

Management consensus guidance for the use of rivaroxaban – an oral, direct factor Xa inhibitor

Alexander G. G. Turpie¹; Reinhold Kreutz²; Juan Llau³; Bo Norrving⁴; Sylvia Haas⁵

¹Department of Medicine, McMaster University, Hamilton, Ontario, Canada; ²Institute of Clinical Pharmacology and Toxicology, Charité, Universitätsmedizin, Berlin, Germany; ³Department of Anaesthesiology and Critical Care, Hospital Clínico, Valencia, Spain; ⁴Department of Clinical Neuroscience, Lund University Hospital, Lund, Sweden; ⁵Institute for Experimental Oncology and Therapy Research, Technical University of Munich, Germany

Summary

A number of novel oral anticoagulants that directly target factor Xa or thrombin have been developed in recent years. Rivaroxaban and apixaban (direct factor Xa inhibitors) and dabigatran etexilate (a direct thrombin inhibitor) have shown considerable promise in large-scale, randomised clinical studies for the management of thromboembolic disorders, and have been approved for clinical use in specific indications. Rivaroxaban is licensed for the prevention of venous thromboembolism in patients undergoing elective hip or knee replacement surgery, the treatment of deep-vein thrombosis and prevention of recurrent venous thromboembolism, and for stroke prevention in patients with non-valvular atrial

fibrillation. Based on the clinical trial data for rivaroxaban, feedback on its use in clinical practice and the authors' experience with the use of rivaroxaban, practical guidance for the use of rivaroxaban in special patient populations and specific clinical situations is provided. Although most recommendations are in line with the European summary of product characteristics for the approved indications, additional and, in several areas, different recommendations are given based on review of the literature and the authors' clinical experience.

Keywords

Anticoagulant, practical management, recommendations, rivaroxaban

Correspondence to:

Alexander G. G. Turpie, MD
Department of Medicine, McMaster University
Hamilton Health Sciences-General Hospital
237 Barton Street East
Hamilton, Ontario L8L 2X2, Canada
Tel.: +1 416 363 6726, Fax: +1 905 628 9505
E-mail: turpiea@mcmaster.ca

Received: March 30, 2012

Accepted after major revision: August 22, 2012

Prepublished online: September 26, 2012

doi:10.1160/TH12-03-0209

Thromb Haemost 2012; 108: 876–886

Introduction

Thromboembolism remains a major cause of morbidity and mortality worldwide. Guidelines recommend the routine use of anticoagulation for the primary prevention of venous thromboembolism (VTE; manifesting as deep-vein thrombosis [DVT] and pulmonary embolism [PE]), VTE treatment and stroke prevention in patients with atrial fibrillation (AF) (1–3). Until recently, anticoagulants were either parenteral – for example, low-molecular-weight heparins (LMWHs) and fondaparinux, which are typically considered for short-term use – or orally administered vitamin K antagonists (VKAs), such as warfarin, phenprocoumon and acenocoumarol, usually used long term.

Rivaroxaban, an oral direct factor Xa inhibitor, is now available for clinical use for the prevention of VTE after elective hip or knee replacement surgery, prevention of stroke and systemic embolism in patients with non-valvular AF, and for the treatment of DVT and prevention of recurrent VTE following an acute DVT. Other novel oral agents (such as dabigatran etexilate and apixaban) are also available for specific indications.

This paper provides practical guidance to clinicians for the use of rivaroxaban in its approved indications, including its use in some special patient populations and specific clinical situations.

These recommendations are based on published clinical trial data, regulatory documents, consensus publications and our clinical experience with the use of anticoagulants in clinical practice. In common with other medications, we are aware that differences exist between the recommendations in the regulatory documents for rivaroxaban among some countries. For example, for VTE prevention after hip or knee replacement surgery, there are subtle differences in the European and US recommendations – such as those for patients with moderate and severe renal impairment. To enable us to provide clinical practice guidance, most of our recommendations reflect the EU summary of product characteristics (SPC), and where appropriate we provide additional guidance for special patient populations or specific clinical situations beyond the EU SPC for the approved indications.

Rivaroxaban: approved indications

An extensive series of phase II studies formed the basis for indication-specific doses of rivaroxaban to be selected and subsequently investigated (4–11). Large-scale, randomised phase III studies of rivaroxaban investigated its use for the prevention and

treatment of VTE, stroke prevention in patients with AF and secondary prevention of coronary events in patients with acute coronary syndromes (ACS). The dose regimens for the approved indications for rivaroxaban are given in ► Table 1.

Prevention of VTE after total hip or knee replacement surgery

Rivaroxaban was evaluated in four phase III studies (the RECORD programme) for the prevention of VTE in patients undergoing elective total hip or knee replacement surgery, compared with enoxaparin 40 mg once daily (od) or 30 mg twice daily (bid) (4–7). In these studies, rivaroxaban was given at a fixed dose of 10 mg once daily (od), and the first dose was administered 6–8 hours (h) post-operatively. Based on the outcomes of the RECORD studies, rivaroxaban 10 mg od was approved for the prevention of VTE after elective hip or knee replacement surgery.

Treatment of DVT and prevention of recurrent VTE

The phase III EINSTEIN DVT and EINSTEIN PE studies assessed a single-drug approach with rivaroxaban for the treatment of acute symptomatic DVT and acute symptomatic PE, versus the current standard of care, and the EINSTEIN EXT study for the prevention of recurrent VTE versus placebo. EINSTEIN DVT and EINSTEIN PE involved an initial intensified treatment period with rivaroxaban 15 mg twice daily (bid) for the first three weeks followed by 20 mg od for continued treatment, and showed non-inferiority compared with the current standard of care and with similar rates of bleeding. In addition, EINSTEIN PE also showed a significant reduction in rates of major bleeding in the rivaroxaban arm (8, 9). EINSTEIN EXT showed significant reductions in the recurrence rates of DVT and PE with longer-term use of rivaroxaban 20 mg od, with a non-significant but numerical increase in the rate of major bleeding compared with placebo (8).

Rivaroxaban is approved for clinical use for the treatment of DVT and prevention of recurrent VTE. The dose for the initial treatment of acute DVT is 15 mg bid for the first three weeks, followed by 20 mg od for the continued treatment and prevention of recurrent DVT and PE, or 15 mg od for patients with moderate (creatinine clearance [CrCl] 30–49 ml/minute [min]) or severe (CrCl 15–29 ml/min) renal impairment. It is important to note that at this time, June 2012, the regulatory filing for the use of rivaroxaban for the treatment of PE is ongoing and the recommendations made in this paper relate only to its use for DVT treatment.

