glicoprotein (P-gp) such as azole-antimycotics (ketoconazole, itraconazole, voriconazole and posaconazole) and HIV protease inhibitors (ritonavir etc.) must be avoided. In case of concomitant use of apixaban with less potent inhibitors of CYP3A4 and/or P-gp, such as diltiazem, naproxen, amiodarone, verapamil and quinidine, no dose adjustement is required, but also in this case can be useful to perform laboratory tests. For example a single dose of naproxen 500 mg., a less potent inhibitor of P-gp but not an inhibitor of CYP3A4, led to a 1.5 fold and 1.6 fold increase in mean apixaban AUC and Cmax respectively . A corresponding 63% increase in mean anti-Xa activity at 3 hours post-dose, was observed when apixaban was co-administered with naproxen.

Concomitant use of apixaban with strong inducers of both CYP3A4 and P-gp such as rifampicin, phenytoin, carbamazepine, phenobarbital, systemic dexamethasone and St. John’s Wort ,must be avoided.
Rifampicine leads to an approximate 54% and 42% decrease in mean apixaban AUC and Cmax respectively.

Because of increased risk of bleeding, apixaban must be used with caution with drugs that inhibit platelet aggregation such as Aspirin, Thienopyridines (prasugrel,clopidogrel and ticlopidine), Cangrelor, Ticagrelor, GPIIb/IIIa receptor antagonists, Dipyridamole, and Non Steroidal Anti-Inflammatory Drugs (NSAIDs) and inhibitors of serotonine reuptake (SSRIs).

For conversion from vitamin K antagonists to apixaban, warfarin or other vitamin K antagonists must be discontinued and apixaban must be started when the international normalized ratio (INR) is < 2.0.

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

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For conversion from apixaban to anticoagulants other than vitamin K antagonists, apixaban must be discontinued, and the other anticoagulant can be started at the next apixaban scheduled dose.
Also in these last two cases, before starting a therapy with another anticoagulant, can be useful to perform a calibrated anti-Xa chromogenic assay.

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Adverse reactions

The most important adverse reaction is bleeding. Major hemorrhages such as intracranial, gastrointestinal, retinal hemorrhages, epidural hematoma and minor hemorrhages have been described. Risk factors that increase possibility of important bleedings are congenital and acquired bleeding diseases, trombocytopenia, (platelets < 90000 per cubic millimeter) a recent stroke, severe uncontrolled hypertension, severe renal impairment, recent major surgery, recent major bleeding such as intracranial, gastrointestinal, pulmonary or intraocular bleeding, concomitant use of drugs that increase apixaban Cmax (see section on " Dosage and drug interactions") and concomitant use of drugs that inhibit platelet aggregation such as aspirin, non steroidal anti-inflammatory drugs (NSAIDs), cangrelor, ticagrelor, and thienopyridines, such as clopidogrel, ticlopidine and prasugrel. At the moment, does not exist an antidote commercially available to neutralize the anticoagulant effect of apixaban. A protein, PRT064445,also known as PRT4445,which binds to direct factor Xa inhibitors as rivaroxaban, apixaban , the investigational agent betrixaban, and to indirect factor Xa inhibitors as fondaparinux, has been developed for use as an antidote to reverse the factor Xa inhibition from rivaroxaban ,apixaban and betrixaban in a dose dependent manner and corrected the prolongation of clotting times caused by these factor Xa inhibitors in ex vivo studies.**(1) (Nature Medicine 2013 vol.19 pp.446-451)** A synthetic small molecule antidote known as PER977 has been tested in human plasma and animals. In an ex vivo study of human plasma, the anti-factor Xa activity of rivaroxaban and apixaban at 100% and 200% of the therapeutic peak plasma concentrations was completely reversed by PER 977 in a dose dependent manner.**(2) (Circulation 2012 vol. 126 Abstract 11395) (3) (Circulation 2012 vol. 126 Abstract 18809)** On October 1, 2014 Portola Pharmaceuticals announced that its first Phase 3 study of andexanet alfa, a potential universal Factor Xa inhibitor antidote, met its primary and secondary endpoints with high statistical significance.
The primary endpoint included anti-Factor Xa levels, and secondary endpoint included levels of plasma unbound (free fraction) of apixaban and thrombin generation. Andexanet alfa has been shown to be well tolerated in Phase 1 and Phase 2 clinical studies, which have included more than 100 healthy volunteers, with no thrombotic events or antibodies to Factor Xa or Factor X observed.
An intravenous bolus of andexanet alfa "immediately and significantly" reversed the anticoagulation of apixaban in the ANNEXA-A study. In total, 33 healthy volunteers in the study were treated with apixaban 5 mg twice daily for four days and then randomized in a 3:1 ratio to andexanet alfa administered as a 400 mg IV or to placebo. In the second ANNEXA-A study, 32 healthy volunteers will be given apixaban 5 mg twice daily for four days and then randomized in a 3:1 ratio to andexanet alfa administered as a 400 mg IV bolus followed by a continuos infusion of 4 mg/min for 120 minutes or placebo. These data are expected in early 2015. Results from three separate Phase 2 proof-of-concept studies with apixaban,rivaroxaban and enoxaparin, in healthy volunteers demonstrated that andexanet alfa immediately reversed the anticoagulation activity of each Factor Xa inhibitor and that the reversal could be sustained. A Phase 2 proof-of-concept study with edoxaban is ongoing, and a Phase 2 proof-of-concept study with Portola's Factor Xa inhibitor Betrixaban is planned. **(4) (www.medscape.com/viewarticle/832648) (5) (www.portola.com)**

