CPC088 Initiating thromboprophylaxis with low molecular weight heparin and transitioning to oral rivaroxaban

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Introduction

- **Rivaroxaban (Xarelto®, Bayer Pharma AG, Wuppertal, Germany) is a potent and selective oral, direct Factor Xa inhibitor[1]**
- **The RECORD clinical trial programme demonstrated that rivaroxaban 10 mg once daily (od) was superior to enoxaparin (low molecular weight heparin [LMWH]) for the prevention of venous thromboembolism (VTE) after elective total hip or knee replacement (THR/TKR) surgery, and had a similar safety profile[2–5]**
- **On the basis of the RECORD results, rivaroxaban 10 mg od was approved for VTE prevention in adult patients undergoing elective hip or knee replacement surgery**
- **Provided that haemostasis has been established, it is recommended to give the first dose of rivaroxaban 6–10 hours post-surgery; in practice, however, postoperative nausea and vomiting may prevent initial oral dosing**
- **Initiating thromboprophylaxis with subcutaneous LMWH and transitioning to oral rivaroxaban could be an attractive strategy in such cases**

Objective

- The Safe, Simple Transitions (SST) study investigated the feasibility of the above approach by considering:
  - The pharmacodynamics of rivaroxaban (assessed primarily by anti-Factor Xa activity) during serial administration compared with those on the day of transition from LMWH to oral rivaroxaban in patients who had received initial VTE prophylaxis with LMWH after THR/TKR surgery
  - The effect of patient age and renal function on the pharmacodynamics of rivaroxaban during the transition from LMWH
  - The safety and tolerability of the strategy

Methods

Patients and study design

- This open-label, single-arm, non-randomized study was conducted at four orthopaedic centres in the US with associated in-house or satellite sub-acute units
- Male and female patients aged ≥18 years who had undergone elective unilateral primary THR or TKR were eligible
- Patients initially received postoperative thromboprophylaxis with subcutaneous enoxaparin 40 mg od or 30 mg twice daily (bid)
- Eligible patients commenced oral rivaroxaban 10 mg od within 2 days of admission to the sub-acute unit; the first dose was given 22–28 hours after the last dose of enoxaparin 40 mg od or 12–18 hours after the last dose of enoxaparin 30 mg bid

Pharmacodynamic evaluations

- Venous blood samples were taken before the first rivaroxaban dose (time 0) and at 2, 4, 6, 8, 12 and 24 hours postdose on study days 1 and 3
- Anti-Factor Xa activity was determined using a validated, specific, standard chromogenic method (Biophen Heparin 6 kit; Aniara, Mason, OH, USA)
- Prothrombin time (PT) was also measured using the STA® Neoplastine® CI Plus kit (Diagnostica Stago Inc., Parsippany, NJ, USA)

Safety assessments

- Adverse events (AEs) were recorded until the final follow-up visit, 30 days after surgery

Populations and endpoints

- The safety population included patients who took at least one dose of study medication, and the intention-to-treat (ITT) population included patients with any post-baseline efficacy assessments
- The primary endpoint was peak anti-Factor Xa activity on study day 1 compared with day 3 for each patient in the ITT population; analyses combined results from all patients

Results

Patients and baseline characteristics

- A total of 56 patients were enrolled in the study; the safety and ITT populations included 53 and 52 patients, respectively
- Selected demographic and baseline characteristics are shown in Table 1
- Of those patients in the safety population, 26 (49%) underwent THR and 27 (51%) underwent TKR surgery
- All patients received at least one dose of enoxaparin before study day 1
  - THR patients: 77% and 23% received od or bid dosing, respectively
  - TKR patients: 11% and 89% received od or bid dosing, respectively

Table 1. Demographic and baseline characteristics (safety population)

Median age, years (range)	73 (32–89)
Gender, n (%)	
Male	24 (45.3)
Female	29 (54.7)
Ethnicity, n (%)	
White	41 (77.4)
Black	10 (18.9)
Asian, Native American or Alaskan native	2 (3.8)
Median body mass index, kg/m^2 (range)	28.7 (19.6–52.3)
eGFR	
Median (ml/min)	88.1
≥60 ml/min, n (%)	47 (88.7)
30–59 ml/min, n (%)	6 (11.3)

eGFR, estimated glomerular filtration rate.