Stroke prevention in patients with AF

In the phase III ROCKET AF study, rivaroxaban (20 mg od, or 15 mg od for patients with CrCl 30–49 ml/min) was compared with warfarin. The study met the primary efficacy endpoint and showed non-inferiority compared with warfarin, and the overall

rates of major and non-major clinically relevant bleeding were similar between the treatment groups. Patients receiving rivaroxaban experienced significantly fewer intracranial haemorrhages and fatal bleeding events compared with those receiving warfarin (10).

Rivaroxaban is approved for clinical use for the prevention of stroke and systemic embolism in patients with AF based on the findings of the ROCKET AF study. The approved doses are 20 mg od for patients with a CrCl of ≥ 50 ml/min and 15 mg for patients with renal impairment (CrCl 15–49 ml/min).

Practical management of rivaroxaban in specific situations

VTE prevention after elective hip or knee replacement: timing of the first dose

The timing of the first anticoagulant dose is important for the balance of efficacy and safety (i.e. risk of bleeding). The first dose of rivaroxaban should be taken 6–10 h after surgery, which under normal circumstances will allow haemostasis to be established (12). In some clinical circumstances, a specific time frame must be followed, such as in patients with an epidural catheter (12). Any invasive procedures should be performed, if possible, at a time

Table 1: Recommended doses of rivaroxaban.

Indication	Dosing schedule
VTE prevention after total hip or knee replacement surgery	
5 weeks (elective hip replacement surgery)	10 mg od
2 weeks (elective knee replacement surgery)	10 mg od
Treatment of DVT and prevention of recurrent DVT and PE	
Days 1–21 (3 weeks)	15 mg bid ^a
Day 22 and onwards ^b	20 mg od (CrCl ≥ 50 ml/min) 15 mg od (CrCl 15–49 ml/min) ^c
Stroke prevention in patients with non-valvular AF	
Continuous administration	20 mg od (CrCl ≥ 50 ml/min)
Continuous administration	15 mg od (CrCl 15–49 ml/min) ^c

^aNo data are available for the use of 15 mg bid in patients with CrCl <30 ml/min; therefore, we do not recommend routine use of rivaroxaban in these patients. In patients with CrCl 30–49 ml/min and an increased risk of bleeding, the benefit–risk should be assessed before initiating rivaroxaban 15 mg bid; conventional therapy may be considered during this initial treatment period.
^bIn patients >75 years of age, renal function should be checked regularly (given the close link between age and decreases in renal function) and a reduced dose (15 mg od) may be used if necessary. ^cIn patients with CrCl 15–29 ml/min, limited data indicate that rivaroxaban plasma concentrations are increased significantly; therefore, rivaroxaban should be used with caution and the benefit–risk should be assessed before initiating rivaroxaban in these patients. AF, atrial fibrillation; bid, twice daily; CrCl, creatinine clearance; DVT, deep-vein thrombosis; od, once daily; PE, pulmonary embolism; VTE, venous thromboembolism.

when the plasma concentration of rivaroxaban is at its lowest (i.e. 24 h after dosing), to minimise the risk of bleeding events.

Recommendations

VTE prevention after elective hip or knee replacement surgery

- Rivaroxaban should be initiated 6–10 h after completion of surgery, provided that haemostasis has been established.
- We do not recommend giving the first dose of rivaroxaban earlier than 6 h after surgery in order not to interfere with haemostasis.
- For patients in whom haemostasis has not been achieved within 10 h, initiation of rivaroxaban should be delayed.
- In situations where oral drug administration is not possible – for example, in patients with severe postoperative vomiting that is not controlled by anti-emetic therapy – we suggest that a parenteral anticoagulant is administered. When oral administration becomes possible, rivaroxaban should be started at the time of the next scheduled dose of parenteral anticoagulant.

Periprocedural management of patients receiving rivaroxaban

To minimise the risk of bleeding in patients receiving rivaroxaban (all doses/indications), invasive procedures should be carried out when the rivaroxaban plasma concentration is at its lowest. The half-life of rivaroxaban is 5–9 h in young individuals and 11–13 h in the elderly, and it takes 2–4 h after tablet intake to reach the peak plasma concentration (13–15). However, rivaroxaban exposure also depends on the dose administered. The suggested time window for any invasive intervention is based on the pharmacokinetic profile of rivaroxaban. Prothrombin time (PT; measured in seconds and using a sensitive reagent such as Neoplastin Plus) may help to establish a qualitative measure of rivaroxaban exposure (refer to the 'Laboratory testing' section).

Recommendations

Elective surgery in patients receiving long-term rivaroxaban therapy

- We recommend that the last tablet should be taken not less than 24 h before the intervention; this applies to patients receiving any dose of rivaroxaban.

Emergency surgery in patients receiving rivaroxaban

- Surgeons should assess the urgency of the surgery against the risk of bleeding complications, and an individualised clinical judgement is essential.
- In patients without bleeding, we do not recommend the prophylactic use of haemostatic blood products such as prothrombin complex concentrate (PCC) for reversal of the effects of rivaroxaban.
 - However, in case of severe bleeding, PCC should be considered (see section on 'Management of bleeding events').

After the surgical (elective or emergency) intervention or invasive procedure, rivaroxaban should be restarted at the relevant dose for the indication as soon as possible, provided the clinical situation allows and adequate haemostasis has been established.

In our opinion, time without anticoagulation should be minimised. Rivaroxaban has a short half-life and bridging with other anticoagulants is not required and should not be done. In patients undergoing procedures with a low risk of bleeding, such as abscess incision or simple tooth extraction, consideration should be given to maintaining anticoagulant treatment. Where possible, interventions at peak rivaroxaban activity (i.e. 2–4 h after dosing) should be avoided.

Neuraxial anaesthesia in patients receiving rivaroxaban

When neuraxial anaesthesia (spinal or epidural anaesthesia) is used, patients receiving anticoagulants are at increased risk of developing an epidural or spinal haematoma, which may cause long-term or permanent paralysis. Therefore, it is recommended that these patients are monitored frequently for signs and symptoms of potential neurological impairment.

VTE prevention after elective hip or knee replacement surgery

For patients anticoagulated with rivaroxaban 10 mg od for VTE prevention after elective hip or knee replacement surgery, we advise to also adhere to the following specific periprocedural time frames.

- Puncture/catheter insertion: in cases of traumatic puncture, the administration of rivaroxaban should be delayed by 24 h.
- Epidural catheter removal: according to the EU SPC, an epidural catheter should not be removed earlier than 18 h after the last dose of rivaroxaban; however, the European Society of Anaesthesiology recommends 22–26 h, taking into account the longer half-life of rivaroxaban in elderly patients (16).
- The next rivaroxaban dose should be administered not earlier than 6 h after catheter removal.

