doi: 10.1111/j.1472-8206.2011.00981.x

REVIEW ARTICLE

Themed series on ''Platelet inhibition and anticoagulation in cardiovascular disorders''

Pharmacodynamic and pharmacokinetic basics of rivaroxaban

Reinhold Kreutz*

Department of Clinical Pharmacology and Toxicology, Charité – Universitätsmedizin, Charitéplatz 1, D-10117 Berlin, Germany

Keywords
anticoagulant,
factor Xa,
pharmacodynamics,
pharmacokinetics,
rivaroxaban

Received 10 January 2011;
accepted 13 July 2011

*Correspondence and reprints:
Reinhold.Kreutz@charite.de

ABSTRACT

Rivaroxaban, an oral, direct factor Xa inhibitor, is a small molecule drug capable of inhibiting not only free factor Xa with high selectivity but also prothrombinase-bound and clot-associated factor Xa in a concentration-dependent manner. Clinical studies have demonstrated predictable anticoagulation and confirmed dose-proportional effects for rivaroxaban in humans with a rapid onset (within 2–4 h) and a half-life of 7–11 h and 11–13 h for young and elderly subjects, respectively. For a 10 mg dose, the oral bioavailability of rivaroxaban is high (80–100%) and is not affected by food intake. These favourable pharmacological properties underpin the use of rivaroxaban in fixed dosing regimens, with no need for dose adjustment or routine coagulation monitoring. Rivaroxaban has a dual mode of excretion with the renal route accounting for one-third of the overall elimination of unchanged active drug. Rivaroxaban is a substrate of CYP3A4 and P-glycoprotein and therefore not recommended for concomitant use with strong inhibitors of both pathways, e.g. most azole antimycotics and protease inhibitors. Rivaroxaban is currently approved for the prevention of venous thromboembolism (VTE) in adult patients undergoing elective hip or knee replacement surgery. Studies using 10 mg rivaroxaban once daily in this indication demonstrated its suitability for a wide range of patients regardless of age, gender or body weight. Further studies in the treatment of VTE, prevention of cardiovascular events in patients with acute coronary syndrome, prevention of stroke in those with atrial fibrillation and prevention of VTE in hospitalized medically ill patients have been reported or are ongoing.

Anticoagulant therapy is used in a variety of clinical settings from the prevention of venous thromboembolism (VTE) after surgery to prophylactic stroke prevention in patients with atrial fibrillation. In recent years, there has been considerable interest in developing oral anticoagulant therapies that offer safe and effective anticoagulation with no need for routine laboratory monitoring. Factor Xa, a coagulation factor that plays a central role in the coagulation pathway [1], has emerged as a promising target for the development of new anticoagulants. Rivaroxaban is the first oral, direct factor Xa inhibitor approved (in the European Union and numerous other countries) for the prevention of VTE in adult patients undergoing elective hip or knee replacement surgery. Further studies of rivaroxaban in the treatment of VTE, prevention of stroke in those with atrial fibrillation, prevention of VTE in hospitalized medically ill patients and prevention of cardiovascular events in patients with acute coronary syndrome have been reported or are ongoing [2].

BASIC PHARMACOLOGICAL PROPERTIES OF RIVAROXABAN

Rivaroxaban (Xarelto®; Bayer Schering Pharma AG, Berlin, Germany) is a direct factor Xa inhibitor with high selectivity [2]. The drug is a small molecule (molecular weight 436 g/mol) that is almost insoluble in water and exhibits high plasma protein binding (92–95%) in humans, with serum albumin being the main binding

component [3]. Rivaroxaban inhibits free factor Xa and prothrombinase-bound and clot-associated factor Xa in a concentration-dependent manner [2]. As a consequence, rivaroxaban prevents thrombin generation by inhibiting factor Xa generated via both the intrinsic and extrinsic coagulation pathways [4]. In vitro studies in platelet-poor and platelet-rich plasma have demonstrated that rivaroxaban prolongs the initiation phase of thrombin generation and reduces the thrombin burst produced in the propagation phase [2]. However, rivaroxaban exhibits no direct effect on platelet aggregation induced by collagen, adenosine diphosphate or thrombin [2]. In human plasma, rivaroxaban effectively and dose dependently inhibits factor Xa activity and prolongs both prothrombin time (PT) and activated partial thromboplastin time (aPTT) [5]. However, PT and aPTT are not useful for monitoring the pharmacodynamic effects of rivaroxaban in clinical practice, because the prolongation of these parameters varies significantly depending on the clotting assays and conditions used [2].