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Just recently in November 2014, The New England Journal of Medicine, published a letter in which a new agent, PER977 (arizapine) is able to bind through non-covalent hydrogen bonding and charge-charge interactions to unfractioned heparin (UF), to low molecular weight heparin (LMWH) and to the new oral factor Xa inhibitors, edoxaban, rivaroxaban and apixaban, and to the oral thrombin inhibitor dabigatran antagonizing their anticoagulant effect. **(6) (New England Journal of Medicine 2014 vol. 371 pp.2141-2142)** For details see review on Dabigatran, section on "Adverse reactions". It is not possible to use dialysis to remove apixaban from plasma because of the strong binding of apixaban with plasmatic proteins. Therapy for severe hemorrhage include supportive therapies as mechanical compression,surgical compression,surgical hemostasis procedures, and transfusional support.
In patients with life-threatening bleeding, must be considered the use of hemostatic agents as recombinant activated factor VII (rFVIIa), activated and non activated prothrombin complex concentrates (PCCs). Because the prothrombotic potential of activated PCCs and rVIIa may be higher than that of non activated PCCs, some guidelines recommend the use of non activated PCCs as the first choice for reversal of the anticoagulant effect of apixaban and of the other new oral anticoagulants. **(7) (Thrombosis and Haemostasis 2012 vol. 108 pp. 876-886)** Because in 4-PCCs there is a wide variation in the amount of factors II, VII, IX and X, and protein C and protein S, and because PCCs are dosed based on FIX, the actual administered doses of the other components can vary considerably among different PCCs. PCCs also contain different amounts of anticoagulants as heparin and antithrombin. For these reasons, at the moment, in absence of clinical studies, we do not know if the results obtained with a PCC can be obtained with another one, and in the same time, we do not know which components of PCCs are more important in improving hemostasis when we use new direct inhibitors of factor Xa. We can have a clinical reversal of bleeding without having a correction of laboratory parameters,and this may be due to the relative insensitivity of some laboratory tests to the presence of the anticoagulant The dosing and the effectiveness of a therapy for reversal of the new oral anticoagulants depend on the level of the anticoagulant present. At the moment a consensus has not yet reached regarding PCCs use in reversing the new oral anticoagulants due to lack of clinical data. **(8) (Thrombosis and Haemostasis 2014 vol. 111 pp. 189-198)**