Treatment of DVT and stroke prevention in patients with AF

We do not recommend the use of neuraxial anaesthesia in patients receiving long-term anticoagulant therapy with rivaroxaban (e.g. doses of 15 mg or 20 mg). No data are currently available in these circumstances and experience has shown that many patients on long-term rivaroxaban may have acetylsalicylic acid (ASA) as a co-medication. According to the recommendations of the European Society of Anaesthesiology, ASA does not need to be interrupted in patients receiving neuraxial anaesthesia. Therefore, we recommend against the use of neuraxial anaesthesia in these patients to minimise the risk of bleeding (see the 'Co-medications' section for further details).

Bridging between anticoagulants before and after surgery

The long-lasting anticoagulant effect of VKAs (17) means that bridging with a parenteral agent (e.g. LMWH) may be necessary in patients requiring temporary interruption of a VKA before surgical or invasive procedures. Rivaroxaban has predictable pharmacokinetics, a relatively short half-life (5–9 h in young individuals and 11–13 h in the elderly) (13–15), and a rapid onset of action after oral administration; the latter is similar to the subcutaneously administered LMWHs (18, 19). Thus, bridging with another anticoagulant is not required when rivaroxaban is discontinued before or initiated after surgery.

There are currently no data available for bridging patients from and to long-acting VKAs with short-acting novel oral anticoagulants during the perioperative phase. We also advise not to use rivaroxaban for bridging of patients treated with VKAs in this vulnerable period.

Converting patients from one anticoagulant to another

In patients who require transition between different anticoagulants, it is important to consider how to convert patients from one anticoagulant to another to ensure optimal clinical outcomes. Therefore, we have provided specific recommendations for different scenarios.

Recommendations

Converting patients from VKAs to rivaroxaban

- Warfarin is the most widely used VKA in double-blind phase III studies of oral anticoagulant therapy. There are, however, a number of other VKAs, all of which have different pharmacokinetic properties, such as phenprocoumon, which has a half-

life of 5–6 days compared with ~40 h for warfarin (20); these differences must be taken into account during the transition.

- If patients receiving VKAs are to transition to rivaroxaban, VKA therapy should be stopped and the international normalised ratio (INR) must be monitored closely to assess the residual effect of the VKAs. Rivaroxaban should be started when the INR is at an appropriate level after the discontinuation of VKA therapy (see ► Fig. 1).
 - When converting from warfarin or acenocoumarol, rivaroxaban should be initiated when the INR is <3.0 .
 - When converting from phenprocoumon, rivaroxaban should be initiated when the INR is ≤ 2.5 .
 - In patients with a higher risk of bleeding, we recommend starting rivaroxaban when the INR is between 2.0 and 2.5 (the lower part of the target range) when converting from any VKA.
 - Once rivaroxaban has been initiated, measurement of INR should not be carried out.

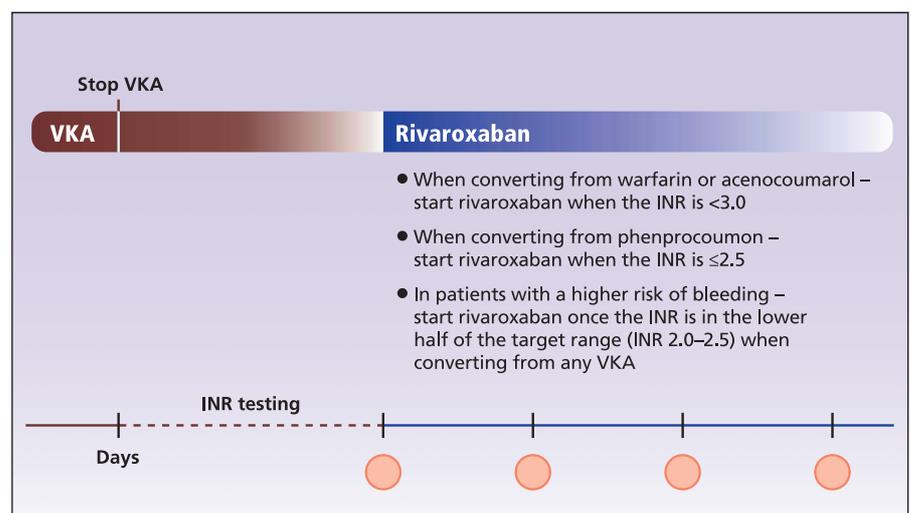
Converting patients from rivaroxaban to VKAs

- In patients converting from rivaroxaban to VKAs, VKA therapy should be given concurrently until the INR is ≥ 2.0 . For the first two days of the conversion period, standard initial dosing of VKA should be used followed by VKA dosing guided by INR testing. While patients are on both rivaroxaban and VKA the INR should be measured 24 h after the previous dose of rivaroxaban but before the next dose because of its influence on the INR. Once rivaroxaban is discontinued, INR testing may be done reliably at least 24 h after the last dose.

Switching from and to parenteral anticoagulants

- For patients currently receiving a parenteral anticoagulant, rivaroxaban should be started at the time of the next scheduled administration of the parenteral anticoagulant, such as subcutaneous LMWH, or at the time of discontinuation of continuous intravenously administered unfractionated heparin.

Figure 1: Converting from VKAs to rivaroxaban. INR, international normalised ratio; VKA, vitamin K antagonist.



- If patients receiving rivaroxaban require switching to a parenteral anticoagulant, the first dose of parenteral anticoagulant should be given when the next rivaroxaban dose is due.

Switching from dabigatran to rivaroxaban

Dabigatran is eliminated primarily as unchanged drug in the urine and there is a potential for accumulation in patients with renal impairment. The half-life of dabigatran is approximately twice as long in patients with severe renal impairment (CrCl 10–30 ml/min) compared with those with normal renal function (21); these factors should be considered when transitioning from dabigatran to another agent.

- Similar to recommendations for switching from dabigatran to parenteral anticoagulants (22), rivaroxaban should be started when the next dose of dabigatran is due in patients without moderate renal impairment.
- In patients with a CrCl of >30–≤50 ml/min, we recommend initiating rivaroxaban 2–4 days after the last dose of dabigatran. A longer period should be considered in patients with a high risk of bleeding; where there is doubt, activated partial thromboplastin time (aPTT) may be assessed (23), and a normal value may suggest no clinically relevant anticoagulant effect of dabigatran.

Co-medications

The pharmacokinetics and pharmacodynamics of anticoagulants may be affected by co-medications and the risk of bleeding may increase with co-administration; this may be particularly important in patients already at an increased risk of bleeding, such as those with renal impairment. In contrast to the VKAs, which have multiple drug–drug interactions, rivaroxaban has no clinically relevant interactions with many co-medications (13, 24–28). Rivaroxaban is metabolised mainly via cytochrome P450 3A4 (CYP3A4) and is a substrate of the transporter protein P-glycoprotein (P-gp). Therefore, caution should be taken when rivaroxaban is co-administered with agents affecting these pathways (13).

