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The impact of elective knee/hip replacement surgery and thromboprophylaxis with Rivaroxaban or Dalteparin on Thrombin Generation

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Summary

Total hip/knee replacement surgeries are associated with an increased risk of venous thromboembolism and post-operative thromboprophylaxis has become standard treatment. The aims of this study were to: (1) assess the impact of hip/knee replacement surgery on *ex vivo* thrombin generation (TG), prothrombin fragments 1+2 (F1+2), thrombin-antithrombin complexes (TAT) and D-dimer; (2) compare the anticoagulant effects of dalteparin and rivaroxaban on TG 24 hours after surgery. Haemostatic variables were assessed in plasma samples of 51 patients taken: pre-operatively; peri-operatively; and 24 hours post-operatively. Prophylaxis, once a day, with dalteparin or rivaroxaban, starting 6-8 hours post-operatively, was administered in 25 (14 knee/11 hip) and 26 patients (13 knee/13 hip) respectively. TG, F1+2, TAT and D-dimer increased during surgery. Dalteparin patients showed a variable TG response 24 hours after surgery: conversely, the effect of rivaroxaban on TG was consistent across individuals. Good correlation was seen between rivaroxaban levels and TG-lag-time (rs=0.46, p=0.01); TG-time-to-Peak (rs=0.53, p=0.005); TG-peak-thrombin (rs=-0.59, p=0.001); and TG-velocity-index-rate (rs=-0.61, p=0.0009). Patients who received rivaroxaban showed a greater decrease of TG, F1+2 and TAT (but not D-dimer) than those on dalteparin. During hip/knee replacement surgery there is an increase in TG. Rivaroxaban inhibits TG more than dalteparin at 24 hours after surgery.

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Keywords: dalteparin, hip/knee replacement surgery, rivaroxaban, *in vivo/ex vivo* thrombin generation

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Introduction

Without thromboprophylaxis, the incidence of venous thromboembolism (VTE) developing after major orthopaedic surgery is estimated to be 40-60%. Factors such as reduced mobility, presence of proximal lower extremity injury, previous VTE, BMI of >30 kg/m^2, advanced age and active cancer, are all contributing factors for the high VTE risk (Geerts *et al*, 2008). In addition, haemostatic changes occurring during total hip and knee replacement (THR and TKR respectively) surgery further contribute to the patho-physiological mechanism of VTE development. There is evidence that elevation of the *in vivo* markers of thrombin generation (prothrombin fragments 1+2 [F1+2]), thrombin-antithrombin complex (TAT), and fibrinolysis (D-dimer) begin during surgery with the greatest risk of clotting activation occurring at the time of joint insertion (Sharrock *et al*, 1995a;Sharrock *et al*, 1995b).

Although activation of coagulation is known to occur during orthopaedic surgery, there generally remains a discrepancy in the timing of thromboprophylaxis initiation between Europe and the USA due to different approaches to: minimising peri-/post- operative bleeding; avoiding pre-surgical hospital admissions; and simplifying conventions adopted for the administering of anaesthesia. In Europe, thromboprophylaxis is generally started 12 hours before major orthopaedic surgery whereas in North America it is initiated 12-24 hours after surgery. It is hoped that the availability of more sensitive clotting tests and more predictable oral anticoagulant agents would reduce some of the above discrepancies and bring about a greater consensus in the timing of thromboprophylaxis therapy.

Low molecular weight heparins (LMWH), unfractionated heparin (UFH) or the synthetic pentasaccharide fondaparinux are the recommended pharmacological prophylaxis for VTE prevention after major orthopaedic surgery (Geerts *et al*, 2008;NICE 2010). More recently in 2008 two new oral anticoagulant agents, namely dabigatran etexilate (Pradaxa® Boehringer-Ingelheim), a direct thrombin inhibitor, and rivaroxaban (Xarelto® Bayer Schering Pharma), a direct Xa inhibitor, were licensed in the European Union by the European Medicines Agency for use after THR and TKR and are currently under review by the Food and Drug Administration in the USA. In the UK they have been recommended by the National Institute for Clinical Excellence for similar indications (NICE 2010).

