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Effects of renal impairment on the pharmacokinetics, pharmacodynamics and safety of rivaroxaban, an oral, direct Factor Xa inhibitor

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WHAT IS ALREADY KNOWN ABOUT THIS SUBJECT

- Prior to the commencement of this study, it was already known that rivaroxaban is partially cleared via the kidneys and an influence of renal insufficiency on rivaroxaban pharmacokinetics and exposure was anticipated.

WHAT THIS STUDY ADDS

- As many patients in the target indications of rivaroxaban will be elderly, a precise quantitative knowledge of the influence of renal function on rivaroxaban pharmacokinetics and exposure is mandatory for adequate labelling recommendations (in the context of benefit/risk provided by phase III studies) to guide therapy. This study provided detailed insight on both rivaroxaban pharmacokinetics and pharmacodynamic behaviour in renal impairment including severely renally impaired subjects.

AIM

This study evaluated the effects of impaired renal function on the pharmacokinetics, pharmacodynamics and safety of rivaroxaban (10 mg single dose), an oral, direct Factor Xa inhibitor.

METHODS

Subjects ($n = 32$) were stratified based on measured creatinine clearance: healthy controls (≥80 ml min^{-1}), mild (50–79 ml min^{-1}), moderate (30–49 ml min^{-1}) and severe impairment (<30 ml min^{-1}).

RESULTS

Renal clearance of rivaroxaban decreased with increasing renal impairment. Thus, plasma concentrations increased and area under the plasma concentration–time curve (AUC) LS-mean values were 1.44-fold (90% confidence interval [CI] 1.1, 1.9; mild), 1.52-fold (90% CI 1.2, 2.0; moderate) and 1.64-fold (90% CI 1.2, 2.2; severe impairment) higher than in healthy controls. Corresponding values for the LS-mean of the AUC for prolongation of prothrombin time were 1.33-fold (90% CI 0.92, 1.92; mild), 2.16-fold (90% CI 1.51, 3.10 moderate) and 2.44-fold (90% CI 1.70, 3.49 severe) higher than in healthy subjects, respectively. Likewise, the LS-mean of the AUC for Factor Xa inhibition in subjects with mild renal impairment was 1.50-fold (90% CI 1.07, 2.10) higher than in healthy subjects. In subjects with moderate and severe renal impairment, the increase was 1.86-fold (90% CI 1.34, 2.59) and 2.0-fold (90% CI 1.44, 2.78) higher than in healthy subjects, respectively.

CONCLUSIONS

Rivaroxaban clearance is decreased with increasing renal impairment, leading to increased plasma exposure and pharmacodynamic effects, as expected for a partially renally excreted drug. However, the influence of renal function on rivaroxaban clearance was moderate, even in subjects with severe renal impairment.

Introduction

Thromboembolic disorders are a common cause of morbidity and mortality in the Western world. Those manifesting as deep vein thrombosis (DVT), pulmonary embolism (PE), stroke or myocardial infarction represent some of the most severe health problems [1–3]. Current guidelines recommend the routine use of anticoagulants, such as vitamin K antagonists (VKAs), unfractionated heparin (UFH) and low molecular weight heparins (LMWHs), for the prevention and treatment of thromboembolic disorders. These different anticoagulants are recommended for different indications [4, 5].

Rivaroxaban is an oral, direct Factor Xa inhibitor approved in more than 90 countries worldwide for the prevention of venous thromboembolism (VTE) after elective hip or knee replacement surgery. Clinical development for the prevention and treatment of thromboembolic disorders in several conditions is ongoing. Factor Xa is a particularly attractive target for anticoagulation because it is the pivotal protease of the coagulation pathway, catalysing the conversion of prothrombin to thrombin (Factor IIa) [6]. Inhibiting Factor Xa will potentially block thrombin generation and diminish the thrombin-mediated activation of coagulation and platelets.

Rivaroxaban is undergoing a comprehensive development programme. In phase I studies, single doses of oral rivaroxaban up to 80 mg and multiple doses up to 30 mg twice daily were well tolerated and were found to have predictable pharmacokinetics and pharmacodynamics in healthy subjects [7, 8]. A phase II study demonstrated that once daily (o.d.) dosing of rivaroxaban was possible for the prevention of VTE in patients undergoing total hip replacement (THR) surgery, and that the optimal combination of efficacy and safety, relative to enoxaparin, was with rivaroxaban 10 mg o.d. [9]. In the phase III RECORD programme, rivaroxaban regimens were significantly more effective than enoxaparin for the prevention of VTE in patients undergoing THR or total knee replacement (TKR) surgery [10–13]. Rivaroxaban demonstrated similar efficacy and safety to standard therapy for the treatment of proximal DVT in two phase II studies [14, 15]. Based on these studies, an initial intensified twice daily regimen (rivaroxaban 15 mg twice daily for 3 weeks) followed by a long-term 20 mg o.d. dosing was subsequently selected for investigation in phase III studies in this indication; EINSTEIN DVT, EINSTEIN PE and EINSTEIN EXT (http://www.clinicaltrials.gov; NCT00440193, NCT00439777 and NCT00439725).

Rivaroxaban has a dual mode of elimination, with two-thirds of the dose being metabolized in the liver through oxidative and hydrolytic pathways catalysed via cytochrome P450 enzymes (CYP3A4, CYP2J2 and CYP-independent mechanisms), half of which is excreted via the kidneys and half via the faecal route. One-third of the dose is eliminated as unchanged drug in the urine [16]. Therefore, it is anticipated that a substantial reduction in renal function would affect the renal clearance of rivaroxaban, and consequently its pharmacokinetics and pharmacodynamics and possibly its safety and tolerability. This study was undertaken to determine the effects of impaired renal function (mild to severe) on the pharmacokinetics, pharmacodynamics, safety and tolerability of rivaroxaban, compared with subjects with normal renal function.

Methods

Study design and subjects

This was a two-centre, non-blinded cohort study. The study was approved by the Ethics Committees of the Medical Faculty of the University of Duisburg-Essen, Essen, Germany and of Schleswig-Holstein, Bad-Segeberg, Germany. The study was conducted in accordance with the Declaration of Helsinki, the International Conference on Harmonization Good Clinical Practice guidelines and German drug law. Written, informed consent was obtained from all subjects.