In healthy subjects, administration of activated charcoal 2 and 6 hours after ingestion of a 20 mg dose of apixaban reduced mean apixaban AUC by 50% and 27%, respectively, and had no impact on Cmax.
Mean half-life of apixaban decreased from 13.4 hours when apixaban was administered alone to 5.3 hours and 4.9 hours, respectively, when activated charcoal was administered 2 and 6 hours after apixaban. Thus, administration of activated charcoal may be useful in the management of apixaban overdose or accidental ingestion. **(9) (Summary of product characteristics, updated 30-Ju--2014)**

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Contraindications

a) Use of apixaban is contraindicated in patients with hepatic disease associated with coagulopathy and clinically relevant bleeding risk including cirrhotic patients with Child Pugh B and C (For Child Pugh score, see section on “Contraindications” in the Rivaroxaban review). Patients with elevated liver enzymes ALT/AST > 2 x upper limit of normal (ULN) were excluded in clinical trials.

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, with 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, arterial aneurysm, concomitant use of drugs that affect hemostasis (Unfractioned Heparin (UFH), low molecular weight heparins (LMWH), Heparin derivatives, (Fondaparinux), with other oral anticoagulants except when we switch therapy to apixaban or from apixaban.

c) In patients with severe renal insufficiency, (CrCl < 30 ml/mn) use of apixaban is contraindicated.

d) Use of apixaban in patients with severe hypertension not well controlled must be avoided

e) Use of apixaban in patients who are receiving concomitant systemic treatment with azole-antimycotics as ketoconazole or HIV protease inhibitor as ritonavir is contraindicated, because these drugs are strong inhibitors of CYP3A4 and of P-glicoprotein (P-gp), and because apixaban is a substrate of CYP3A4. (see section on “Dosage and drug interactions”). In these cases, apixaban plasma concentrations increases and can cause an important bleeding.
Use in patients who are in treatment with strong inducers of CYP3A4 and P-gp as carbamazepine, phenytoin and rifampicin must be avoided, because apixaban plasma concentrations can decrease to a clinically relevant degree causing an increase of thrombotic risk.

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

g) In case of invasive or surgical procedures, if these procedures cannot be delayed, it is useful to use a calibrated anti-Xa chromogenic assay to evaluate the apixaban concentration (see section on “Laboratory tests”) and eventually use PCCs . In case of an elective surgery procedure, apixaban must be discontinued for a sufficient period of time prior to the procedure, to reduce the risk of anticoagulant related bleeding.
Because the half-life of apixaban is about 12 hours, in case of procedures at low risk of bleeding, apixaban must be discontinued at least 24 hours prior to elective surgery or invasive procedures.

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In case of procedures at moderate or high risk of bleeding, apixaban must be discontinued at least 48 hours prior to elective surgery or invasive procedures . In any case, before the elective surgery, also after 48 hours the apixaban discontinuation, is useful to perform a calibrated anti-Xa chromogenic assay to evaluate apixaban plasma concentration.

h) Although in the ARISTOTLE trial **(1) (New England Journal of Medicine 2011 vol. 365 pp. 981 992)** it was recommended to reduce apixaban dose at 2,5 mg. twice daily in patients with two of the following criteria : age =/ > 80 years, weight =/ < 60 kg. and serum creatinine = / > 1,5 mg/dl , in this study, the median age was 70 years, and the median weight was 82 kg. For these reasons, because at the moment patients very elderly =/ > 80 years, and also patients with extreme body weight =/ < 60kg. or =/ > 110 kg., treated with apixaban are few, it is not recommend to use apixaban in these categories of patients, until we will not gain more clinical experience treating them in controlled clinical trials in the next years . This is particularly true for very elderly patients in whom renal function, already reduced, can precipitate suddendly for some reasons as dehidration, very common in this category of patients.
Also in these cases, in patients with extreme body weight and in elderly patients, if we decide to use apixaban, it is useful to monitor these patients with a calibrated chromogenic anti-Xa assay.