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Rivaroxaban is an oral, highly selective and potent direct inhibitor of factor Xa (FXa). It inhibits not only free FXa but also the prothrombinase and clot bound FXa (Perzborn *et al*, 2005;Gulseth *et al*, 2008). Its terminal half-life is approximately 5-9 hours in healthy young subjects (Kubitza *et al*, 2005) and approximately 13 hours in healthy elderly subjects (Laux *et al*, 2009). Around 60% of the drug is excreted via the renal route (~ 1/3 unchanged) with the rest being eliminated via the fecal-biliary tract (Weinz *et al*, 2009). Rivaroxaban inhibits thrombin generation (TG) (Graff *et al*, 2007) and prolongs prothrombin time (PT) and activated partial thromboplastin time (APTT) in a dose-dependent manner. Due to the predictable dose-response relationship, it is suggested that laboratory monitoring is not required (Kubitza *et al*, 2005).

LMWH exhibit their overall anticoagulant activity via the antithrombin-mediated anti Xa and anti IIa effects and through the release of tissue factor pathway inhibitor (TFPI) from the endothelium (Hoppensteadt *et al*, 1995). Although the relative anti Xa:IIa ratio varies between different LMWH preparations, depending on their molecular size distribution (Baglin *et al*, 2006), their clinical efficacies in the prevention of VTE after surgery are similar (White & Ginsberg, 2003). Being composed of smaller molecules than UFH, LMWH have better bioavailability, longer plasma half life (approximately 4 hours) and better anticoagulant response predictability; thus rendering laboratory monitoring unnecessary in most instances (Hirsh *et al*, 2008). However in selected groups, e.g. obese or underweight patients, during pregnancy, children, those at increased risk of bleeding, and patients with severe renal impairment, measurement of LMWH antithrombotic activity is of utmost importance. The currently available assays of anti-Xa activity are limited in their ability to predict bleeding and/or thrombotic risks (Greaves, 2002;Leizorovicz *et al*, 1993), thus highlighting the need for more physiologically relevant tests.

All anticoagulant agents directly or indirectly inhibit TG. Recent studies have shown that *ex vivo* measurement of an individual's potential to generate thrombin over time (via the TG test), may be more sensitive than the current tests at measuring the effect of anticoagulation (al Dieri *et al*, 2004;2006). Furthermore, to our knowledge no studies investigating *ex vivo* TG during orthopaedic surgery have yet been published.

The objectives of this study were to: (a) prospectively assess the peri-operative effects of elective total knee/hip replacement surgery on TG, F1+2, TAT and D-dimer; (b) compare the impact of

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prophylactic doses of dalteparin and rivoraxaban on TG 24 hours after surgery. PT, APTT, antithrombin and anti-Xa levels were also measured.

Methods and Materials

Patients

The study was approved by the local ethics and Research and Development Office at University College London Hospitals (UCLH) NHS Trust. After informed consent, a total of 51 patients, age ≥ 50 years with no upper limit, were recruited **from July to September 2009 for the dalteparin group, and from October 2009 to January 2010 for the rivaroxaban group**. Inclusion criteria were eligibility to receive thromboprophylaxis therapy after elective THR or TKR surgery. Exclusion criteria were: acquired/inherited bleeding disorders, history of VTE recurrence, platelets of < 100 x 10^9/L and active malignancies. Aspirin and/or warfarin were stopped 7 and 5 days respectively prior to surgery. Mechanical VTE prophylaxis with thigh length graduated compression stocking was given to all patients from the time of admission. **In UCLH chemical prophylaxis is administered post-operatively in order to avoid: peri-/post-operative bleeding; pre-surgical hospital admissions; and the risk of spinal haematoma.** Therefore thromboprophylaxis with dalteparin (subcutaneously) or rivaroxaban (orally), once a day, was administered 6-8 hours after surgery, in 25 and 26 patients respectively. A description of patient demographics and their renal function prior to surgery is presented in Table 1. In 3/25 patients weighing <50kg, the dose of dalteparin given was 2500 units and 21/25 received 5000 units**.** The remaining patient, who received dalteparin 5000 units post-operatively, declined to provide a blood sample 24 hours after the surgery; however the pre- and the peri- operative samples have been included in this analysis. All patients in the rivaroxaban group received the dose of 10 mg. Surgeries were performed at UCLH by a team of 3 senior surgeons using similar surgical techniques.