Recommendations

- Rivaroxaban is not recommended in patients receiving concomitant systemic treatment with azole-antimycotics (such as ketoconazole, itraconazole, voriconazole and posaconazole) or HIV protease inhibitors (e.g. ritonavir). These drugs are strong inhibitors of both CYP3A4 and P-gp and may increase plasma rivaroxaban concentrations and, consequently, may increase the risk of bleeding (► Table 2).
- Co-administration of rivaroxaban with other drugs that are moderate to strong inhibitors of CYP3A4 and/or P-gp may increase rivaroxaban plasma concentrations to a lesser extent and is, therefore, not deemed clinically relevant. Nevertheless, these co-medications should be used with caution, particularly in patients with increased risk of bleeding or who have renal impairment (► Table 2).

- Strong CYP3A4 inducers (e.g. rifampicin, phenytoin, carbamazepine, phenobarbital or St John's wort) may reduce plasma rivaroxaban concentrations and thus decrease its efficacy. Therefore, co-administration should be used with caution (► Table 2).
- Substrates of CYP3A4 and/or Pgp, such as midazolam (substrate of CYP3A4), digoxin (substrate of P-gp) and atorvastatin (substrate of CYP3A4 and P-gp) show no clinically relevant effect on rivaroxaban plasma concentrations, and may be co-administered (► Table 2).
- Co-administration of anticoagulant and antiplatelet agents increases the risk of bleeding; therefore, care must be taken with these combinations and the benefit–risk should be assessed.
 - Rivaroxaban and ASA at doses ≤100 mg per day can be used but caution is advised because the risk of bleeding is increased.
 - Co-administration of rivaroxaban (10 mg or higher) with ASA alone >100 mg per day should be avoided.
 - We recommend against co-administration of daily doses of rivaroxaban 10 mg or higher with ASA plus clopidogrel or other thienopyridines (such as ticlopidine, prasugrel) or plus other ADP P2Y₁₂ receptor antagonists (such as ticagrelor).
- Non-steroidal anti-inflammatory drugs (such as naproxen and ibuprofen) increase the risk of bleeding; therefore, co-administration of rivaroxaban and non-steroidal anti-inflammatory drugs can be used, but the risk of bleeding will be increased.

Patient characteristics – special considerations

Patient characteristics may influence the efficacy and safety of anticoagulant therapy. For example, with drugs eliminated predominantly via the kidneys, the risk of bleeding may increase in patients with impaired renal function. It is important that patient characteristics such as age, gender, body weight and renal function are not considered in isolation; the combined influence of these factors should be considered when deciding whether a reduced rivaroxaban dose (15 mg od) should be used for long-term therapy (i.e. secondary prevention of VTE or stroke prevention in patients with AF).

Age

Increased age is an important risk factor for both thromboembolic events and bleeding events (29, 30). There is also a strong link between age and renal function; the rate of glomerular filtration decreases with increasing age (31). The half-life of rivaroxaban is longer in elderly subjects (11–13 h) (15) compared with younger subjects (5–9 h) (13–15). A consistent clinical benefit has been demonstrated across the different age groups including the elderly (e.g. those aged >75 years) as evident from subgroup analyses of data from the phase III studies (8–10, 32).

Table 2: Concomitant use with agents affecting cytochrome P450 3A4 and P-glycoprotein pathways.

	Strong inhibitors of both CYP3A4 and P-gp	Moderate to strong CYP3A4 and/or P-gp inhibitors	Strong inducers of CYP3A4	Substrates of CYP3A4 and/or P-gp
Effect on rivaroxaban plasma concentration	Increase rivaroxaban plasma concentration	Increase plasma concentrations but the effect is not clinically relevant	Decrease rivaroxaban plasma concentration	No clinically relevant effect on rivaroxaban plasma concentration
Drugs	HIV protease inhibitors Azole-antimycotics (Ketoconazole, Itraconazole, Voriconazole, Posaconazole)	Fluconazole Erythromycin Clarithromycin Amiodarone ^a Verapamil	Rifampicin Phenobarbital Phenytoin Carbamazepine St John's wort	Digoxin Atorvastatin Midazolam
Recommendation	Not recommended	Permitted Use with caution in patients with renal impairment and increased risk of bleeding	Permitted Use with caution	Permitted

^aGiven the limited clinical data available with dronedarone, co-administration with rivaroxaban should be avoided. CYP, cytochrome P450; P-gp, P-glycoprotein.

Recommendations

- Rivaroxaban is not recommended for patients under 18 years of age; there are currently no data to support its use in this patient population.
- Rivaroxaban for VTE prevention after total hip or knee replacement surgery: based on the data from the phase III studies and subgroup analyses, we do not recommend dose adjustment for age.
- Rivaroxaban for stroke prevention and DVT treatment: renal function in elderly (i.e. aged >75 years) patients should be monitored regularly. A reduced dose is indicated (15 mg od instead of 20 mg od) for patients with CrCl <50 ml/min (see ► Table 1 for appropriate dose adjustment).

Gender

Gender has no significant influence on the pharmacokinetics and pharmacodynamics of rivaroxaban (33), and the efficacy and safety outcomes of the phase III studies in several indications were similar between male and female patients (8–10, 32).

Recommendation

- No dose adjustment is required for gender alone.

Body weight

Extremes of body weight (<50 kg or >120 kg) have only a minor influence on rivaroxaban plasma concentrations, which is not clinically relevant. In addition, no lower or upper limits for weight were applied in any of the clinical trials, although there are limited data for patients at each end of the weight spectrum.

Recommendation

- No dose adjustment is necessary for body weight alone.
- However, for long-term treatment we suggest 15 mg od instead of 20 mg od for patients aged >75 years and with a body weight of ≤50 kg) to avoid increased rivaroxaban exposure.

Renal impairment

Of the administered rivaroxaban dose, approximately two-thirds undergo metabolic degradation, with half being eliminated renally and the other half eliminated by the hepatobiliary route. The final one-third of the administered dose undergoes direct renal excretion as unchanged active substance in the urine (34). Consequently, increasing renal insufficiency is associated with decreased rivaroxaban clearance (35).

Recommendations

For recommendations for patients with renal impairment please also see ► Table 1 and ► Figure 2.

- For patients who are receiving long-term rivaroxaban therapy, we recommend that renal function should be estimated by determination of CrCl using the Cockcroft–Gault formula before initiating rivaroxaban therapy. Attention should be paid subsequently to situations known to alter renal function during long-term treatment.
- For VTE prevention after major orthopaedic surgery (10 mg od): no dose adjustment is necessary in patients with mild (CrCl 50–80 ml/min) or moderate (CrCl >30–49 ml/min) renal impairment.
- For DVT treatment, the standard initial three-week treatment dose is 15 mg bid for all patients.