CLINICAL PHARMACOLOGY OF RIVAROXABAN

Pharmacokinetic profile

During the initial clinical development, the pharmacokinetic profile of rivaroxaban in healthy subjects was established and demonstrated a favourable safety and tolerability profile. The bioavailability of a 10 mg dose of rivaroxaban is high (80–100%), and rivaroxaban is rapidly absorbed, reaching a maximal plasma concentration (C_{max}) within 2–4 h after oral administration (*Figure 1*) [3,6]. The volume of distribution is moderate (approximately 50 L at steady state). At single daily doses up to 15 mg administered orally to healthy subjects, rivaroxaban displays near linear pharmacokinetics, with a half-life of 7–11 h (mean 9 h) for young subjects and no significant accumulation after repeat dosing [3,6]. In elderly subjects, the half-life of rivaroxaban is 11–13 h for doses up to 50 mg [7]. The pharmacokinetic profile for the 10 mg once-daily dose of rivaroxaban has been shown to be unaffected by food or treatments to reduce gastric acidity such as antacids or ranitidine [3,8]. Rivaroxaban does not inhibit or induce CYP450 isoforms. It is a substrate of CYP3A4 and CYP2J2 and is metabolized by these enzymes as well as via CYP-independent mechanisms [3]. Rivaroxaban has a dual mode of elimination; two-thirds of the drug undergoes metabolic degradation in the liver, half of which is excreted via the kidneys and half via the hepatobiliary route. One-third of the dose is eliminated as unchanged drug in the urine [3]. Rivaroxaban has no major or active circulating metabolites (*Figure 2*).

Pharmacodynamic profile

The dose-proportional pharmacodynamic effect of rivaroxaban as an anticoagulant agent was initially demonstrated in a single-centre, randomized, placebo-controlled, dose-escalation study in 108 healthy white male volunteers (aged 19–45 years) [6]. After single oral doses of 1.25–80 mg, rivaroxaban effectively and dose dependently prolonged PT (*Figure 3a*) and aPTT (not shown) [6]. A separate phase I study in healthy subjects confirmed the dose-dependent factor Xa inhibition after multiple dosing, with consequent dose-dependent PT

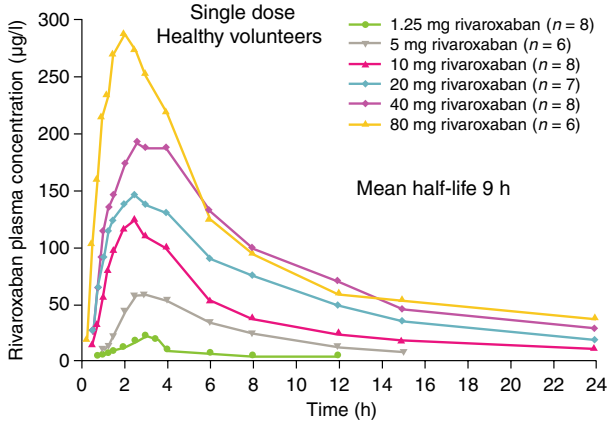

Figure 1 Pharmacokinetic profile of rivaroxaban according to the plasma concentration over time after single oral dosing [6].

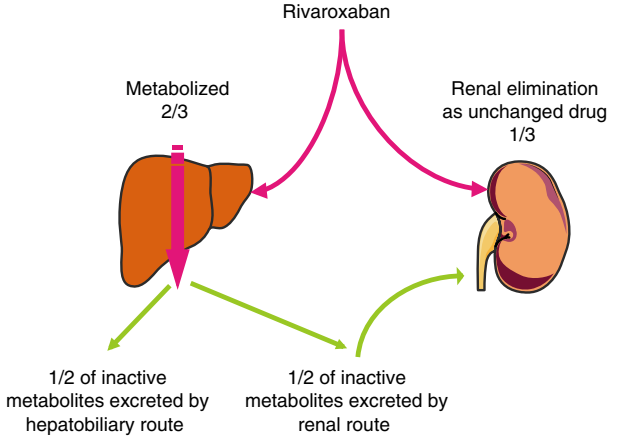

Figure 2 Routes of elimination of rivaroxaban and excretion of inactive metabolites.