The study included 32 male and female subjects aged 36–69 years with a body mass index between 21 and 36 kg m^{-2}. Twenty-four of the subjects had different degrees of renal impairment and eight subjects had normal renal function. Subjects (matched by age and gender) were assigned to one of four groups according to their measured creatinine clearance (CL_{Cr}) rates, calculated as a 24 h clearance from the creatinine concentrations measured in serum and urine at screening (1–2 weeks before dosing): (i) CL_{Cr} $\geq$80 ml min^{-1} healthy controls, (ii) CL_{Cr} 50–79 ml min^{-1} mild impairment, (iii) CL_{Cr} 30–49 ml min^{-1} moderate impairment and (iv) CL_{Cr} <30 ml min^{-1} severe impairment, but who had not had dialysis in the 4 weeks before enrolment until the end of the study (it was planned to recruit four patients with CL_{Cr} 20–30 ml min^{-1} and four with <20 ml min^{-1}). The healthy control subjects were specifically asked about any condition that could lead to an increased bleeding risk, which would be an exclusion criterion. Subjects with renal impairment had stable disease, defined as <20% variation in serum creatinine concentration measured 3 months before screening compared with baseline. No specific inclusion or exclusion criteria were stated regarding the underlying diseases leading to impaired renal function. The main general exclusion criteria for patients were as follows: diagnosed malignancy, psychiatric disorders, thyroid disorders (unless controlled by appropriate drug therapy), history of definite myocardial infarction, cerebrovascular accident, percutaneous transluminal coronary angioplasty or coronary artery bypass graft within 6 months prior to the screening visit, congestive heart failure (New York Heart Association class 3 or 4), significant uncorrected rhythm or conduction disturbances, prolongation of the QRS complex or QTc, history of gastrointestinal disease, anaemia (haemoglobin <10 g dl^{-1}), known liver

disease and/or elevated serum transaminases (alanine transaminase and aspartate transaminase) greater than two times the upper limit of normal and/or clinically relevant hepatosplenomegaly.

Rivaroxaban was given as a single oral dose of 10 mg (two 5 mg tablets) in the morning under fasting conditions (at least 10 h). Subjects remained at the clinic for at least 30 h after rivaroxaban administration and returned for a final examination approximately 1–2 weeks after dosing.

Pharmacokinetics

To investigate pharmacokinetics, plasma and urine concentrations of rivaroxaban were determined at prespecified time points. Venous blood samples (4 ml) were collected immediately before (0) and 0.5, 1, 2, 3, 4, 6, 8, 12, 15, 24, 30, 48 and 72 h after rivaroxaban administration. Additional blood samples (6 ml) were collected 2, 4 and 8 h after study drug administration to determine the unbound fraction of total plasma drug concentration (f_u) of rivaroxaban and serum albumin concentrations. To determine renal excretion of rivaroxaban, urine was collected 0–4, 4–8, 8–12, 12–24 and 24–30 h after dosing. All samples were stored below −15°C until analysis.

Plasma and urine rivaroxaban concentrations were measured using a fully validated HPLC/MS/MS method (Hewlett-Packard system 1100 coupled with tandem mass spectrometer API 3000), after solid/liquid extraction of rivaroxaban and the internal standard from the matrix using C_{18} cartridges. A close chemical analogue of rivaroxaban was used as an internal standard [17]. Monitored ions were 436 → 145 (rivaroxaban) and 464 → 145 (internal standard). The concentrations of rivaroxaban were validated by assaying quality control samples of blank plasma or urine, spiked with known concentrations of rivaroxaban. Plasma concentrations above the lower limit of quantification (LLOQ) of 0.5 μg l^{-1} were determined with a precision of 5.13–8.16% and an accuracy of 96.1–100.6%. Urine concentrations above the LLOQ of 1.0 mg l^{-1} were determined with a precision of 2.6–4.5% and an accuracy of 94.8–103.7%.

Pharmacokinetic parameters were calculated using non-compartmental methods, and included the area under the plasma concentration–time curve (AUC), AUC divided by dose kg^{-1} bodyweight (AUC_{norm}), maximum plasma concentration (C_{max}), C_{max} divided by dose kg^{-1} body-weight ($C_{max,norm}$), time to reach C_{max} (t_{max}), terminal elimination half-life ($t_{1/2}$), f_u, CL/*F* (apparent oral clearance), amount of drug excreted via urine (Ae_{ur}) and renal clearance (CL_R).

A population pharmacokinetic model that was determined previously was used to describe both plasma and urine rivaroxaban concentrations [18]. At the time of the study, no data were available on the absolute bioavailability (*F*) of rivaroxaban; therefore, *F* was used to describe potential differences in relative bioavailability between the different dosing regimens. As a result, the clearance (CL) and volume of distribution (*V*) of the pharmacokinetic parameters were modelled as CL/*F* and *V*/*F*, respectively. However, as the oral bioavailability of rivaroxaban 10 mg o.d. is high (80–100%) [7, 16], *F* can be assumed to be close to 1, thus delivering uncompromised CL and *V* data.

For a better mechanistic understanding of how renal impairment influences rivaroxaban exposure, its clearance was modelled using the following formulae to describe the hepatic clearance and renal clearance (glomerular filtration and active secretion) behaviour of rivaroxaban:

$$CL = CL_{NR} + CL_R$$

$$CL_R = CL_{Rf}\ (= GFR \times f_u) + CL_{Rs}$$

where

CL_{NR} = non-renal (=hepatic) clearance
CL_R = renal clearance
CL_{Rf} = the glomerular filtration fraction of CL_R
CL_{Rs} = the active secretion fraction of CL_R
f_u = unbound fraction of total plasma drug concentration
GFR = glomerular filtration rate, assessed via CL_{Cr} determination

Pharmacodynamics

The pharmacodynamic effects of rivaroxaban were assessed by evaluating the inhibition of Factor Xa activity and prolongation of prothrombin time (PT) in blood samples collected immediately before (0) and 0.5, 1, 2, 3, 4, 6, 8, 12, 15, 24, 30, 48 and 72 h after rivaroxaban administration. Factor Xa activity was determined by a photometric assay using a two-step process: Factor X in plasma was activated using Russell's viper venom in the presence of calcium ions, leading to Factor Xa. The chromogenic substrate Z-D-Arg-Gly-Arg-pNA (S-2765™; Haemochrom, Essen, Germany) was then hydrolysed by Factor Xa, releasing pNA, which was quantified by spectrophotometry at 405 nm. Concentrations above 0.1 IU ml^{-1} (LLOQ) were determined with a precision of 4.03–5.52% and an accuracy of 100.0–113.6%. PT was assessed using freeze-dried thromboplastin from rabbit brain with an international sensitivity index of 1.23 (Neoplastin Plus®; Diagnostica Stago, Asnières-sur-Seine, France).