- After the first three weeks, patients should receive 20 mg od (CrCl \geq 50 ml/min), or 15 mg od in those with moderate renal impairment (CrCl 30–49 ml/min).
- For stroke prevention in patients with non-valvular AF, the standard dose is 20 mg od for patients with CrCl $>$ 50 ml/min and 15 mg od for patients with moderate renal impairment (CrCl 30–49 ml/min).
- Patients with severe renal impairment (CrCl $<$ 30 ml/min) were excluded from all phase III trials, and limited data in patients with CrCl 15–29 ml/min indicate that rivaroxaban plasma concentrations are increased significantly (35). Therefore, rivaroxaban should be used with caution and the benefit–risk should be assessed before initiating rivaroxaban and during treatment in patients with CrCl 15–29 ml/min.
- Rivaroxaban is not recommended in patients with CrCl $<$ 15 ml/min; rivaroxaban should be discontinued if/when renal function deteriorates to CrCl $<$ 15 ml/min, irrespective of the cause.
- For long-term treatment we suggest 15 mg od instead of 20 mg od for patients aged $>$ 75 years and CrCl $<$ 50 ml/min.

Hepatic impairment

Cirrhotic patients with mild hepatic impairment (Child–Pugh A) exhibited only minor changes in rivaroxaban pharmacokinetics, similar to matched healthy control subjects. In cirrhotic patients with moderate hepatic impairment (classified as Child–Pugh B), rivaroxaban exposure was increased, leading to an increase in its pharmacodynamic effects (36).

Recommendations

- Rivaroxaban is contraindicated in patients with hepatic disease associated with coagulopathy and clinically relevant risk of bleeding, including cirrhotic patients (Child–Pugh B and C).
- No dose adjustment is required in patients with mild hepatic impairment (Child–Pugh A).

Patients with AF and ACS

There are currently no data available for rivaroxaban (or other novel oral anticoagulants) for stroke prevention in patients with AF who are also presenting with ACS. Therefore, patients with ACS who are receiving dual antiplatelet therapy should not be given the rivaroxaban doses 20 mg (or 15 mg) approved for stroke prevention in AF. We recommend that such patients should receive VKA therapy (INR 2.0–2.5) in accordance with the ESC guidelines (2).

Pregnancy and breast feeding

- We do not recommend the use of rivaroxaban during pregnancy. Preclinical studies in animals have shown that rivaroxaban crosses the placenta.
- Similarly, data from animal studies indicate that rivaroxaban is secreted into milk and we do not recommend its use during breastfeeding.

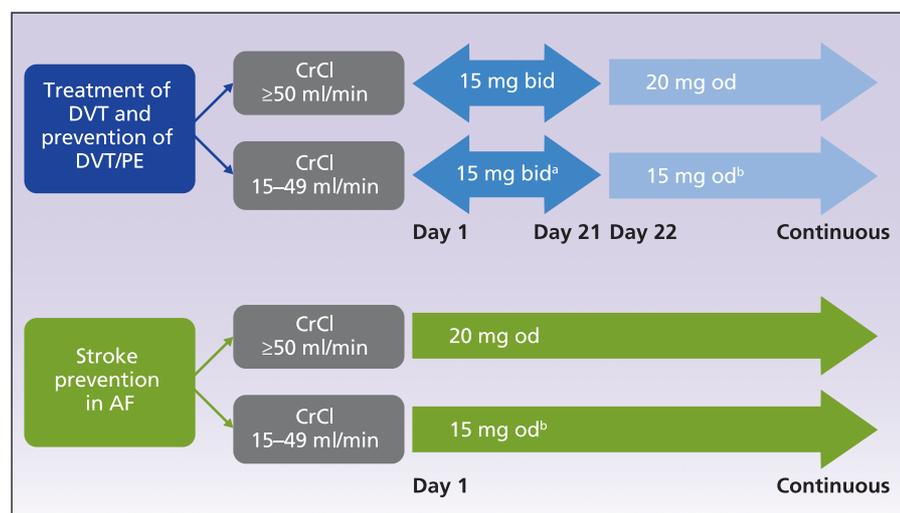


Figure 2: Recommended doses of rivaroxaban in patients with renal impairment: Treatment of DVT and prevention of recurrent VTE and stroke prevention in patients with AF. ^aNo data are available for the use of 15 mg bid in patients with CrCl $<$ 30 ml/min; therefore, we do not recommend routine use of rivaroxaban in these patients. In patients with CrCl 30–49 ml/min and an increased risk of bleeding, the benefit–risk should be assessed before initiating rivaroxaban 15 mg bid; conventional therapy may be considered during this initial treatment period. ^bIn patients $>$ 75 years of

age, renal function should be checked regularly (given the close link between age and decreases in renal function) and a reduced dose (15 mg od) may be used if necessary. In patients with CrCl 15–29 ml/min, limited data indicate that rivaroxaban plasma concentrations are significantly increased; therefore, rivaroxaban should be used with caution and the benefit–risk should be assessed before initiating rivaroxaban in these patients. AF, atrial fibrillation; bid, twice daily; CrCl, creatinine clearance; DVT, deep-vein thrombosis; od, once daily; PE, pulmonary embolism; VTE, venous thromboembolism.

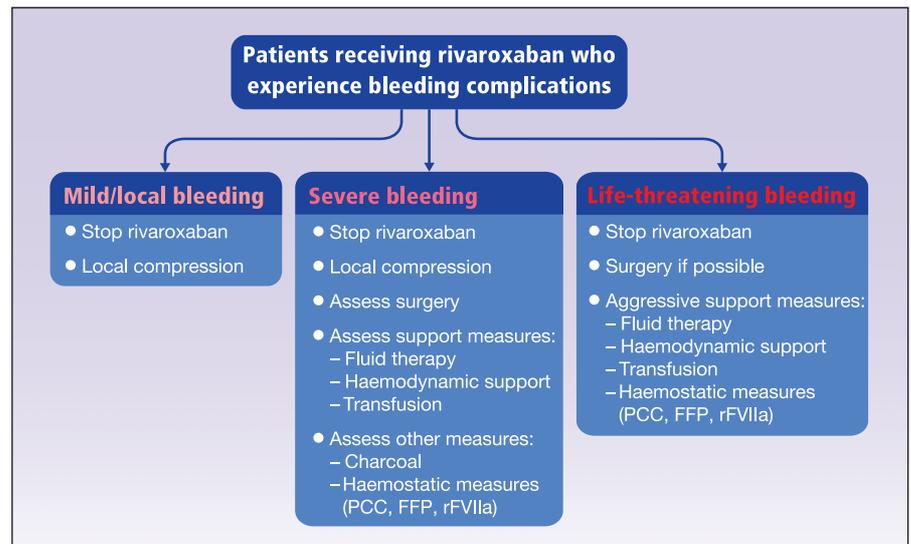


Figure 3: Recommended strategies for the management of bleeding events. FFP, fresh frozen plasma; PCC, prothrombin complex concentrate; rFVIIa, recombinant factor VIIa.