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

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Laboratory tests

Measurement of the anticoagulant effect of apixaban is indicated in many situations :

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

b) Unexplained bleeding in patients taking the drug

c) Thrombotic events during the treatment

d) To assess patients compliance

e) In patients with moderate or severe renal insufficiency because they have an increase in apixaban plasma concentration

f) In patients with mild or moderate hepatic impairment because apixaban is metabolized by the liver for about 70%

g) In case of bridging with other anticoagulants

h) In case of extreme body weight

i) In elderly patients because of frequent presence of renal insufficiency in this category of patients and more bleeding episodes

l) In patients requiring reversal of anticoagulation because of life-threatening hemorrhage

m) In patients taking other drugs that increase apixaban concentration as inhibitors of CYP3A4 and of P-gp,
or that decrease its concentration as inducers of CYP3A4 and P-gp (see section on "Dosage and drug interactions")

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

o) Before surgical or invasive procedures, to know the residual amount of apixaban in plasma after having discontinued this drug

p) When chronic anticoagulation is achieved, 1-2 weeks after initation

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q) At regular intervals during clinical visits

r) Soon before and after introducing additional drugs that may interfere with apixaban plasma concentration

Laboratory results are dependent on when the last dose of drug was taken. Apixaban maximum plasma concentration was achieved about 3 hours after oral administration. Apixaban steady-state concentrations were reached by day 3 with an accumulation index of 1.3-1.9. Its half-life is about 12 hours. In healthy subjects, at the dose of 2.5 mg. twice daily, apixaban Cmax at day 1 and at day 7 is 51.0 ng/ml and 62.3 ng/ml respectively, with a coefficient of variation of 27% and of 37%. Apixaban Cmin (minimum observed concentration) with the same dosage at day 1 and at day 7 is 14.2 ng/ml and 21.0 ng/ml respectively with a coefficient of variation of 53% and of 17%.
At the dose of 5 mg. twice daily, apixaban Cmax at day 1 and at day 7 is 81.9 ng/ml and 128.5 ng/ml respectively, with a coefficient of variation of 18% and of 10%. Apixaban Cmin at day 1 and day 7 is 25.3 ng/ml and 49.6 ng/ml respectively, with a coefficient of variation of 20% at day 1 and at day 7.
At the dose of 10 mg. twice daily apixaban Cmax at day 1 and at day 7 is 226.2 ng/ml and 329.8 ng/ml respectively, with a coefficient of variation of 38% and of 45%. Apixaban Cmin at day 1 and at day 7 is 72.7 ng/ml and 103.8 ng/ml respectively, with a coefficient of variation of 27% and of 57%.
(1) (British Journal of Clinical Pharmacology 2013 vol. 76 (5) pp. 776-786) Apixaban generally exhibits dose-proportional increases in exposure after administration of the first dose as well as at steady-state exposure. The PT and APTT are the most used tests to study coagulation in many laboratories, but in case of apixaban, also if the PT shows a concentration-dependent prolongation of clotting time, the sensitivity depends on the reagent used and for example, we can have a normal prothrombin time with therapeutic concentrations of apixaban. The aPTT shows a non linear concentration-dependent prolongation of clotting time. These tests cannot be used to evaluate apixaban plasma concentrations.
Thrombin Time (TT), Ecarin Clotting Time (ECT), and Reptilase Time (RT) are not influenced by apixaban.
In case of determination of Lupus Anticoagulant, the PTT-LA and the STA-Staclot-LA are both prolonged in a concentration-dependent manner in presence of apixaban. Staclot-DRVV Screen and Confirm are also prolonged dose dependently. For these reasons, the presence of Lupus Anticoagulant in patients taking apixaban cannot be evaluated.
In case of clinically relevant concentrations of apixaban, for measurement of clotting factor activities, the aPTT-based clotting method does not show a linearity, and for this we cannot measure these activities in patients who are in therapy with apixaban, also if it seems that factor V and factor II coagulant activities are slightly affected by apixaban concentration until 500 ng/ml.
(2) (Thrombosis and Haemostasis 2014 vol. 111 (2) 240-248)
Determinations of Protein C by a chromogenic assay (Hemosil Protein C),of Free Protein S by an immunoturbidimetric method (STA-Staclot P Protein S), of Fibrinogen by Clauss method (STA-Fibrinogen), of Antithrombin III by a thrombin based chromogenic assay and not by a FXa-based chromogenic assay, are not influenced by apixaban plasma concentrations. Determinations of Protein S by a chronometric method (STA-Staclot Protein S) and of Activated Protein C resistance