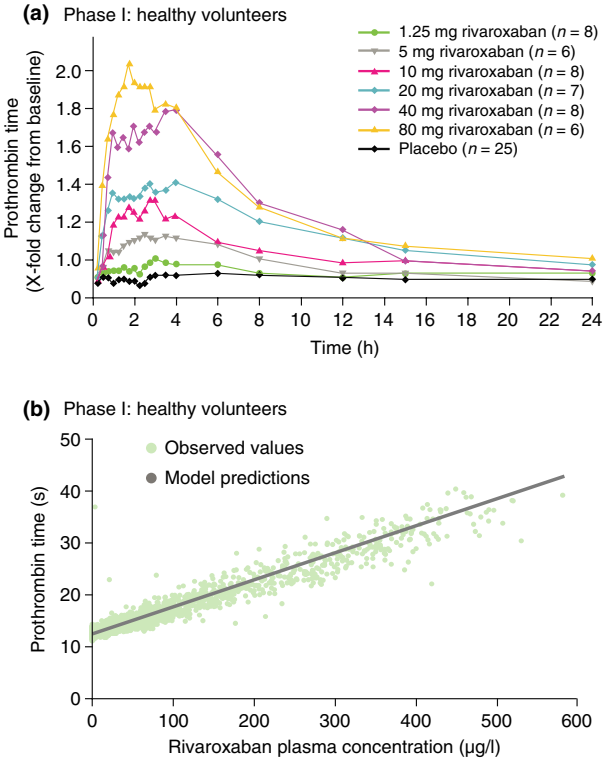

Figure 3 Prothrombin time inhibition after single oral dosing over time (a) and after multiple dosing in relation to rivaroxaban plasma concentration (b) [6,9].

prolongation and, ultimately, inhibition of thrombin generation [9]. Rivaroxaban plasma concentrations correlated closely with PT prolongation in both healthy volunteers (*Figure 3b*) [9] and patients undergoing either total hip or knee replacement [10].

Potential for drug interactions

The potential for drug interactions with rivaroxaban has been comprehensively investigated. A study in healthy volunteers showed that co-administration of rivaroxaban (15 mg) with 500 mg acetylsalicylic acid (ASA) had no additional effect on collagen-induced platelet aggregation vs. ASA alone [11]. Moreover, ASA exhibited no effect on rivaroxaban pharmacokinetics, and co-administration of ASA with rivaroxaban did not affect clotting parameters compared with rivaroxaban alone [10]. Bleeding time was prolonged with the combination of rivaroxaban and ASA compared with ASA alone, but this effect was small and was not considered clinically relevant [10]. Separate studies analysing the co-administration of rivaroxaban with the non-steroidal anti-inflammatory drug naproxen revealed similar results [12]. Consequently, co-administration of rivaroxaban with ASA or non-steroidal anti-inflammatory drugs was permitted in the RECORD study programme involving patients undergoing major orthopaedic surgery [13].

As noted above, rivaroxaban is a substrate of CYP3A4 and the drug transporter P-glycoprotein (P-gp) but is neither an inhibitor nor inducer of these metabolic pathways. The potential for drug interactions involving CYP3A4 and/or P-gp has been specifically evaluated during the clinical development of rivaroxaban [3]. These studies indicated that only co-administration of drugs that are potent inhibitors of both CYP3A4 and P-gp leads to clinically relevant increases in rivaroxaban plasma concentrations. Consequently, the use of rivaroxaban is not recommended in patients receiving concomitant systemic treatment with such drugs including azole antimycotics (such as ketoconazole, itraconazole, voriconazole and posaconazole) or HIV protease inhibitors such as ritonavir [3]. Rifampicin and other strong inducers of CYP3A4, such as phenytoin, carbamazepine, phenobarbital and St John's Wort, should be co-administered with rivaroxaban with caution [3]. No clinically significant interactions with other substrates of these two enzymes have been noted, and rivaroxaban can be co-administered with agents such as midazolam (a substrate of CYP3A4), digoxin (a substrate of P-gp) and atorvastatin (a substrate of both CYP3A4 and P-gp).

USE OF RIVAROXABAN IN SPECIAL POPULATIONS

A number of studies have also been undertaken to define the pharmacokinetic and pharmacodynamic profile and safety of rivaroxaban in various subpopulations of patients for whom anticoagulant therapy might be indicated in clinical practice.

Effects of body weight and gender

In a single-blind, placebo-controlled study in healthy male and female subjects, the pharmacokinetics and pharmacodynamics of rivaroxaban 10 mg were unchanged over the weight range ≤50 kg – >120 kg (range 45–173 kg), suggesting that it can be used at a fixed dose irrespective of weight [14]. There were no differences owing to body weight in the incidence or nature of adverse events in the healthy volunteers studied. Gender did not affect the pharmacokinetic or pharmacodynamic profile of rivaroxaban 10 mg [14].