Blood sample collection

Venous blood samples for measurement of haemostatic markers were obtained: (1) immediately pre-operatively, in the anaesthetic room; (2) peri-operatively at the time when the joint was inserted; and (3) **a mean of 16.4 hours (range 15 – 18) after thromboprophylaxis had been administered (i.e. approximately 24 hours after surgery).** Blood was taken using a 21 gauge

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butterfly needle with minimal stasis, and drawn into 5ml citrate Vacutainers™ (BD Diagnostics, Oxford, UK) containing 0.5 ml of 0.109 M buffered tri-sodium citrate.

It is well recognised that contact activation can interfere with TG assay and therefore immediately after the venepuncture corn trypsin inhibitor (a factor XIIa inhibitor [Cambridge Bioscience, Cambridge, UK]) was added to the whole blood for TG measurement, at a final concentration of 18.3 µg/mL (Luddington & Baglin, 2004). Within 1 hour of collection platelet poor plasma (PPP) was prepared by double centrifugation at ambient temperature (2000g for 12 minutes) and aliquots of PPP were frozen to -80ºC. On the day of assay samples were thawed to 37ºC.

Laboratory analysis

Full blood counts (FBC) were performed using a KX-21 analyser (Sysmex UK Ltd, Milton Keynes, UK). Unless otherwise stated coagulation assays were performed on a CS-2000i automated coagulation analyser (Sysmex UK Ltd), and all reagents were from Siemens Healthcare Diagnostics (Marburg, Germany). Innovin and Actin FS were used in PT and APTT tests respectively. D-Dimer (Innovance D-Dimer) was measured by an immunoturbidometric technique. F1+2 and TAT complexes were measured by ELISA (Enzygnost F1+2 and Enzygnost TAT respectively). Antithrombin assay and dalteparin/rivaroxaban-anti-Xa activities were performed by chromogenic assay using Berichrom® Antithrombin kit and Berichrom® Heparin kit respectively. Standard curves for anti-Xa activities were constructed by adding known concentration of dalteparin (Pfizer Pharmaceutical) or rivaroxaban (Bayer Schering Pharma) to the standard human plasma (Siemens Healthcare Diagnostics) obtaining a final concentration of 1.0 IU/ml anti-Xa activity for dalteparin and 0.6 µg/ml anti Xa activity for rivaroxaban (the limit of detection for LMWH was 0.05 IU/mL and for rivaroxaban 0.01 µg/ml). The relative potencies of the anticoagulants in patient's plasma were derived from the appropriate calibration curve.

Thrombin generation

The TG was performed using the Calibrated Automated Thrombogram (CAT) system (Thrombinoscope BV, Maastricht, The Netherlands) as described by Hemker et al (2003) in conjunction with the manufacturer's PPP-Low reagents, which gave reaction concentrations of 1 pmol/L tissue factor (TF) and 4 µmol/L Phospholipid (Thrombinoscope BV). We decided to use

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a low level of TF, as this concentration had been shown to increase the sensitivity of TG assays; in order to reduce TG intra-assay variations, contact pathway activation was inhibited with CTI (Chantarangkul *et al*, 2003;van Veen *et al*, 2008) and the pre-, peri- and post-operative samples from each patient were tested at the same time. All sample TG reactions and sample specific calibrators were tested in triplicate. The following parameters of the TG curve were measured: lag time; time to the peak (ttP); peak thrombin; area under the curve, known also as the endogenous thrombin potential (ETP); and the velocity-index-rate of TG calculated by the formula Peak/(ttP – lag-time) and expressed as nM/minutes. **The mean intra-assay coefficient of variation (CV) for TG lag time, ETP, peak thrombin and ttP were: 4.9%, 6.8%, 6.5%, and 3.1%; whereas mean inter-assay CV were: 8.8%, 10.7%, 11.6% and 5.5% respectively.**

Statistical analysis

Data analysis was performed using Analyse-It® software version 2.03 (Analyse-It Software Ltd, Leeds, UK). The results are presented as a median with the 25th and 75th percentiles in parenthesis. Differences in haemostatic markers between the pre-, peri- and post-operative periods were analysed using the non parametric 'Wilcoxon signed rank' test. Comparisons between dalteparin and rivaroxaban groups were made using the un-paired 'Mann-Whitney' test whereas association between different variables were performed using the 'Spearman rank correlation coefficient'. A 2-tailed p value of < 0.05 was considered significant.

Results

Thrombin Generation test and anti Xa levels

The median TG lag time and ttP decreased from the pre-operative to the peri-operative period while ETP, peak thrombin and velocity-index-rate increased, indicating enhanced coagulability during the peri-operative period (Figure 1). The increase in TG was similar between THR and TKR surgery and did not correlate with the body mass index (BMI) (data not shown).