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also by a chronometric method (Hemosil Factor V Leiden) are influenced by apixaban concentrations . **(3) (Thrombosis and Haemostasis 2013 vol. 110 (2) pp. 283-294)** The most accurate laboratory tests to evaluate apixaban concentrations are chromogenic assays using appropriate calibrators and controls. For apixaban, the Rotachrom anti-Xa chromogenic assay was particularly suitable since the dynamic range of the assay covered the plasma concentration range of apixaban associated with the 2.5 mg. and 5 mg. dose twice daily. This assay showed minimal inter-subject variation and no additional treatment as diluition, is expected for most patients.
(4) (Thrombosis and Haemostasis 2010 vol. 104 (6) pp. 1263-1271) In a recent study, three anti-Xa assays where evaluated to assess apixaban plasma levels. In this study, good results were achieved with liquid ready-to-use reagents, and with lyophilised calibrators and controls,which should be soon commercialised and with a standardised method and protocol. The three anti-Xa assays were Anti-Xa Hyphen, Anti-Xa Stago and Anti-Xa IL and accurate measurements of apixaban concentrations were obtained using specific and dedicated calibrators and controls with a high inter-laboratory precision and accuracy. **(2) (Thrombosis and Haemostasis 2014 vol. 111 (2) 240-248)**
Laboratory measurements are dependent on when the last dose of apixaban was taken, and more data are necessary to define ranges of plasma concentrations in some particular categories of patients, in some indications and situations, such as for example to define the safety values for invasive procedures. The fact that laboratory monitoring is not necessary for patients in treatment with apixaban and with other new oral anticoagulants is not completely true. An evaluation of apixaban concentration not only is necessary in some particular conditions, (see the beginning of this section) but we might suggest to perform laboratory testing for all patients once the treatment's steady state is reached. This basal value can after be compared with the value obtained at the time of an eventual bleeding. **(5) (Clinical Chemistry 2013 vol. 59 (2) pp. 353-362)**