Pharmacodynamic results

- Mean anti-Factor Xa activity was not increased on day 1 compared with day 3; in fact, there was a slight but significant increase on day 3 versus day 1 (p<0.01) (Figure 1A, Table 2)
- The areas under the concentration–time curves (AUCs) for anti-Factor Xa activity on days 1 and 3 were not significantly different (p=0.87) (Figure 1A, Table 2)
- Mean PT was not significantly higher on day 1 than on day 3 (p=0.11) (Figure 1B, Table 2)
- The AUC for PT after rivaroxaban administration was increased in the day 1 samples compared with similar samples on day 3 (p<0.0001) (Figure 1B, Table 2)

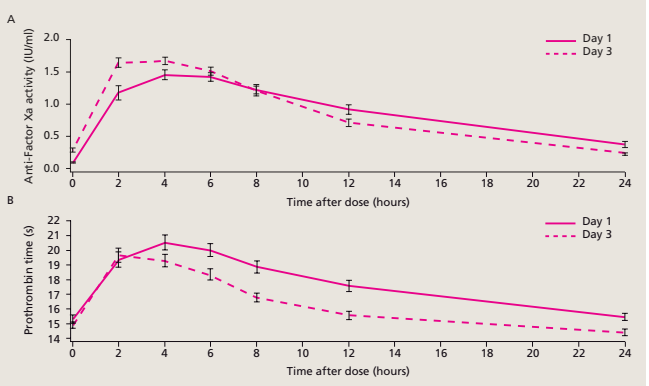

Figure 1. Time courses of mean ± standard error (A) anti-Factor Xa activity and (B) PT (ITT population).

Table 2. Mean changes in maximum values and AUCs for coagulation tests (ITT population)

		Day 1	Day 3	Change	p value*
Anti-Factor Xa activity (IU/ml)	Mean	1.66	1.83	0.20 (–0.05, 0.34)	<0.01
	AUC	21.35	20.74	–0.21 (–2.05, 0.22)	0.87
Prothrombin time (s)	Mean	21.57	20.51	–0.91	0.11
	AUC	420.46	391.37	–35.13 (–48.01, –22.26)	<0.0001

*Paired t-test testing for the mean change between day 3 and day 1.
AUC, area under the concentration–time curve; ITT, intention-to-treat; IU, international units.

Impact of age and renal function

- Renal function decreased with increasing age in the study population, as indicated by a moderate and negative correlation between age and estimated glomerular filtration rate (eGFR) (r = –0.48)
- Anti-Factor Xa activity was slightly higher in patients aged ≥73 years (the median age) versus <73 years and in those with eGFR <88.1 ml/min (the median value) versus ≥88.1 ml/min (Figure 2)
- The age-stratified PT time courses showed a similar trend to the time courses for anti-Factor Xa activity but were slightly lower in patients with an eGFR below the median compared with those with an eGFR above the median (Figure 3)

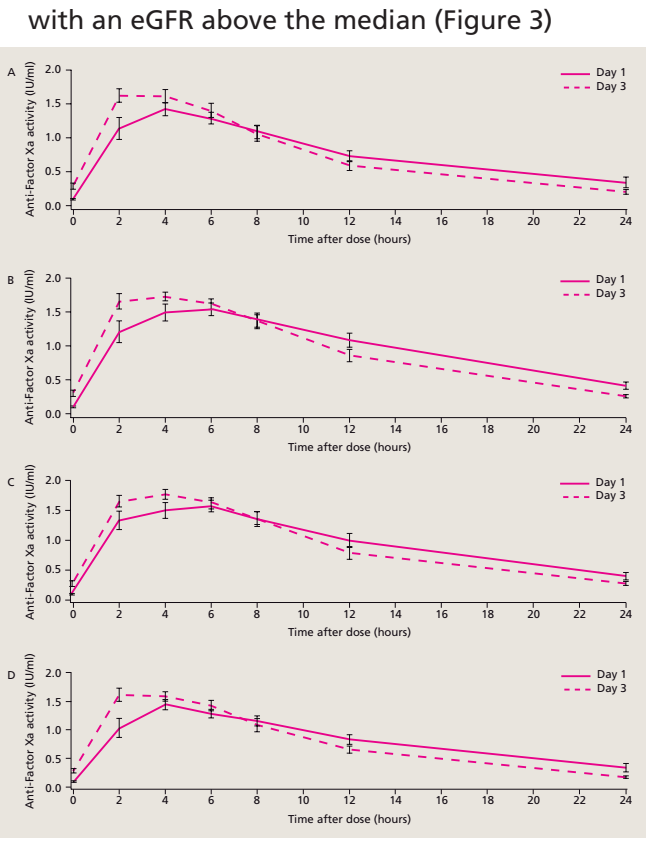

Figure 2. Anti-Factor Xa activity (± standard error) by age and renal function in the ITT population in: (A) patients aged less than the median, (B) patients aged older than or equal to the median, (C) patients with eGFR less than the median, (D) patients with eGFR greater than or equal to the median.