Effects of age and renal impairment

Overall exposure to rivaroxaban (area under the plasma concentration–time curve) was higher in elderly than in younger individuals [3,15] with a prolongation of the half-life up to 13 h. This observation is largely attributable to the overall decreased renal function observed in the elderly. Consistent with this, studies in otherwise healthy volunteers have demonstrated that renal impairment results in decreased renal clearance of a single rivaroxaban 10 mg dose and increases overall exposure to the drug (*Figure 4a*) [16]. A recent study confirmed increased plasma exposure and pharmacodynamic effects in subjects with increasing renal impairment [16]. However, the influence of renal function on rivaroxaban clearance was moderate, as expected for a drug only partially renally excreted [16]. Accordingly, for the approved indication of 10 mg rivaroxaban once daily in patients undergoing elective hip or knee replacement surgery, no dose adjustment is required in mild (creatinine clearance [CrCl] 50–80 mL/min) or moderate (CrCl 30–49 mL/min) renal impairment. However, rivaroxaban should be used with caution in patients with moderate renal impairment concomitantly receiving other drugs that might increase rivaroxaban plasma concentrations and in patients with severe renal impairment (CrCl 15–29 mL/min). The drug is not recommended in patients with CrCl <15 mL/min.

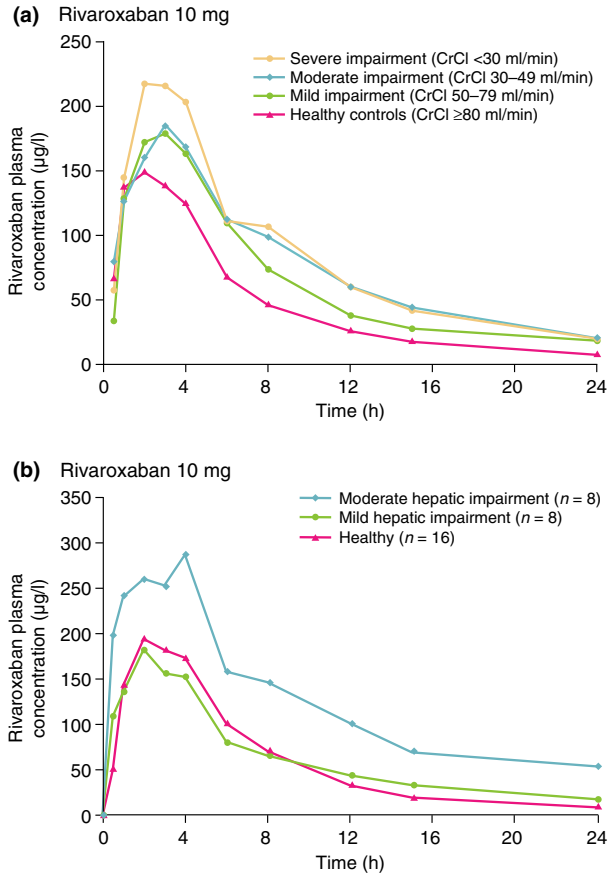

Figure 4 Pharmacokinetic profile of rivaroxaban in healthy controls and subjects with renal impairment (Panel a) or hepatic impairment (Panel b) [17]. CrCl, creatinine clearance.

Effects of hepatic impairment

There were no relevant differences in the pharmacokinetic or pharmacodynamic profile of rivaroxaban in patients with mild hepatic impairment (Child-Pugh A) after a single 10 mg dose. However, individuals with moderate hepatic impairment (Child-Pugh B) displayed increased and prolonged exposure with reduced total body clearance of rivaroxaban and increased inhibition of factor Xa compared with healthy individuals (*Figure 4b*) [17]. Consequently, rivaroxaban is contraindicated in patients with significant hepatic disease associated with coagulopathy leading to a clinically relevant bleeding risk [3]. Rivaroxaban can be used with caution in cirrhotic patients with moderate hepatic impairment if it is not associated with coagulopathy and does not require dose adjustment in patients with other hepatic diseases [3].

Modelling for extremes of age, weight and kidney function

A pooled population analysis (data from two phase IIb studies in patients undergoing major orthopaedic surgery) was undertaken to investigate the potential effects of extremes of age, weight and kidney function on the pharmacokinetic and pharmacodynamic profile of rivaroxaban [10]. The simulations showed that only in the case of a 90-year-old patient with a lean body mass of 30 kg, would the predicted rivaroxaban plasma concentration exceed the 90% confidence interval of the average (mean) patient [10].