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Conclusions

Apixaban has been approved in Europe, Canada and United States for thromboprophylaxis in patients who have a total knee or a total hip replacement surgery, to prevent stroke and systemic embolism in patients with non valvular atrial fibrillation, for treatment of patients with Deep Vein Thrombosis (DVT) and Pulmonary Embolism (PE), for the prevention of recurrent DVT and PE. In the section "Indications" are discussed all the clinical trials in which apixaban was used. In the ADVANCE-1 trial, **(1) (NEJM 2009 vol.361 pp. 594-604)** apixaban at the dose of 2.5 mg. twice daily was compared to enoxaparin 30 mg. twice daily for thromboprophylaxis in case of a total knee replacement surgery as prescribed by U.S. recommendations. Apixaban did not meet statistical criteria for noninferiority, but its use was associated with lower rates of bleeding. In the ADVANCE-2 trial, **(2) (The Lancet 2010 vol. 375 pp. 807-815)** apixaban at the dose of 2.5 mg. twice daily, was compared to enoxaparin 40 mg. once daily for thromboprophylaxis in case of a total knee replacement surgery as prescribed by European guidelines, and was found a significant reduction of asymptomatic and symptomatic deep vein thrombosis, non-fatal pulmonary embolism and all-cause death during treatment in the apixaban group. Major or clinically non-relevant major bleeding were about the same in the two groups, apixaban and enoxaparin group. In the ADVANCE-3 trial, **(3) (NEJM 2010 vol. 363 pp. 2487-2498)** apixaban at a dosage of 2.5 mg. twice daily was compared to enoxaparin 40 mg daily for thromboprophylaxis in case of a total hip replacement surgery. Lower rates of asymptomatic or symptomatic deep vein thrombosis, non fatal pulmonary embolism, or death from any cause during treatment period were obtained in the apixaban group, and major and clinically relevant nonmajor bleeding had about the same rate in the apixaban and in the enoxaparin group. Because in Europe we normally use 40 mg. of enoxaparin once daily for thromboprophylaxis in orthopedic surgery, and because in the U.S. physicians normally use 30 mg. of enoxaparin twice daily, analyzing the results of the ADVANCE trials, we can understand why apixaban had been approved for this indication in the U.S.A. only recently, in March 2014. In fact in the U.S.A. there was not a clinical advantage of apixaban over enoxaparin, differently from Europe where, on the contrary, using 40 mg. of enoxaparin once daily, there is a certain clinical advantage of apixaban over enoxaparin. In any case, if we want to use apixaban for thromboprophylaxis in orthopedic surgery, it is better if we use this drug in large hospitals where can be eventually managed an important bleeding provoked by apixaban and where there is a laboratory that must be able to perform a calibrated anti-Xa chromogenic assay to evaluate apixaban concentrations. For every patient, I recommend to perform this chromogenic assay 1-2 weeks after initiation and at 3 hours and after 12 hours the drug administration to know the Cmax and Cmin concentration of apixaban .
In the AVERROES trial, **(4) (NEJM 2011 vol. 364 pp. 806-817)** apixaban at the dosage of 5 mg. twice daily was compared to aspirin (81 to 324 mg. per day) in patients with non valvular atrial fibrillation at increased risk for stroke for whom vitamin K antagonists therapy was unsuitable as for example patients who had an intracranial hemorrhage while in treatment with a vitamin K antagonist. The study was terminated ahead of schedule because a clear benefit in favor of apixaban.

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In the ARISTOTLE trial, **(5) (NEJM 2011 vol. 365 pp. 981-992)** apixaban at the dosage of 5 mg. twice daily, was compared to warfarin in preventing stroke or systemic embolism in patients with non valvular atrial fibrillation. The conclusions of the study were that apixaban was superior to warfarin in preventing stroke or systemic embolism, caused less bleeding , and resulted in lower mortality. This study was a large study of 18201 patients conducted in north america, latin america, in europe,in asia and in the pacific area. The majority of patients, 7343 patients, were in europe. If we analyze the results for geographic area, we can see that in Europe, in 7343 patients, there were stroke and systemic embolism in 1.1% patients per year both in the apixaban group and in the warfarin group. Major bleedings occurred in 1.7% patients per year in the apixaban group and in 2.2% patients per year in the warfarin group. In North America, in 4474 patients, stroke and systemic embolism occurred in 1.0% patients per year in the apixaban group and in 1.3% patients per year in the warfarin group. Major bleedings occurred in 2.8% patients per year in the apixaban group and in 3.6% patients per year in the warfarin group. In Latin America, in 3468 patients, stroke and systemic embolism occurred in 1.4% patients per year in the apixaban group and in 1.8% patients per year in the warfarin group. Major bleedings occurred in 2.1% patients per year in the apixaban group and in 3.5% patients per year in the warfarin group. In Asia and the Pacific area, in 2916 patients, stroke and systemic embolism occurred in 2.0% patients per year in the apixaban group, and in 3.1 % patients per year in the warfarin group. Major bleedings occurred in 2.1% patients per year in the apixaban group and in 4.1% patients per year in the warfarin group.
Although in this study is reported an INR in the therapeutic range for a median of 66% of the time and a mean of 62.2% of the time, from the analysis of these results, we can assume that there is not a clinical advantage of apixaban over warfarin in Europe and a minimal advantage over warfarin for less major bleedings when apixaban is used in North America. This confirm that, as for dabigatran and rivaroxaban, we cannot use on a large scale apixaban in patients with non valvular atrial fibrillation in countries that have anticoagulation clinics with a good clinical and laboratory control of anticoagulation therapy with vitamin K antagonists, as West European Countries, Canada and United States. A clear clinical advantage of the use on a large scale of these new oral anticoagulants is true only for developing countries and for all the other countries that have a poor quality control of anticoagulant therapy with vitamin K antagonists.
In west countries which have specialised anticoagulation clinics, the use of apixaban and of the other new oral anticoagulants in patients with non valvular atrial fibrillation, is useful only in some particular cases of which we have already discussed in dabigatran and rivaroxaban review, expecially if we consider that at the moment we do not have an antidote commercially available to antagonize the anticoagulant effect of the new oral anticoagulants and, for this, also if are described less intracranial hemorrhages with their use compared to warfarin, if an intracranial hemorrhage occurs, it is difficult to stop it.
Also if we make the most sophisticated statistical analyses to try to demonstrate a superiority of apixaban and of the other new oral anticoagulants in the treatment of patients with non valvular atrial fibrillation, also in countries with a good clinical and laboratory control of anticoagulant therapy with vitamin K antagonists, we will not reach our goal because a good laboratory control of a patient in therapy with warfarin must reach a TTR of about 70-80%. We will write a paper only. If anticoagulation clinics are managed by skilled physicians and by skilled laboratory technicians,