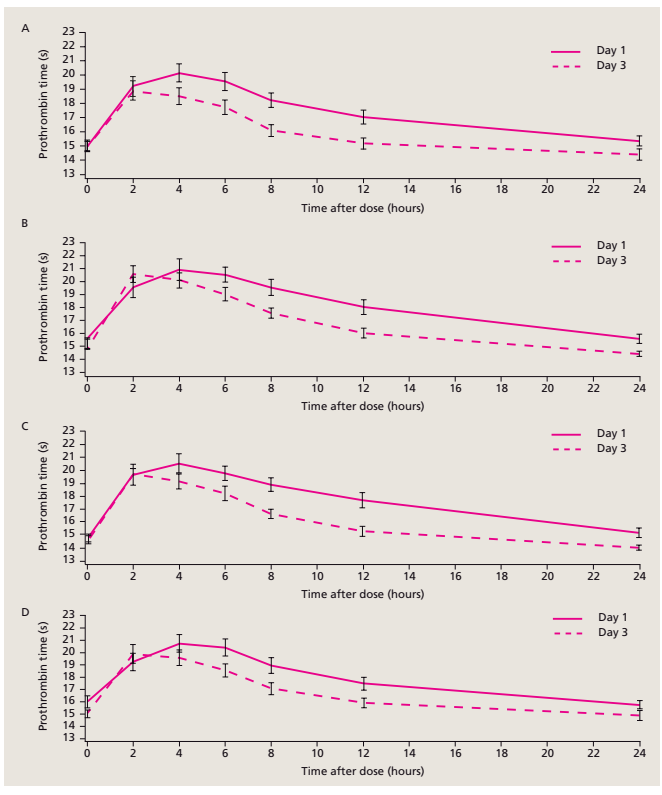

Figure 3. PT (± standard error) by age and renal function in the ITT population in: (A) patients aged less than the median, (B) patients aged older than or equal to the median, (C) patients with eGFR less than the median, (D) patients with eGFR greater than or equal to the median.

Safety and tolerability

- There were no deaths during the study and no patients developed deep vein thrombosis or pulmonary embolism, or experienced bleeding events
- A total of 44 (83%) patients experienced ≥1 AE up to 30 days post-surgery (Table 3); three serious AEs were reported (one wound infection, one lumbar vertebral fracture after a fall and one case of anxiety that required urgent medical attention), none of which were considered to be related to study medication

Table 3. Adverse events occurring up to 30 days postoperatively (safety population)

	n (%)
Patients with at least one adverse event	44 (83.0)
Gastrointestinal disorders	20 (37.7)
Constipation	12 (22.6)
Nausea	9 (17.0)
General disorders and administration-site conditions	20 (37.7)
Asthenia	7 (13.2)
Pyrexia	7 (13.2)
Oedema	4 (7.5)
Injury, poisoning and procedural complications	6 (11.3)
Fall	3 (5.7)
Investigations	7 (13.2)
Blood iron decreased	5 (9.4)
Metabolism and nutrition disorders	2 (3.8)
Diabetes mellitus	1 (1.9)
Hypokalaemia	1 (1.9)
Musculoskeletal and connective tissue disorders	8 (15.1)
Muscle spasms	5 (9.4)
Psychiatric disorders	7 (13.2)
Insomnia	5 (9.4)
Renal and urinary disorders	1 (1.9)
Pollakiuria	1 (1.9)
Surgical and medical devices	3 (5.7)
Transfusion	3 (5.7)

Conclusions

- **After initial LMWH prophylaxis, anti-Factor Xa activity was not increased after the first rivaroxaban dose compared with that seen on day 3 after serial rivaroxaban dosing in patients who underwent THR/TKR surgery**
- **Mean PT was slightly prolonged on day 1 compared with day 3**
- **Age and renal function had little influence on coagulation tests**
- **No clinically observed bleeding or venous thromboembolic events occurred, and there were no serious AEs related to treatment**
- **In patients for whom initial parenteral prophylaxis is clinically indicated after THR or TKR surgery, initiating oral rivaroxaban 10 mg od 12–18 hours or 24–28 hours after the last dose of LMWH (depending on LMWH regimen) provides a simple and well-tolerated strategy for thromboprophylaxis**

References

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Disclosure of conflict of interest
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