Non-compartmental kinetic parameters were calculated using the effect–time profiles for percentage inhibition of Factor Xa activity compared with baseline and the percentage prolongation of PT from baseline. Parameters calculated were the area under the effect curve (AUEC) between rivaroxaban administration and the time of last observation and the maximum effect (E_{max}).

Safety and tolerability

Subjective tolerability was evaluated by questioning the subjects about any adverse events or by spontaneous reporting of adverse events. All events were classified according to their degree of severity. Objective tolerability

was evaluated by monitoring vital signs (e.g. heart rate, blood pressure), electrocardiogram (ECG) variables and clinical laboratory tests (haematology, clinical chemistry, urinalysis).

Statistical methods

The pharmacokinetic parameters AUC, C_{max} and f_u were analysed assuming log-normally distributed data, as were the derived parameters AUEC and E_{max} of the effect–time curves for the inhibition of Factor Xa activity and prolongation of PT. The logarithms of these parameters were assessed using analysis of variance (ANOVA), including a stratum (healthy controls *vs.* renally impaired subjects) and gender effect, and their interaction. Exploratory 90% confidence intervals (CIs) for the strata ratios were calculated by retransformation of the logarithmic results given by the ANOVA. The relationship between the individual pharmacokinetic parameters (AUC, C_{max}, CL/*F*, $t_{1/2}$, CL_R and f_u), pharmacodynamic parameters (AUEC and E_{max}), CL_{Cr} and serum albumin was investigated by calculating Pearson correlation coefficients, the associated 95% CIs, and performing linear regression analysis.

Results

Study population

A total of 32 subjects (18 male and 14 female) were enrolled in the study (mean age ± SD 51.8 ± 9.0 years) and received a single 10 mg dose of rivaroxaban (Table 1). Subjects were assigned to one of four groups of eight age- and gender-matched subjects (healthy controls), according to their CL_{Cr} at screening (Table 1). All subjects completed the study and were included in the pharmacokinetic, pharmacodynamic and safety analyses. The baseline characteristics are presented in Table 1.

Pharmacokinetics

The mean plasma concentration–time curves of a single 10 mg o.d. dose of rivaroxaban in healthy controls and subjects with renal impairment are shown in Figure 1, and the mean calculated pharmacokinetic parameters are summarized in Table 2.

Decreased CL_{Cr} in renally impaired subjects was associated with decreased CL_R (Pearson correlation coefficient $r = 0.83$, $P < 0.001$), and consequently decreased CL/*F* ($r = 0.48$, $P = 0.006$) of rivaroxaban. The amount of unchanged rivaroxaban excreted in the urine decreased from 29% of the dose in healthy controls to 20% in subjects with mild renal impairment, 13% in subjects with moderate impairment and 10% in subjects with severe impairment.

Decreased renal clearance led to increased rivaroxaban plasma concentrations (Figure 1). ANOVA demonstrated that the AUC was increased by 44% in subjects with mild renal impairment, 52% in those with moderate renal impairment, and by 64% in those with severe impairment, compared with healthy controls (Table 2). The effect of decreasing CL_{Cr} on the AUC was statistically significant ($P < 0.03$) and there was a significant correlation between CL_{Cr} and AUC values ($r = -0.45$, $P = 0.012$). The C_{max} of rivar-

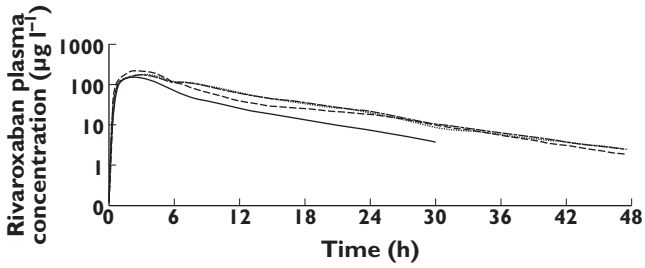

Figure 1

Mean rivaroxaban plasma concentration–time curves on a semi-logarithmic scale in healthy controls (CL_{Cr} ≥80 ml min^{-1}; $n = 8$) and subjects with mild renal impairment (CL_{Cr} 50–79 ml min^{-1}, $n = 8$), moderate renal impairment (CL_{Cr} 30–49 ml min^{-1}, $n = 8$) and severe renal impairment (CL_{Cr} <30 ml min^{-1}, $n = 8$) after the administration of a single 10 mg dose of rivaroxaban. CL_{Cr}, creatinine clearance. Healthy controls (CL_{Cr} ≥80 ml min^{-1}) (——); Mild renal impairment (CL_{Cr} 50–79 ml min^{-1}) (- - -); Moderate renal impairment (CL_{Cr} 30–49 ml min^{-1}) (–·–·–); Severe renal impairment (CL_{Cr} <30 ml min^{-1}) (·····)

Table 1

Summary of characteristics of all subjects included in the study ($n = 32$) by degree of renal impairment based on creatinine clearance rates

	Healthy controls* ($n = 8$)	Renally impaired groups: Mild impairment† ($n = 8$)	Moderate impairment‡ ($n = 8$)	Severe impairment§ ($n = 8$)	All subjects ($n = 32$)
Male/female (*n*)	5/3	5/3	4/4	4/4	18/14
Age (years)	51.3 ± 8.7	49.4 ± 7.7	54.9 ± 10.5	51.8 ± 9.9	51.8 ± 9.0
Weight (kg)	76.6 ± 12.6	80.8 ± 16.6	75.3 ± 9.9	72.5 ± 12.7	76.3 ± 12.9
Height (cm)	168.0 ± 6.7	173.1 ± 11.3	170.6 ± 7.1	170.3 ± 7.7	170.5 ± 8.2
BMI (kg m^{-2})	27.0 ± 2.8	26.8 ± 4.0	25.9 ± 3.4	25.0 ± 4.6	26.2 ± 3.7
CL_{Cr} (ml min^{-1})	117.1 ± 29.3	66.5 ± 8.1	42.6 ± 5.0	22.2 ± 4.6	62.7 ± 39.4

Data are given as mean ± SD, unless indicated otherwise.