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there is no way to demonstrate less adverse events with new oral anticoagulants compared with vitamin K antagonists and to deny the superiority of these last drugs in the treatment of patients with non valvular atrial fibrillation, until other manufacturer-indipendent trials will not be done. and until an antidote will not be commercially available. In fact, this was already demonstrated by an interesting paper published in 2014 in which Poller et al. compared the results obtained with warfarin and dabigatran in the RE-LY study (6022 patients) with the results obtained with warfarin in the European Action on Anticoagulation (EAA) study (5939 patients). The impressive better results obtained with warfarin in the EAA study, confirm the fact that it is possible to obtain better results with warfarin compared to direct oral anticoagulants when patients are controlled in specialized anticoagulation clinics. **(6) (Journal of Thrombosis and Haemostasis 2014 vol. 2014 vol. 12 pp. 1193-1195)** (for details, see review on Dabigatran, " Abstract" and section on "Indications") In any case, if we want to use direct oral anticoagulants also in patients treated at anticoagulation clinics in west countries, we must monitor them by a diluted thrombin time (Hemoclot) in case of direct thrombin inhibitors such as dabigatran, by a modified rivaroxaban PT or by a calibrated chromogenic anti-Xa assay in case of a direct Xa inhibitor such as rivaroxaban , or by a calibrated chromogenic anti-Xa assay in case of other direct Xa inhibitors such as apixaban and edoxaban, although in many papers be affirmed that they have a predictable pharmacokinetics and pharmacodynamics.

This last statement is not completely true as clearly demonstrated for dabigatran and for rivaroxaban. (see review on Dabigatran, "Abstract", and review on Rivaroxaban, section on "Absorption and metabolism") Probably we need to monitor these patients less times than patients taking warfarin, but we have to do it. We cannot do these tests only in case of a thrombotic or bleeding event, or before surgery. So the advantage that using these drugs we do not need laboratory monitoring , simply does not exist.

In the ADOPT trial, **(7)(NEJM 2011 vol. 365 pp. 2167-2177)** apixaban at a dose of 2.5 mg. twice daily for 30 days, was compared to enoxaparin 40 mg. once daily for 6-14 days, for thromboprophylaxis in medically ill patients. Apixaban was not superior to a shorter course with enoxaparin and was associated with a more significant rate of bleeding events than enoxaparin.