Management of bleeding events

All anticoagulants carry a risk of bleeding, and some patients may be at an increased risk of bleeding complications because of specific characteristics. Vitamin K administration for coagulopathy associated with VKA therapy takes up to 24 h or longer to reverse the effect (37), and the method for the reversal of VKAs depends on the clinical situation and the severity of bleeding. For example, PCC plus vitamin K are used for the rapid reversal of VKA therapy (38). Protamine is used for heparin, but it can only partially reverse the effects of LMWHs (39). It should be noted that protamine and vitamin K do not affect the anticoagulant activity of rivaroxaban.

Rivaroxaban has a relatively short half-life (5–13 h) (13–15). Drug discontinuation is recommended in case of bleeding events and routine protocols for bleeding management should be applied generally.

Recommendations

Please also see ► Figure 3 for recommendations for management of bleeding events.

- Management should be individualised according to the severity and location of the haemorrhage.
- If a bleeding complication occurs in a patient receiving rivaroxaban, the next rivaroxaban dose should be delayed or treatment discontinued as appropriate.
- Appropriate symptomatic treatment should be used, such as mechanical compression, surgical haemostasis with bleeding control procedures, fluid replacement and haemodynamic support, or blood products (packed red cells and/or fresh frozen plasma), depending on the severity of the bleeding event.
- In case of a severe, life-threatening bleeding event PCC should be administered (40, 41). Depending on the severity of bleeding we suggest to use the same dosing of PCC as recommended for reversal of VKA-induced bleeding, i.e. 25–50 IU per kg body-weight. Activated PCC (FEIBA) and recombinant factor VIIa

have also been tested in experimental settings for reversal of the anticoagulant effect of rivaroxaban (41), but their prothrombotic potential may be higher than that of PCC. We recommend the use of PCC as the first choice.

- In case of overdose of rivaroxaban, activated charcoal may be useful to reduce its absorption; if the overdose is accompanied by bleeding events, it is recommended to follow the methods suggested above for the general management of bleeding (13).
- Because it has high plasma protein binding, rivaroxaban is not dialysable.
- The risk of thrombotic events should be assessed when bleeding has ceased and rivaroxaban should be restarted according to the recommended regimens when appropriate.

Laboratory testing

Rivaroxaban has been shown to have predictable pharmacokinetics and pharmacodynamics, a wide therapeutic window (13, 15, 42–44) and does not warrant routine coagulation monitoring. However, simple, reliable assays to assess rivaroxaban exposure are useful in certain clinical circumstances, such as in suspected overdose, in patients who require emergency surgery, in those with a thromboembolic or haemorrhagic event, in candidates for thrombolysis, or as a measure of compliance when non-compliance is suspected. As with other novel oral anticoagulants, rivaroxaban influences global coagulation assays, such as PT and aPTT, and this has been further demonstrated in recent *in vitro* and *ex vivo* studies (45–48). However, routine coagulation tests (such as PT and aPTT) do not reflect the circulating levels of rivaroxaban and are not suitable for quantitative assessment of rivaroxaban exposure.

Of note, as seen with other anticoagulants, rivaroxaban may interfere with functional testing for thrombophilia (49). False-positive results for lupus anticoagulant testing have also been re-

ported in patients receiving rivaroxaban (50). To minimise the potential influence of rivaroxaban on thrombophilia testing, blood samples should be taken 24 h or later after the last rivaroxaban dose.

Prothrombin time

PT assayed using Neoplastin Plus is influenced by rivaroxaban in a dose-dependent manner, with a close correlation to plasma rivaroxaban concentrations (14, 42). However, PT (expressed in seconds) varies markedly with different thromboplastins because of their different response sensitivities to rivaroxaban. The conventional INR system, which was developed specifically for monitoring the VKAs, does not correct for these variations and must not be used (51, 52).

Recommendation

Please also see ► Table 3 for recommendations for measuring PT.

- We do not recommend the use of PT/INR or CoaguCheck tests, or PT with insensitive reagents (such as Innovin and others) to assess levels of anticoagulation with rivaroxaban. However, normal values of PT measured in seconds using an agent sensitive to rivaroxaban (such as Neoplastin Plus) suggest no clinically relevant anticoagulation effects of rivaroxaban. For the measurement of peak activity at the time of maximum plasma concentration, blood should be taken 2–4 h after dosing.
- If PT is used with a sensitive reagent, measurement of trough activity immediately before the next dose could indicate whether there is accumulation.

Table 3: Laboratory assays for assessing rivaroxaban exposure (51).

Assay	Suitability/limitations
Prothrombin time	<ul style="list-style-type: none"> • Expressed in 'seconds': marked variations with different reagents • Conventional INR does not correct for the variations and must not be used • The use of PT/INR or CoaguCheck tests, or PT with insensitive reagents (such as Innovin and others) to assess levels of anticoagulation with rivaroxaban is not recommended • Normal values of PT measured in seconds using an agent sensitive to rivaroxaban (such as Neoplastin Plus) suggest no clinically relevant anticoagulant effect of rivaroxaban
Anti-factor Xa chromogenic assay	<ul style="list-style-type: none"> • Specific and sensitive for quantitative measurements • Requires rivaroxaban calibrators and controls (commercially available) • Results need to be interpreted in relation to the timing of tablet intake in accordance with the pharmacokinetic profile
Routine measurement of the drug effects or plasma rivaroxaban concentrations is not necessary	
INR, international normalised ratio; PT prothrombin time.	

Anti-factor Xa chromogenic assay

Inhibition of factor Xa activity correlates closely with plasma rivaroxaban concentrations, and anti-factor Xa chromogenic assays have been shown to be specific and sensitive for measuring a wide range of plasma rivaroxaban concentrations that cover the expected rivaroxaban concentrations after therapeutic doses; the measurements showed acceptable accuracy and precision (47, 51, 53). Trough values could be measured to indicate if there is drug accumulation.

Recommendations

Please also see ► Table 3 for recommendations on using the anti-factor Xa chromogenic assay.

- An anti-factor Xa chromogenic assay is recommended for quantitative measurements of rivaroxaban exposure.
- Rivaroxaban calibrators and controls (commercially available, e.g. from Technoclone, Hyphen-Biomed) should be used for calibration, with results expressed as ng/ml of rivaroxaban.
- Assessment of rivaroxaban concentrations must be interpreted in relation to the timing of drug administration in accordance with the pharmacokinetic profile of rivaroxaban.