*Measured CL_{Cr} ≥80 ml min^{-1}. †Measured CL_{Cr} 50–79 ml min^{-1}. ‡Measured CL_{Cr} 30–49 ml min^{-1}. §Measured CL_{Cr} <30 ml min^{-1}. BMI, body mass index; CL_{Cr}, creatinine clearance.

Table 2

Pharmacokinetic parameters of rivaroxaban after the administration of a single 10 mg dose of oral rivaroxaban to healthy controls and subjects with mild, moderate and severe renal impairment

	Healthy controls (n = 8)	Renally impaired groups Mild impairment (n = 8)	Moderate impairment (n = 8)	Severe impairment (n = 8)
AUC (μg l^{-1} h)	1247 (49.3)	1 863 (30.9)	2 068 (33.1)	2 228 (37.0)
AUC$_{norm}$ (g l^{-1} h)	9439 (49.6)	14 780 (31.6)	15 440 (28.1)	15 940 (48.5)
C_{max} (μg l^{-1})	172.3 (30.7)	217.5 (37.9)	206.2 (26.0)	232.2 (33.1)
$C_{max,norm}$ (g l^{-1})	1304 (25.9)	1 725 (37.4)	1 540 (23.9)	1 662 (34.6)
$t_{1/2}$ (h)	8.3 (38.4)	8.7 (50.1)	9.0 (38.6)	9.5 (31.8)
CL/F (l h^{-1})	8.0 (49.3)	5.4 (30.8)	4.8 (33.1)	4.5 (37.0)
f_u (%)	7.3 (19.3)	5.4 (30.7)	8.2 (32.4)	7.6 (23.2)
t_{max} (h)*	2.0 (0.5–4.0)	2.0 (1.0–6.0)	3.0 (1.0–4.0)	3.0 (2.0–4.0)
CL_R (l h^{-1})	2.4 (46.5)†	1.2 (29.2)	0.7 (33.1)	0.5 (40.4)
Ae_{ur} (%)	29.2 (25.8)†	20.2 (28.0)	13.1 (53.1)	10.4 (35.8)
AUC ratio (90% CI) *vs.* healthy controls‡	–	1.44 (1.08, 1.91)	1.52 (1.15, 2.01)	1.64 (1.24, 2.17)
C_{max} ratio (90% CI) *vs.* healthy controls‡	–	1.28 (1.07, 1.55)	1.12 (0.93, 1.34)	1.26 (1.05, 1.51)

Data are given as geometric mean (% coefficient of variation) unless indicated otherwise.
*Median (range). †n = 7. ‡Calculated by analysis of variance. Ae_{ur}, amount of drug excreted via urine; AUC, area under the plasma concentration–time curve; AUC_{norm}, bodyweight and dose-normalized AUC; CI, confidence interval; CL/F total body clearance; CL_R, renal clearance of drug; C_{max}, maximum plasma concentration; $C_{max,norm}$, bodyweight and dose-normalized C_{max}; f_u, fraction of unbound drug in plasma; $t_{1/2}$, terminal elimination half-life; t_{max}, time to reach C_{max}.

oxaban was less affected by renal impairment than the AUC. There was a mean increase of approximately 30% in those with renal impairment compared with healthy controls. The t_{max} was slightly prolonged in subjects with moderate or severe renal impairment (3 h *vs.* 2 h for healthy controls) and the $t_{1/2}$ of rivaroxaban was only slightly prolonged in renally impaired subjects (Table 2).

The f_u of rivaroxaban was not affected in renally impaired subjects compared with healthy controls (7.3%, 5.4%, 8.2% and 7.6% in healthy controls, and mildly, moderately and severely impaired subjects, respectively). There was no correlation between the f_u and CL_{Cr} (r = –0.065, P = 0.73). However, because of increased total plasma rivaroxaban concentrations, the plasma concentrations of unbound rivaroxaban were increased in subjects with renal impairment. Serum albumin concentrations were similar in all groups and had no effect on the pharmacokinetics of rivaroxaban.

Modelling of the rivaroxaban plasma and urine concentration data using a population pharmacokinetic model was performed, using a model previously described [18]. A two-compartment model with first-order absorption and explicit formulae to describe the non-renal (hepatic) and renal (both active secretion and glomerular filtration) clearance behaviour of rivaroxaban was used (Figure 2). As expected with full-profile data, the model described the data well, with residual (unexplained) variability of 29% for the description of rivaroxaban in plasma and 34% for the description of rivaroxaban in urine. The model predicted an approximate mean ratio of 4:1 between active renal secretion and glomerular filtration of unchanged rivaroxaban. It also predicted that, as renal function decreased, both active renal excretion and glomerular filtration would be equally affected, whereas non-renal (hepatic) clearance would remain constant.

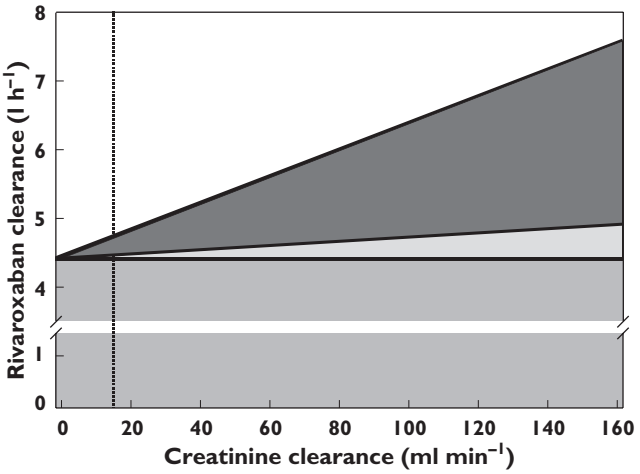

Figure 2

Relationship between rivaroxaban clearance and renal function (assessed via measured CL_{Cr}) according to the two-compartment model with first-order absorption and explicit formulae to describe the non-renal and renal (glomerular filtration and active secretion) clearance behaviour of rivaroxaban (data are population means). CL_{Cr}, creatinine clearance. Active renal secretion: CL_{Rs} (▬); Glomerular filtration: CL_{Rf} (▭); Non-renal (= hepatic) clearance: CL_{NR} (▭); CL_{Cr} = 15 ml min^{-1} (·····)

Pharmacodynamics

Administration of rivaroxaban inhibited Factor Xa activity and prolonged PT. These pharmacodynamic effects were increased with decreasing renal function (Figure 3, Table 3).