In the AMPLIFY trial, **(8) (NEJM 2013 vol. 369 pp. 799-808)** apixaban at a dose of 10 mg. twice daily for 7 days, followed by 5 mg. twice daily for 6 months, was compared to standard therapy, (subcutaneous enoxaparin followed by warfarin) in patients with venous thromboembolism. Apixaban was not inferior to standard therapy and was associated with significantly less bleeding. In fact recurrent symptomatic venous thromboembolism or death related to venous thromboembolism occurred in 2.3% of patients in the apixaban group and in 2.7% of patients in the standard therapy group. Major bleeding and clinically relevant nonmajor bleeding occurred in 4.3% of patients in the apixaban group and in the 9.7% of patients in the standard therapy group.

If we analyze the provenance of the patients randomized in this study, we can see that a robust group of patients, about one fifth of patients, were enrolled in Ukraine, Russia and Hungary and other patients in countries that do not also have an optimal laboratory control of oral anticoagulant therapy with vitamin K antagonists, such as India, Romania, Mexico, Brazil and China. Other patients, on the contrary, were enrolled in countries with a good control of oral anticoagulant therapy such as Italy, Canada, France, U.S.A., Israel, Denmark, Germany, Spain etc. For these

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reasons, also if statistical analyses were correct, I do not think that we can apply the results of this study in patients controlled at specialized anticoagulation clinics in West European Countries and in North America. Also in this case, we need manufacturer-independent trials conducted only in countries with an optimal control of oral anticoagulant therapy, in specialized anticoagulation clinics to avoid any bias, and hopefully in a near future,we will have an antidote commercially available to neutralize the anticoagulant effect of apixaban.

In the AMPLIFY-EXTENSION trial, **(9) (NEJM 2013 vol. 368 pp. 699-708)** apixaban at two doses, of 2.5 mg. and of 5 mg. twice daily, was compared with placebo in patients with venous thromboembolism who had completed 6 to 12 months of anticoagulation therapy and for whom we were not clinically obliged to continue the anticoagulat therapy. The drugs were administered for 12 months. Symptomatic recurrent venous thromboembolism or death from venous thromboembolism occurred in 8.8% of patients in the placebo group and in 1.7% of patients in the two apixaban groups (2.5 mg. and 5 mg.). The rates of major bleeding were 0.5% in the placebo group, 0.2% in the 2.5 mg.apixaban group and 0.1% in the 5 mg. apixaban group.

The rates of clinically relevant nonmajor bleeding were 2.3% in the placebo group, 3.0% in the 2.5 mg. apixaban group and 4.2% in the 5 mg. apixaban group. In this study apixaban was compared to placebo, but what we really need, also in this case, are studies in which extension therapy with apixaban must be compared with vitamin K antagonists in countries with a good clinical and laboratory control of this therapy. Also in this study, there are patients recruited in countries in which there is not a good laboratory control of patients in treatment with vitamin K antagonists and where very probably there is not also a good clinical follow-up of this kind of patients such as Russia, Ukraine, Brazil, India etc. For this reasons, I do not think we can apply the results of this study to our health systems in west countries.

In the APPRAISE-2 trial, **(10) (NEJM 2011 vol. 365 pp. 699-708)** apixaban at a dose of 5 mg. twice daily was added to standard antiplatelet therapy in patients with a recent acute coronary syndrome and at least two additional risk factors for recurrent ischemic events. The trial was terminated prematurely because of an increase in major bleeding events with apixaban, in the absence of reduction in recurrent ischemic events.

In conclusion, the use on a large scale in West European countries and in North America is not indicated. Its use can be useful only in particular cases, when the patient has difficulties to arrive to a specialized anticoagulation clinic, when he refuses a blood sample or when he had for example an intracranial bleeding with warfarin and after he needs to take an anticoagulant therapy again, considered the high probability of recurrence with warfarin as demonstrated by the Italian collaborative study **CHIRONE** (**C**erebral **H**aemorrhage **I**n patients **R**estarting **O**ral a**N**ticoagulant th**E**rapy). **(11) (Neurology 2014 vol. 82 (12) pp. 1020-1026)**.

In any case, if we care about the health and the life of our patients we need to monitor apixaban therapy not only clinically, but by a calibrated chromogenic anti-Xa assay too, although with a laboratory monitoring apixaban and the other DOACs would lose their commercial appeal.

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