Clinical development

Rivaroxaban is approved in more than 100 countries worldwide for VTE prevention after elective hip or knee replacement in adults and is under evaluation for use in a number of other thromboembolic indications, including treatment for VTE, prevention of secondary ischaemic events in acute coronary syndromes and stroke prevention in patients with atrial fibrillation.

EINSTEIN DVT, EINSTEIN EXT and EINSTEIN PE are phase III studies designed to evaluate the efficacy and safety of rivaroxaban in the treatment and/or prevention of recurrent, symptomatic VTE in patients with acute symptomatic deep vein thrombosis or pulmonary embolism. The EINSTEIN DVT study investigated rivaroxaban compared with initial enoxaparin treatment followed by a vitamin K antagonist (VKA; standard of care) in an open-label non-inferiority trial [18]. Patients received rivaroxaban 15 mg bid for 21 days followed by 20 mg od. The study reported that rivaroxaban was non-inferior to standard treatment for reducing the cumulative incidence of symptomatic recurrent VTE with similar rates of bleeding. EINSTEIN EXT compared rivaroxaban 20 mg od with placebo in the secondary prevention of recurrent symptomatic VTE in patients who had already completed 6–12 months of anticoagulant treatment for an index event. The findings showed that rivaroxaban was associated with a significant reduction in the risk of recurrent VTE with a low incidence of major bleeding compared with placebo [18]. EINSTEIN PE is currently evaluating rivaroxaban compared with enoxaparin/VKA (dosing regimens are identical to EINSTEIN DVT) for the prevention of recurrent VTE in patients with acute symptomatic pulmonary embolism.

For stroke prevention in atrial fibrillation, rivaroxaban was compared with dose-adjusted VKA in the phase III ROCKET AF trial. Preliminary results were recently reported and demonstrated in patients with atrial fibrillation receiving active treatment with rivaroxaban a reduced risk of stroke and non-CNS systemic embolism vs. warfarin, with similar rates of bleeding [19].

For the secondary prevention of acute coronary syndrome [20], two regimens of rivaroxaban – 2.5 mg and 5 mg bid – are undergoing evaluation in the ongoing phase III ATLAS ACS TIMI 51 study.

CONCLUSION

Rivaroxaban has been found to have a predictable clinical pharmacology profile providing the basis for the use of a fixed-dose regimen with no need for dose adjustment irrespective of age, weight and gender, essentially eliminating the need for routine coagulation monitoring. Published studies have demonstrated that the drug is suitable for a wide range of patients across a spectrum of thromboembolic diseases. Rivaroxaban thus promises more convenience than current standards of care for the prevention and treatment of venous and selected arterial thrombotic disease.

ACKNOWLEDGEMENTS

The author would like to acknowledge Richard Ogilvy-Stewart for editorial assistance with funding from Bayer Schering Pharma AG and Johnson & Johnson Pharmaceutical Research & Development, L.L.C.

CONFLICTS OF INTEREST

The author has received funding or honoraria for lectures, participation in review activities and consultancy fees from Bayer Schering Pharma.