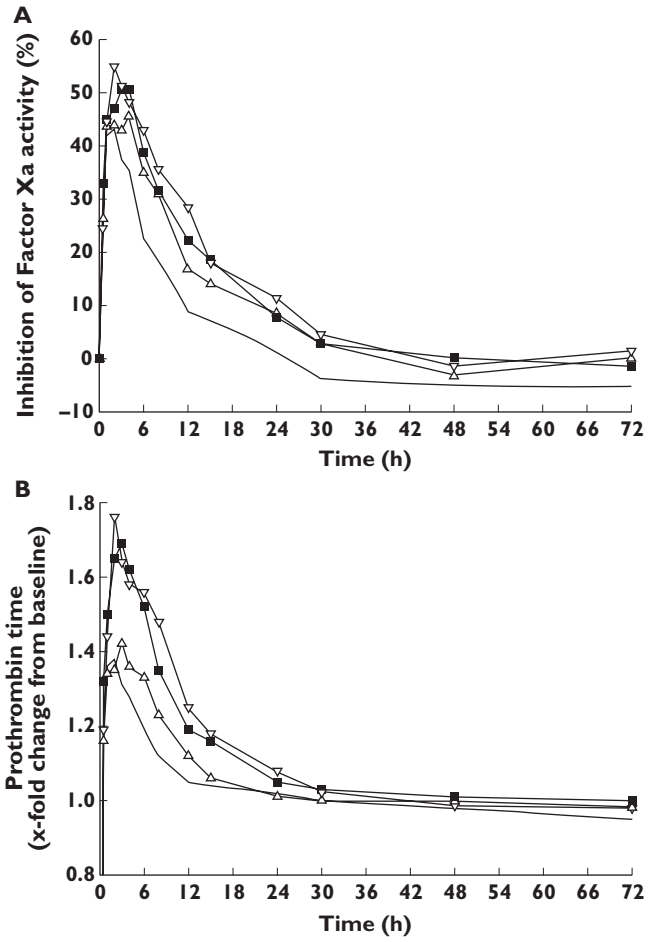

Figure 3

Time courses of (A) inhibition of Factor Xa activity and (B) prolongation of prothrombin time after a single 10 mg dose of rivaroxaban in healthy controls (CL_{Cr} ≥80 ml min^{-1}, n = 8) and subjects with mild renal impairment (CL_{Cr} 50–79 ml min^{-1}, n = 8), moderate renal impairment (CL_{Cr} 30–49 ml min^{-1}, n = 8) and severe renal impairment (CL_{Cr} <30 ml min^{-1}, n = 8). Median results are shown. CL_{Cr}, creatinine clearance. Healthy controls (CL_{Cr} ≥80 ml min^{-1}) (—); Mild renal impairment (CL_{Cr} 50–79 ml min^{-1}) (–△–); Moderate renal impairment (CL_{Cr} 30–49 ml min^{-1}) (–■–); Severe renal impairment (CL_{Cr} <30 ml min^{-1}) (–▽–)

The AUC for Factor Xa inhibition in subjects with mild renal impairment was 1.50-fold (90% CI 1.07, 2.10) higher than in healthy subjects. In subjects with moderate and severe renal impairment, the increase was 1.86-fold (90% CI 1.34, 2.59) and 2.0-fold (90% CI 1.44, 2.78) higher than in healthy subjects, respectively. The total stratum effect was significant (P = 0.0067, Figure 3A, Table 3). The E_{max} of rivaroxaban on the inhibition of Factor Xa activity was less affected by reduced CL_{Cr}. An increase of 9–12% for the renally impaired subgroups was not significantly different from healthy controls (P = 0.44). The correlation (Pearson correlation coefficient) between CL_{Cr} and the percentage inhibition of Factor Xa activity was significant for AUC (r = –0.49, P = 0.005), but not for E_{max} (r = –0.26, P = 0.16).

Prolongation of PT with rivaroxaban was more pronounced in subjects with impaired renal function, particularly those with moderate or severe renal impairment. The AUC for prolongation of PT in subjects with mild renal impairment was 1.33-fold (90% CI 0.92, 1.92) higher than in healthy subjects. In subjects with moderate and severe renal impairment, the increase was 2.16-fold (90% CI 1.51, 3.10) and 2.44-fold (90% CI 1.70, 3.49) higher than in healthy subjects, respectively. The total stratum effect was significant (P = 0.0006; Figure 3B, Table 3). The E_{max} of rivaroxaban on the prolongation of PT was less affected by renal impairment than AUEC, with increases of 1.0- to 1.2-fold compared with healthy controls. However, the total stratum effect was significant (P < 0.0001). There was a significant correlation between CL_{Cr} and the prolongation of PT (AUC: r = –0.56, P = 0.001; E_{max}: r = –0.61, P < 0.001).

Serum albumin concentrations did not influence the inhibition of Factor Xa activity or the prolongation of PT caused by rivaroxaban.

ANOVA of the slopes of the regression line of the correlation between PT and rivaroxaban plasma concentration indicated a slightly (~30%) more pronounced response (PT prolongation) in the moderately and severely impaired groups compared with healthy controls and subjects with mild renal impairment. The slopes of the correlations were 3.4 s/(100 μg l^{-1}) (95% CI 3.0, 3.9 s/[100 μg l^{-1}]) and 2.9 s/(100 μg l^{-1}) (95% CI 2.5, 3.3 s/[100 μg l^{-1}]) in healthy subjects and subjects with mild renal impairment, compared with 4.4 s/(100 μg l^{-1}) (95% CI 3.9, 4.8 s/[100 μg l^{-1}]) and 3.9 s/(100 μg l^{-1}) (95% CI 3.5, 4.3 s/[100 μg l^{-1}]) in subjects with moderate and severe renal impairment, respectively. The overall P value for the difference between the groups was significant (<0.003).