Although there was no statistical difference between the TG pattern seen in 3 patients who received 2500 units of dalteparin and those who received 5000 units, we have excluded the former from the peri- vs. post-operative analysis. Post-operatively not all patients on dalteparin exhibited the same pattern of TG. Allowing for the TG intra-assay CV of 10%, we define a "favourable" TG response as exhibiting both: (a) reduction of the ETP and peak

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thrombin and (b) increase of lag time and ttP (measured against peri-operative values); similarly the "adverse" TG response is defined as both: (c) increase of ETP and Peak thrombin and (d) shortening of lag time and ttP. **Seven of 21 of dalteparin patients had a favourable TG response and only 1/21 had an adverse response. The remainder lack a clear TG pattern and were difficult to group.**

Analysis of the TG parameters for all dalteparin patients (n=21), from the peri- to post-operative period, showed a significant increase in the lag time and decrease in ETP (Figure 1); from the pre- to post-operative period, no significant changes were seen in TG parameters. No correlation was seen between the TG changes and: (a) the BMI or (b) renal function tests (data not shown). The pre-operative antithrombin levels of the dalteparin patients were within the normal reference range (80-130 iu/dL) and at 24 hours post-operatively the median dalteparin anti Xa activity was undetectable in all patients.

In contrast 23/26 of rivaroxaban patients showed a favourable TG response from the peri- to the post-operative period with no adverse instances. The effect of rivaroxaban on TG was noted to be greatest on the lag time, ttP, the peak thrombin and velocity-index-rate for both pre- to post- and peri- to post-operative periods (Table 2). The median rivaroxaban level was 0.03µg/ml (inter quartile range: 0.01-0.06). There was a good correlation between rivaroxaban levels and: (a) lag time (rs= 0.46, p= 0.01); (b) ttP (rs= 0.53, p= 0.005); (c) peak thrombin (rs = -0.59, p= 0.001) and velocity-index-rate (rs = -0.61, p=0.0009) at 24 hours after surgery. Comparison of the TG parameter changes between dalteparin and rivaroxaban groups show that the latter significantly reduced TG more than the former at 24 hours after surgery (Table 2).

Other haemostatic markers

FBC, PT and APTT were normal in all patients prior to surgery. PT and APTT in both groups were within the normal reference range (10.0 – 12.0 seconds and 21.0 – 31.5 seconds respectively) during the peri- and post-operative periods. D-dimer increased during and after surgery in all patients with no significant difference between dalteparin and rivaroxaban groups (Figure 2). F1+2 and TAT increased during surgery (n= 51); from the peri-to post-operative period these markers decreased significantly in the rivaroxaban group, but not in the dalteparin (Figure 2).

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Clinical outcome

There was no peri-operative blood loss necessitating transfusion of red blood cells or platelets during this period. Two patients in each group required > 2 units of red blood cells from the time of administering thromboprophylaxis to the time when the final blood sample was taken.

Discussion

During THR surgery, a combination of venous stasis/hypoxia and local trauma to the vessels and bone causes the release of tissue factor leading to activation of the coagulation system (Sharrock *et al*, 1995a) which, in turn, generates large amounts of thrombin. In the case of TKR surgery, although there is evidence that activation of the clotting system begins during surgery (Sharrock *et al*, 1995b), the mechanism of its initiation is less clear. The amount of thrombin that is produced cannot be quantified directly and therefore *in vivo* surrogate markers, namely F1+2, and TAT complexes, are used in measuring TG. F1+2 is released during the activation of thrombin from its precursor prothrombin; TAT complexes are produced in proportion to the amount of thrombin generated (resulting in regulation of the latter). However these markers have a very short half-life (in minutes) and provide only a partial picture of the entire TG process. The TG test, on the other hand, measures the *ex vivo* potential of plasma to generate thrombin over time and provides more information on the initiation, propagation and decay phases of TG, leading to a more complete view of the coagulation process (Hemker *et al*, 2006).