It should be noted, however, that routine measurement of the drug effects or plasma concentrations of rivaroxaban is not necessary, and assessment of rivaroxaban exposure should only be carried out in emergency situations or to confirm patient compliance.

Conclusions

Although the new anticoagulants may replace some of the traditional agents, certain changes in hospital routine and patient management strategies are required when introducing these new agents to clinical practice. Rivaroxaban is currently used worldwide for the prevention of VTE in adult patients undergoing elective hip or knee replacement surgery, and has received further approval for the treatment of DVT and long-term secondary prevention of VTE, and for stroke prevention in patients with non-valvular AF. It is anticipated that rivaroxaban and other newly approved oral agents may simplify the patient management routine and, thereby, improve overall clinical outcomes. However, it is important to understand the potential challenges with the use of the novel oral agents and to follow recommendations, particularly in specific patient groups and clinical situations, to achieve optimal patient outcomes.

Acknowledgements

The authors would like to acknowledge Yong-Ling Liu, who provided editorial support with funding from Bayer HealthCare Pharmaceuticals and Janssen Research & Development, LLC.

Conflicts of interest

This paper is based on recommendations from the committee members; the recommendations outlined in this paper are based

on their clinical expertise. All the authors contributed to the development of this manuscript and are fully responsible for all contents. The authors received no financial support or other compensation related to the development of this paper. Bayer HealthCare reviewed the paper for the factual correctness of the rivaroxaban data but had no influence on the recommendations. Editorial assistance for the preparation of this manuscript was provided by Yong-Ling Liu, with funding from Bayer HealthCare Pharmaceuticals and Janssen Research & Development, LLC. A. G. G. Turpie has been a consultant to Bayer HealthCare, Janssen Research & Development, LLC, Astellas, Portola and Takeda and a member of the speakers' bureau for GSK and Pfizer. R. Kreutz has received funding or honoraria for lectures, participation in review activities and consultancy fees from Bayer HealthCare. J. Llau has been a member of steering committees for Bayer, Boehringer Ingelheim, Pfizer and BMS, and a consultant to Bayer, Sanofi, Pfizer and BMS. B. Norrving has received consultancy payments from Bayer for scientific committee work on the ROCKET AF trial, payment for lectures from Allergan and Bayer, and royalties for a book published by Karolinska University Press. S. Haas has received honoraria from Bayer HealthCare, BMS, Boehringer Ingelheim, CSL Behring, Novartis and Sanofi-Aventis.

References

- Falck-Ytter Y, Francis CW, Johanson NA, et al. Prevention of VTE in orthopedic surgery patients: antithrombotic therapy and prevention of thrombosis: American College of Chest Physicians evidence-based clinical practice guidelines (9th Edition). *Chest* 2012; 141: e278S–e325S.
- Hamm CW, Bassand JP, Agewall S, et al. ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation: The Task Force for the Management of Acute Coronary Syndromes (ACS) in Patients Presenting without Persistent ST-segment Elevation of the European Society of Cardiology (ESC). *Eur Heart J* 2011; 32: 2999–3054.
- Lansberg MG, O'Donnell MJ, Khatri P, et al. Antithrombotic and thrombolytic therapy for ischemic stroke: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. *Chest* 2012; 141: e601S–e636S.
- Eriksson BI, Borris LC, Friedman RJ, et al. Rivaroxaban versus enoxaparin for thromboprophylaxis after hip arthroplasty. *N Engl J Med* 2008; 358: 2765–2775.
- Kakkar AK, Brenner B, Dahl OE, et al. Extended duration rivaroxaban versus short-term enoxaparin for the prevention of venous thromboembolism after total hip arthroplasty: a double-blind, randomised controlled trial. *Lancet* 2008; 372: 31–39.
- Lassen MR, Ageno W, Borris LC, et al. Rivaroxaban versus enoxaparin for thromboprophylaxis after total knee arthroplasty. *N Engl J Med* 2008; 358: 2776–2786.
- Turpie AGG, Lassen MR, Davidson BL, et al. Rivaroxaban versus enoxaparin for thromboprophylaxis after total knee arthroplasty (RECORD4): a randomised trial. *Lancet* 2009; 373: 1673–1680.
- The EINSTEIN Investigators. Oral rivaroxaban for symptomatic venous thromboembolism. *N Engl J Med* 2010; 363: 2499–2510.
- The EINSTEIN-PE Investigators. Oral rivaroxaban for the treatment of symptomatic pulmonary embolism. *N Engl J Med* 2012; 366: 1287–1297.
- Patel MR, Mahaffey KW, Garg J, et al. Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. *N Engl J Med* 2011; 365: 883–891.
- Mega JL, Braunwald E, Wiviott SD, et al. Rivaroxaban in patients with a recent acute coronary syndrome. *N Engl J Med* 2012; 366: 9–19.
- Rosencher N, Bonnet MP, Sessler DI. Selected new antithrombotic agents and neuraxial anaesthesia for major orthopaedic surgery: management strategies. *Anaesthesia* 2007; 62: 1154–1160.
- Bayer Pharma AG. Xarelto® (rivaroxaban) Summary of Product Characteristics. 2012. Available at: http://www.xarelto.com/html/downloads/Xarelto-Prescribing_Information-May-2012.pdf. Accessed July 31, 2012.
- Kubitza D, Becka M, Voith B, et al. Safety, pharmacodynamics, and pharmacokinetics of single doses of BAY 59–7939, an oral, direct Factor Xa inhibitor. *Clin Pharmacol Ther* 2005; 78: 412–421.
- Kubitza D, Becka M, Roth A, et al. Dose-escalation study of the pharmacokinetics and pharmacodynamics of rivaroxaban in healthy elderly subjects. *Curr Med Res Opin* 2008; 24: 2757–2765.
- Gogarten W, Vandermeulen E, Van Aken H, et al. Regional anaesthesia and anti-thrombotic agents: recommendations of the European Society of Anaesthesiology. *Eur J Anaesthesiol* 2010; 27: 999–1015.
- Ageno W, Gallus AS, Wittkowsky A, et al. Oral anticoagulant therapy: antithrombotic therapy and prevention of thrombosis, 9th ed: American College of Chest Physicians evidence-based clinical practice guidelines. *Chest* 2012; 141: e44S–e88S.
- Kubitza D, Becka M, Voith B, et al. Effect of enoxaparin on the safety, tolerability, pharmacodynamics and pharmacokinetics of BAY 59–7939 – an oral, direct Factor Xa inhibitor. *J Thromb Haemost* 2005; 3 (Suppl 1): Abstract P1704.
- Garcia DA, Baglin TP, Weitz JI, et al. Parenteral anticoagulants: antithrombotic therapy and prevention of thrombosis: American College of Chest Physicians evidence-based clinical practice guidelines (9th Edition). *Chest* 2012; 141: e24S–e43S.
- Heni N, Glogner P. Pharmacokinetics of phenprocoumon in man investigated using a gas chromatographic method of drug analysis. *Nuunyn-Schmiedeberg's Arch Pharmacol* 1976; 293: 183–186.
- Boehringer Ingelheim International GmbH. Pradaxa (dabigatran etexilate) Summary of Product Characteristics. 2012. Available at: http://www.ema.europa.eu/docs/en_GB/document_library/Other/2012/05/WC500127777.pdf. Accessed August 2, 2012.
- Huisman MV, Lip GY, Diener HC, et al. Dabigatran etexilate for stroke prevention in patients with atrial fibrillation: resolving uncertainties in routine practice. *Thromb Haemost* 2012; 107: 838–847.
- Haas S, Spannagl M, Schellong S. Novel oral anticoagulants – key messages for the angiologist. *Vasa* 2012; 41: 177–191.
- Kubitza D, Becka M, Zuehlsdorf M, et al. No interaction between the novel, oral direct Factor Xa inhibitor BAY 59–7939 and digoxin. *J Clin Pharmacol* 2006; 46: 702: Abstract 11.
- Kubitza D, Becka M, Mueck W, et al. 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.
- Kubitza D, Becka M, Mueck W, et al. 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.
- Kubitza D, Mueck W, Becka M. No interaction between rivaroxaban – a novel, oral, direct Factor Xa inhibitor – and atorvastatin. *Pathophysiol Haemost Thromb* 2008; 36: A40: Abstract P062.
- Kubitza D, Becka M, Mueck W, et al. Effect of co-administration of rivaroxaban and clopidogrel on bleeding time, pharmacodynamics and pharmacokinetics: a phase I study. *Pharmaceuticals* 2012; 5: 279–296.
- López-Jiménez L, Montero M, González-Fajardo JA, et al. Venous thromboembolism in very elderly patients: findings from a prospective registry (RIETE). *Haematologica* 2006; 91: 1046–1051.
- Spencer FA, Gore JM, Lessard D, et al. Venous thromboembolism in the elderly. A community-based perspective. *Thromb Haemost* 2008; 100: 780–788.
- Glasscock RJ, Winearls C. Ageing and the glomerular filtration rate: truths and consequences. *Trans Am Clin Climatol Assoc* 2009; 120: 419–428.
- Turpie AGG, Lassen MR, Eriksson BI, et al. Rivaroxaban for the prevention of venous thromboembolism after hip or knee arthroplasty. Pooled analysis of four studies. *Thromb Haemost* 2011; 105: 444–453.
- Kubitza D, Becka M, Roth A, et al. The influence of age and gender on the pharmacokinetics and pharmacodynamics of rivaroxaban – an oral, direct Factor Xa inhibitor. *J Clin Pharmacol* 2012; in press.
- Weinz C, Schwarz T, Kubitza D, et al. Metabolism and excretion of rivaroxaban, an oral, direct Factor Xa inhibitor, in rats, dogs and humans. *Drug Metab Dispos* 2009; 37: 1056–1064.
- 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.