Safety and tolerability

Rivaroxaban was well tolerated. A total of 17 treatment-emergent adverse events were reported by 10 of the 32 subjects. Five subjects in the healthy control group reported at least one adverse event, one subject in each of the mild and moderate renal impairment subgroups reported at least one adverse event, and three subjects in the subgroup with severe impairment reported at least one adverse event. All adverse events were mild (15 events) or moderate (two events) in intensity, all had resolved by the end of the study, and no subject withdrew because of adverse events. A total of nine adverse events were considered possibly related to rivaroxaban: headache (one healthy control and two subjects with severe renal impairment), migraine (one subject with mild renal impairment), vertigo (one healthy control subject), eyelid oedema (one subject with mild renal impairment), raised creatinine kinase (one healthy control subject and one subject with mild renal impairment) and raised lipase (one healthy control subject). No adverse events related to bleeding were reported. Overall, rivaroxaban had no impact on vital signs or ECG parameters.

Table 3

Pharmacodynamic parameters (inhibition of Factor Xa activity and relative prolongation of prothrombin time) after the administration of a single 10 mg dose of oral rivaroxaban to healthy controls and subjects with mild, moderate and severe renal impairment

	Healthy controls (n = 8)	Renally impaired groups Mild impairment (n = 8)	Moderate impairment (n = 8)	Severe impairment (n = 8)
Inhibition of Factor Xa activity				
AUEC (% h)	355.0 (40.1)	536.1 (46.8)	692.0 (33.3)	743.5 (34.2)
AUEC ratio (90% CI) *vs.* healthy controls*	–	1.50 (1.07, 2.10)	1.86 (1.34, 2.59)	2.00 (1.44, 2.78)
E_{max} (%)	46.5 (18.6)	49.7 (30.9)	53.2 (15.1)	54.0 (16.8)
E_{max} ratio (90% CI) *vs.* healthy controls*	–	1.09 (0.96, 1.25)	1.10 (0.97, 1.26)	1.12 (0.99, 1.27)
Prolongation of prothrombin time				
AUEC (% h)	15.4 (41.4)	21.0 (47.8)	33.6 (24.0)	37.9 (43.7)
AUEC ratio (90% CI) *vs.* healthy controls*	–	1.33 (0.92, 1.92)	2.16 (1.51, 3.10)	2.44 (1.70, 3.49)
E_{max} (%)	1.4 (5.7)	1.5 (7.9)	1.7 (10.5)	1.7 (7.8)
E_{max} ratio (90% CI) *vs.* healthy controls*	–	1.04 (0.98, 1.10)	1.17 (1.11, 1.24)	1.20 (1.13, 1.27)

Data are given as geometric mean (% coefficient of variation) unless indicated otherwise. *Calculated by analysis of variance. AUEC, area under the effect curve between rivaroxaban administration and time of last observation (48 h); CI, confidence interval; E_{max}, maximum effect.

Discussion

Rivaroxaban has been approved in more than 90 countries worldwide for the prevention of VTE after elective hip or knee replacement in adult patients. It is also in advanced clinical development for the prevention and treatment of other thromboembolic disorders in other indications (including the treatment of VTE, stroke prevention in atrial fibrillation and secondary prevention in patients with acute coronary syndrome, and the prevention of VTE in hospitalized, medically ill patients). Many patients with these disorders who might be prescribed rivaroxaban are likely to be older and may often have a decrease in renal function, which is a consequence of accumulating concomitant diseases during ageing [19]. Because rivaroxaban is eliminated partially via the kidneys, it is necessary to evaluate the effects of renal impairment on the pharmacokinetics, pharmacodynamics, safety and tolerability of rivaroxaban.

In this study, the influence of varying levels of renal impairment on the pharmacokinetics, pharmacodynamics, safety and tolerability of a single 10 mg dose of oral rivaroxaban were evaluated in healthy subjects and patients with varying degrees of impaired renal function. Subjects were grouped according to their renal function based on measured CL_{Cr}. Renal clearance and, consequently, total body clearance of rivaroxaban decreased in subjects with increasing renal impairment, leading to increased plasma concentrations and increased pharmacodynamic effects (inhibition of Factor Xa activity and prolongation of PT).

Rivaroxaban is eliminated by metabolic degradation (approximately two-thirds of the administered dose) as well as by direct renal excretion of unchanged compound (approximately one-third of the administered dose) [16]. Therefore, it was anticipated that renal impairment would influence the pharmacokinetics and pharmacodynamics of rivaroxaban. As expected, increasing impairment decreased the total body clearance of rivaroxaban and, consequently, increased the AUC of rivaroxaban. There was a close correlation between the total body clearance of rivaroxaban and CL_{Cr}, and the effect of CL_{Cr} on the AUC of rivaroxaban was statistically significant. The increased rivaroxaban exposure was due to decreased clearance of rivaroxaban rather than increased absorption, as confirmed by the C_{max} of rivaroxaban being less affected by renal function. It is also important to note that the t_{max} and $t_{1/2}$ of rivaroxaban were only slightly increased in moderately and severely renally impaired subjects.

The f_u of rivaroxaban ranged between 5.4% and 8.2% and was not affected by renal impairment. There was no correlation between f_u and CL_{Cr}.

Modelling of the pharmacokinetic data using a two-compartment model with first-order absorption and explicit formulae to describe the renal and non-renal (hepatic) clearance behaviour of rivaroxaban predicted a decrease in both active renal excretion and glomerular filtration of unchanged rivaroxaban with decreasing CL_{Cr}. By contrast, hepatic clearance was unaltered by decreased renal function.

Progressive renal impairment led to an increase of percentage inhibition of Factor Xa activity. The percentage increase in AUEC of inhibition of Factor Xa activity was 50%, 86% and 100% compared with healthy subjects for mild, moderate and severe renal impairment, respectively, whereas E_{max} was unaffected. Relative prolongation of PT was also affected by renal impairment and was more pronounced with moderate and severe renal impairment compared with the inhibition of Factor Xa activity. The percentage increase in AUEC of prolongation of PT was 33%, 116% and 144%, compared with healthy subjects for mild, moderate and severe renal impairment, respectively, whereas the maximal increase in E_{max} was 20% for subjects with renal impairment.

The single 10 mg dose of rivaroxaban was well tolerated in all groups, regardless of the severity of renal impairment. Unusually, there were more adverse events reported in the healthy controls than in the groups with impaired renal function. However, all of the adverse events reported were mild or moderate in nature and were transient. Furthermore, the subject groups were too small to draw statistical conclusions about the incidence of adverse events. The incidence and nature of adverse events in all groups in this study were similar to those observed in other studies of rivaroxaban conducted in healthy subjects, and were also similar to the rates observed in subjects receiving placebo in these studies [7, 8]. There was specifically no increased risk of bleeding identified in patients with renal impairment.