REFERENCES

1 Turpie A.G.G. Oral, direct Factor Xa inhibitors in development for the prevention and treatment of thromboembolic diseases. Arterioscler. Thromb. Vasc. Biol. (2007) **27** 1238–1247.
2 Perzborn E., Roehrig S., Straub A., Kubitza D., Mueck W., Laux V. Rivaroxaban: a new oral factor Xa inhibitor. Arterioscler. Thromb. Vasc. Biol. (2010) **30** 376–381.
3 Bayer Schering Pharma AG. Xarelto® summary of product characteristics. (2009). http://www.xarelto.com/html/downloads/Xarelto_Summary_of_Product_Characteristics_May2009.pdf. [accessed 10 March 2011].
4 Graff J., von Hentig N., Misselwitz F. et al. Effects of the oral, direct Factor Xa inhibitor rivaroxaban on platelet-induced thrombin generation and prothrombinase activity. J. Clin. Pharmacol. (2007) **47** 1398–1407.
5 Perzborn E., Strassburger J., Wilmen A. et al. *In vitro* and *in vivo* studies of the novel antithrombotic agent BAY 59-7939 – an oral, direct Factor Xa inhibitor. J. Thromb. Haemost. (2005) **3** 514–521.
6 Kubitza D., Becka M., Voith B., Zuehlsdorf M., Wensing G. Safety, pharmacodynamics, and pharmacokinetics of single doses of BAY 59-7939, an oral, direct factor Xa inhibitor. Clin. Pharmacol. Ther. (2005) **78** 412–421.
7 Kubitza D., Becka M., Roth A., Mueck W. Dose-escalation study of the pharmacokinetics and pharmacodynamics of rivaroxaban in healthy elderly subjects. Curr. Med. Res. Opin. (2008) **24** 2757–2765.
8 Kubitza D., Becka M., Zuehlsdorf M., Mueck W. Effect of food, an antacid, and the H2 antagonist ranitidine on the absorption of BAY 59-7939 (rivaroxaban), an oral, direct Factor Xa inhibitor, in healthy subjects. J. Clin. Pharmacol. (2006) **46** 549–558.
9 Kubitza D., Becka M., Wensing G., Voith B., Zuehlsdorf M. Safety, pharmacodynamics, and pharmacokinetics of BAY 59-7939 – an oral, direct Factor Xa inhibitor – after multiple dosing in healthy male subjects. Eur. J. Clin. Pharmacol. (2005) **61** 873–880.
10 Mueck W., Eriksson B.I., Bauer K.A. et al. Population pharmacokinetics and pharmacodynamics of rivaroxaban – an oral, direct factor Xa inhibitor – in patients undergoing major orthopaedic surgery. Clin. Pharmacokinet. (2008) **47** 203–216.

11 Kubitza D., Becka M., Mueck W., Zuehlsdorf M. Safety, tolerability, pharmacodynamics, and pharmacokinetics of rivaroxaban – an oral, direct Factor Xa inhibitor – are not affected by aspirin. J. Clin. Pharmacol. (2006) **46** 981–990.
12 Kubitza D., Becka M., Mueck W., Zuehlsdorf M. Rivaroxaban (BAY 59-7939) – an oral, direct Factor Xa inhibitor – has no clinically relevant interaction with naproxen. Br. J. Clin. Pharmacol. (2007) **63** 469–476.
13 Eriksson B.I., Turpie A.G., Lassen M.R., Kakkar A.K., Gent M.; on behalf of the RECORD1–4 investigators. Pooled analysis of four rivaroxaban studies: NSAIDs, ASA and platelet inhibitors. J. Thromb. Haemost. (2009) **7**(Suppl 2) 761.
14 Kubitza D., Becka M., Zuehlsdorf M., Mueck W. Body weight has limited influence on the safety, tolerability, pharmacokinetics, or pharmacodynamics of rivaroxaban (BAY 59-7939) in healthy subjects. J. Clin. Pharmacol. (2007) **47** 218–226.
15 Kubitza D., Becka M., Mueck W., Zuehlsdorf M. The effect of extreme age, and gender, on the pharmacology and tolerability of rivaroxaban – an oral, direct Factor Xa inhibitor. Blood (ASH Annual Meeting Abstracts) (2006) **108** Abstract 905.
16 Kubitza D., Becka M., Mueck W. et al. Effects of renal impairment on the pharmacokinetics, pharmacodynamics and safety of rivaroxaban – an oral, direct Factor Xa inhibitor. Br. J. Clin. Pharmacol. (2010) **70** 703–712.
17 Halabi A., Kubitza D., Zuehlsdorf M., Becka M., Mueck W., Maatouk H.. Effect of hepatic impairment on the pharmacokinetics, pharmacodynamics and tolerability of rivaroxaban – an oral, direct Factor Xa inhibitor. J. Thromb. Haemost. (2007) **5**(Suppl 2) Abstract P-M-635.
18 Bauersachs R., Berkowitz S.D., Brenner B. et al. Oral rivaroxaban for symptomatic venous thromboembolism. N. Engl. J. Med. (2010) **363** 2499–2510.
19 Patel M.R.. Stroke prevention using the oral direct factor Xa inhibitor rivaroxaban compared with warfarin in patients with nonvalvular atrial fibrillation (ROCKET AF). http://sciencenews.myamericanheart.org/pdfs/Abstract_ROCKET_AF.pdf. [accessed 15 March 2011].
20 Mega J.L., Braunwald E., Mohanavelu S. et al. Rivaroxaban versus placebo in patients with acute coronary syndromes (ATLAS ACS-TIMI 46): a randomised, double-blind, phase II trial. Lancet (2009) **374** 29–38.