36. Halabi A, Kubitzka D, Zuehlsdorf M, et al. 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.
37. Baker RI, Coughlin PB, Gallus AS, et al. Warfarin reversal: consensus guidelines, on behalf of the Australasian Society of Thrombosis and Haemostasis. *Med J Aust* 2004; 181: 492–497.
38. Hanley JP. Warfarin reversal. *J Clin Pathol* 2004; 57: 1132–1139.
39. Garcia DA, Baglin TP, Weitz JI, et al. Parenteral anticoagulants: antithrombotic therapy and prevention of thrombosis, 9th ed: American College of Chest Physicians evidence-based clinical practice guidelines. *Chest* 2012; 141: e24S–e43S.
40. Eerenberg ES, Kamphuisen PW, Sijpkens MK, et al. Reversal of rivaroxaban and dabigatran by prothrombin complex concentrate: a randomized, placebo-controlled, crossover study in healthy subjects. *Circulation* 2011; 124: 1573–1579.
41. Marlu R, Hodaj E, Paris A, et al. Effect of non-specific reversal agents on anti-coagulant activity of dabigatran and rivaroxaban. A randomised crossover *ex vivo* study in healthy volunteers. *Thromb Haemost* 2012; 108: 217–224.
42. Kubitzka D, Becka M, Wensing G, et al. 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.
43. Mueck W, Becka M, Kubitzka D, et al. Population model of the pharmacokinetics and pharmacodynamics of rivaroxaban – an oral, direct Factor Xa inhibitor – in healthy subjects. *Int J Clin Pharmacol Ther* 2007; 45: 335–344.
44. Mueck W, Eriksson BI, Bauer KA, 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.
45. Gerotziafas GT, Hatmi M, Samama MM, et al. Optimisation of the assays for the measurement of clotting factor activity in the presence of rivaroxaban. *Thromb Res* 2012; 129: 101–103.
46. Mani H, Hesse C, Stratmann G, et al. Rivaroxaban differentially influences *ex vivo* global coagulation assays based on the administration time. *Thromb Haemost* 2011; 106: 156–164.
47. Asmis LM, Alberio L, Angelillo-Scherrer A, et al. Rivaroxaban: quantification by anti-FXa assay and influence on coagulation tests: a study in 9 Swiss laboratories. *Thromb Res* 2012; 129: 492–498.
48. Freyburger G, Macouillard G, Labrousse S, et al. Coagulation parameters in patients receiving dabigatran etexilate or rivaroxaban: two observational studies in patients undergoing total hip or total knee replacement. *Thromb Res* 2011; 127: 457–465.
49. Tichelaar V, de Jong H, Nijland H, et al. Interference of rivaroxaban in one-stage and chromogenic factor VIII:C assays. *Thromb Haemost* 2011; 106: 990–992.
50. Merriman E, Kaplan Z, Butler J, et al. Rivaroxaban and false positive lupus anti-coagulant testing. *Thromb Haemost* 2011; 105: 385–386.
51. Lindhoff-Last E, Samama MM, Ortel TL, et al. Assays for measuring rivaroxaban: their suitability and limitations. *Ther Drug Monit* 2010; 32: 673–679.
52. Samama MM, Martinoli JL, Le Flem L, et al. Assessment of laboratory assays to measure rivaroxaban – an oral, direct Factor Xa inhibitor. *Thromb Haemost* 2010; 103: 815–825.
53. Samama MM, Contant G, Spiro TE, et al. Evaluation of the anti-Factor Xa chromogenic assay for measuring rivaroxaban plasma concentrations using calibrators and controls. *Blood (ASH Annual Meeting Abstracts)* 2010; 116: 1363–1364 (Abstract 3330).