Rivaroxaban has undergone phase II and phase III studies to investigate its efficacy and safety for the prevention of VTE after TKR or THR, in which patients with mild to moderate renal impairment (CL_{Cr} >30 ml min^{-1}) were eligible to participate [10–13, 20, 21]. In an analysis of the population pharmacokinetics and pharmacodynamics of rivaroxaban in patients taking part in two of these studies [22], renal function was found to affect the clearance of rivaroxaban, as was observed in the present study. The influence of renal function on the clearance of rivaroxaban in these patients was moderate, and predictions of rivaroxaban plasma concentrations in patients with moderately impaired renal function (calculated CL_{Cr} >30 ml min^{-1}) did not exceed the 90% CI of the general population. This suggested that it should be possible to give the same fixed dose of rivaroxaban to orthopaedic patients with moderate renal impairment as given to those with normal renal function.

Patients with severe renal impairment (CL_{Cr} 15–30 ml min^{-1}) receiving 10 mg o.d. rivaroxaban may be exposed to rivaroxaban plasma concentrations similar to those patients receiving a total daily dose of 20 mg. Two phase II studies with rivaroxaban for the prevention of VTE after THR or TKR surgery showed that total daily doses of rivaroxaban of 5–20 mg had a similar safety profile as compared with o.d. 40 mg doses of enoxaparin, suggesting that exposures equivalent to a 20 mg dose of rivaroxaban may be used safely in patients [20, 21]. As a result, moderate increases in rivaroxaban exposure in patients with renal impairment receiving 10 mg o.d. are unlikely to be clinically relevant. As patients with advanced stages of renal impairment have an increased risk of bleeding due to their underlying disease [23–25], more clinical data are warranted to evaluate fully the safety of repeated 10 mg doses of rivaroxaban in patients with severe renal impairment. The rivaroxaban dose that was administered in this study (10 mg o.d.) was used in the phase III RECORD studies, resulting in a similar safety profile across all patient groups while being significantly more effective than enoxaparin for the prevention of VTE after THR or TKR [10–13].

Other anticoagulants, including UFH, LMWHs and the indirect Factor Xa inhibitor fondaparinux, are eliminated primarily via the kidneys. Decreased clearance and increased exposure to these anticoagulants may place patients with renal impairment at increased risk of major bleeding episodes, even at standard doses. Exposure to the LMWH enoxaparin is significantly increased in patients with severe renal impairment, and lower doses are recommended in such patients [26]. Lower doses of fondaparinux may also be required in patients with moderate renal impairment compared with patients with normal renal function. The dose should be reduced to 1.5 mg o.d. in patients with CL_{Cr} in the range of 20–50 ml min^{-1}. Fondaparinux should not be used in patients with CL_{Cr} <20 ml min^{-1} [27]. VKAs, such as warfarin, may require dose adjustment in patients with renal insufficiency [28]. The direct thrombin inhibitor dabigatran is excreted predominantly by the kidneys, and moderately impaired renal function (CL_{Cr} <50 ml min^{-1}) leads to increases in plasma concentrations [29]. Therefore, anticoagulants that are influenced to a smaller degree by diminishing renal function, such as rivaroxaban, may be easier to use in patients with renal impairment, because deteriorating renal function during the course of the treatment is less likely to result in undesirable increases in exposure. However, no clinical data are available about rivaroxaban treatment in patients with severe renal impairment (CL_{Cr} <30 ml min^{-1}) or patients undergoing dialysis. Consequently, no recommendation can be given for this patient population at this point in time.

In summary, this study has demonstrated that the clearance of rivaroxaban is decreased in subjects with renal impairment, as would be expected for a drug that is partially dependent on renal excretion, leading to a moderate increase in exposure. This, in turn, leads to increases in the pharmacodynamic effects of rivaroxaban, such as the inhibition of Factor Xa activity and PT. Fixed doses of rivaroxaban were given to patients with mild to moderate renal impairment in phase II to III studies, resulting in a safety profile of rivaroxaban that was similar in patients with different levels of renal impairment. Population pharmacokinetic and pharmacodynamic analysis of these studies showed that the influence of renal function on the clearance of rivaroxaban was moderate, in agreement with the findings of the present study [22, 30].

Competing interests

Dagmar Kubitza and Wolfgang Mueck are employees of Bayer Schering Pharma AG. Wolfgang Mueck also owns shares in Bayer. This study was approved by Bayer Health Care. The other authors have no competing interests to declare.

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REFERENCES

1 Thom T, Haase N, Rosamond W, Howard VJ, Rumsfeld J, Manolio T, Zheng ZJ, Flegal K, O'Donnell C, Kittner S, Lloyd-Jones D, Goff DC Jr, Hong Y, Adams R, Friday G, Furie K, Gorelick P, Kissela B, Marler J, Meigs J, Roger V, Sidney S, Sorlie P, Steinberger J, Wasserthiel-Smoller S, Wilson M, Wolf P. American Heart Association Statistics Committee and Stroke Statistics Subcommittee. Heart disease and stroke statistics – 2006 update: a report from the American Heart Association Statistics Committee and Stroke Statistics Subcommittee. Circulation 2006; 113: e85–151.

2 White RH. The epidemiology of venous thromboembolism. Circulation 2003; 107: I4–8.

3 Heit JA. The epidemiology of venous thromboembolism in the community: implications for prevention and management. J Thromb Thrombolysis 2006; 21: 23–9.

4 Geerts WH, Bergqvist D, Pineo GF, Heit JA, Samama CM, Lassen MR, Colwell CW. American College of Chest Physicians. Prevention of venous thromboembolism: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition). Chest 2008; 133: 381S–453S.

5 Singer DE, Albers GW, Dalen JE, Fang MC, Go AS, Halperin JL, Lip GY, Manning WJ. American College of Chest Physicians. Antithrombotic therapy in atrial fibrillation: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition). Chest 2008; 133: 546S–92S.

6 Mann KG, Butenas S, Brummel K. The dynamics of thrombin formation. Arterioscler Thromb Vasc Biol 2003; 23: 17–25.

7 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: 412–21.

8 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: 873–80.

9 Eriksson BI, Borris LC, Dahl OE, Haas S, Huisman MV, Kakkar AK, Muehlhofer E, Dierig C, Misselwitz F, Kälebo P. ODIXa-HIP Study Investigators. A once-daily, oral, direct Factor Xa inhibitor, rivaroxaban (BAY 59-7939), for thromboprophylaxis after total hip replacement. Circulation 2006; 114: 2374–81.

10 Eriksson BI, Borris LC, Friedman RJ, Haas S, Huisman MV, Kakkar AK, Bandel TJ, Beckmann H, Muehlhofer E, Misselwitz F, Geerts W. RECORD1 Study Group. Rivaroxaban versus enoxaparin for thromboprophylaxis after hip arthroplasty. N Engl J Med 2008; 358: 2765–75.

11 Kakkar AK, Brenner B, Dahl OE, Eriksson BI, Mouret P, Muntz J, Soglian AG, Pap AF, Misselwitz F, Haas S. 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: 31–9.

12 Lassen MR, Ageno W, Borris LC, Lieberman JR, Rosencher N, Bandel TJ, Misselwitz F, Turpie AG. Rivaroxaban versus enoxaparin for thromboprophylaxis after total knee arthroplasty. N Engl J Med 2008; 358: 2776–86.

13 Turpie AGG, Lassen MR, Davidson BL, Bauer KA, Gent M, Kwong LM, Cushner FD, Lotke PA, Berkowitz SD, Bandel TJ, Benson A, Misselwitz F, Fisher WD. Rivaroxaban versus enoxaparin for thromboprophylaxis after total knee arthroplasty (RECORD4): a randomised trial. Lancet 2009; 373: 1673–80.

14 Agnelli G, Gallus A, Goldhaber SZ, Haas S, Huisman MV, Hull RD, Kakkar AK, Misselwitz F, Schellong S. ODIXa-DVT Study Investigators. Treatment of proximal deep-vein thrombosis with the oral direct Factor Xa inhibitor rivaroxaban (BAY 59-7939): the ODIXa-DVT (oral direct Factor Xa inhibitor BAY 59-7939 in patients with acute symptomatic deep-vein thrombosis) study. Circulation 2007; 116: 180–7.

15 Buller HR, Lensing AW, Prins MH, Agnelli G, Cohen A, Gallus AS, Misselwitz F, Raskob G, Schellong S, Segers A. Einstein-DVT Dose-Ranging Study investigators. A dose-ranging study evaluating once-daily oral administration of the Factor Xa inhibitor rivaroxaban in the treatment of patients with acute symptomatic deep vein thrombosis. The EINSTEIN-DVT Dose-Ranging Study. Blood 2008; 112: 2242–7.

16 Bayer Schering Pharma AG. Xarelto® summary of product characteristics. Available at http://www.xarelto.com/html/downloads/Xarelto_Summary_of_Product_Characteristics_May2009.pdf (Updated 9 September 2009; last accessed 15 February 2010).

17 Weinz C, Buetehorn U, Daehler HP, Kohlsdorfer C, Pleiss U, Sandmann S, Schlemmer KH, Schwarz T, Steinke W. Pharmacokinetics of BAY 59-7939 – an oral, direct Factor Xa inhibitor – in rats and dogs. Xenobiotica 2005; 35: 891–910.

18 Mueck W, Becka M, Kubitza D, Voith B, Zuehlsdorf M. 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: 335–44.

19 Clark B. Biology of renal aging in humans. Adv Ren Replace Ther 2000; 7: 11–21.

20 Turpie AGG, Fisher WD, Bauer KA, Kwong LM, Irwin MW, Kälebo P, Misselwitz F, Gent M. BAY 59-7939: an oral, direct factor Xa inhibitor for the prevention of venous thromboembolism in patients after total knee replacement. A phase II dose-ranging study. J Thromb Haemost 2005; 3: 2479–86.

21 Eriksson BI, Borris L, Dahl OE, Haas S, Huisman MV, Kakkar AK, Misselwitz F, Kälebo P. ODIXa-HIP Study Investigators. Oral, direct Factor Xa inhibition with BAY 59-7939 for the prevention of venous thromboembolism after total hip replacement. J Thromb Haemost 2006; 4: 121–8.

22 Mueck W, Eriksson BI, Bauer KA, Borris L, Dahl OE, Fisher WD, Gent M, Haas S, Huisman MV, Kakkar AK, Kälebo P, Kwong LM, Misselwitz F, Turpie AGG. Population pharmacokinetics and pharmacodynamics of rivaroxaban – an oral, direct factor Xa inhibitor – in patients undergoing major orthopaedic surgery. Clin Pharmacokinet 2008; 47: 203–16.

23 Holden RM, Harman GJ, Wang M, Holland D, Day AG. Major bleeding in hemodialysis patients. Clin J Am Soc Nephrol 2008; 3: 105–10.

24 Falga C, Capdevila JA, Soler S, Rabunal R, Sanchez Munoz-Torrero JF, Gallego P, Monreal M. Clinical outcome of patients with venous thromboembolism and renal insufficiency. Findings from the RIETE registry. Thromb Haemost 2007; 98: 771–6.

25 Boccardo P, Remuzzi G, Galbusera M. Platelet dysfunction in renal failure. Semin Thromb Hemost 2004; 30: 579–89.

26 Sanofi-aventis. Lovenox (enoxaparin sodium injection) for subcutaneous and intravenous use. Prescribing information. Available at http://products.sanofi-aventis.us/lovenox/lovenox.pdf (Updated December 2009; last accessed 24 August 2010).

27 Glaxo Group Ltd. Arixtra 2.5 mg/0.5 ml solution for injection, pre-filled syringe. Summary of product characteristics. Available at http://www.medicines.org.uk/emc/medicine/15123 (Updated 25 March 2009; last accessed 24 August 2010).

28 Grand'Maison A, Charest AF, Geerts WH. Anticoagulant use in patients with chronic renal impairment. Am J Cardiovasc Drugs 2005; 5: 291–305.

29 Eriksson BI, Quinlan DJ, Weitz JI. Comparative pharmacodynamics and pharmacokinetics of oral direct thrombin and factor Xa inhibitors in development. Clin Pharmacokinet 2009; 48: 1–22.

30 Mueck W, Borris LC, Dahl OE, Haas S, Huisman MV, Kakkar AK, Kalebo P, Muelhofer E, Misselwitz F, Eriksson BI. Population pharmacokinetics and pharmacodynamics of once- and twice-daily rivaroxaban for the prevention of venous thromboembolism in patients undergoing total hip replacement. Thromb Haemost 2008; 100: 453–61.