The current study measured TG of 51 patients who underwent elective hip/knee replacement surgery. The peri-operative sample was taken at the time when the new hip/knee joint had just been inserted - believed to coincide with the moment of maximum surgical trauma. We, like others (Sharrock *et al*, 1995a;Sharrock *et al*, 1995b;Dahl *et al*, 1993), found that F1+2, TAT, and D-dimer increased during surgery. Moreover, for the first time, we demonstrated that *ex vivo* TG also increases during major orthopaedic surgery to a similar extent for THR and TKR. These results support the view that thrombogenecity in these orthopaedic patients begins during the surgery. Therefore it follows that initiation of thromboprophylaxis prior to orthopaedic surgery could be more effective at preventing or reducing these peri-operative changes.

Additionally, in the pre-operative period, 50%, 27% and 60% of all patients (n=51) had D-dimer, TAT and F1+2 levels above the normal range respectively. Advanced age and chronic

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inflammatory conditions like osteoarthritis are factors known to account for the hypercoagulability in these patients (Mari *et al*, 2008).

As the risk of VTE is triggered during surgery and peaks about 3-7 days after, when clinical VTE first develops (Planes *et al*, 1996;Scurr *et al*, 1988), it is critical to deliver effective thromboprophylaxis in the immediate post-operative period. We compared the effect of prophylactic doses of dalteparin (n= 21) and rivaroxaban (n= 26) on TG approximately 24 hours after surgery. This timing corresponded to a mean of 16.4 hours after thromboprophylaxis had been administered. In the dalteparin group, from peri- to post-operative period, there was a large variation in individuals' responses in TG with ~ 30% of patients showing TG reduction (i.e. 'favourable' response as defined previously). The remaining patients, despite dalteparin, had no detectable anticoagulant effect in TG 24 hours after surgery. The effect of LMWH on TG has been investigated by several groups (Petros *et al*, 2006;al Dieri *et al*, 2004;Gerotziafas *et al*, 2007b). One *in vitro* study (Gerotziafas *et al*, 2007b), using healthy individuals' platelet rich plasma (PRP) and the CAT system, showed that at equivalent anti-FXa activity concentrations, the inhibitory effect of LMWH (enoxaparin, nadroparin and dalteparin) upon TG was different. In the case of dalteparin a concentration of ≥0.4 anti-FXa IU/mL significantly reduced TG; however no significant changes were seen at lower concentrations (Gerotziafas *et al*, 2007b). In the dalteparin group the anti-FXa levels were undetectable: yet in ~30% of patients (through a mechanism unknown to us), a suppression of TG was seen. However, even though the anticoagulant mechanism of LMWH is not fully understood, its efficacy for VTE prophylaxis after orthopaedic surgery, being given as a once-daily dose, has been conclusively demonstrated in large clinical trials (Geerts *et al*, 2008). This is largely due to its inhibitory effects at different stages of the coagulation pathway, making its resultant anticoagulant action quite complex and variable amongst different individuals, as reflected in our TG results.

In contrast, rivaroxaban reduced TAT, F1+2 and *ex vivo* TG more than dalteparin at ~24 hours after surgery. The higher inhibitory effect of rivaroxaban on TG could be explained by the highly specific and direct inhibition of FXa and its longer plasma half-life. Rivaroxaban inhibits not only free FXa but also the prothrombinase and clot bound FXa (Perzborn *et al*, 2005;Gulseth *et al*, 2008). Therefore, as one should expect, it is highly effective in retarding the initiation and propagation phases of TG (*in vivo* and *ex vivo*) but has less effect on the ETP. This is confirmed

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by our *in vivo* findings, as well as those of Gerotziafas *et al*, who studied the *in vitro* TG effect (CAT system) of rivaroxaban on PRP (2007a); admittedly, in this study, the use of platelet poor plasma to perform TG is an unavoidable limitation. There was a good correlation between the rivaroxaban levels and the lag time, ttP, peak thrombin and velocity-index-rate. More interesting was the fact that small amounts of rivaroxaban which could not be detected by the traditional tests (PT) were manifested in TG. One *in vivo* study has even demonstrated that the TG test is more sensitive than FXa activity in detecting small amounts of rivaroxaban (Graff *et al*, 2007).

This study and others (Bendetowicz *et al*, 1994;Petros *et al*, 2006;Gerotziafas *et al*, 2007a;Gerotziafas *et al*, 2007b;Samama *et al*, 2010) have highlighted a few important findings: (1) the different TG parameters are important for understanding the mechanism of action of different anticoagulants, (2) ETP alone should not be used to compare the efficacy of different anticoagulants, and (3) the TG test can be used as a tool to describe the pharmacodynamics of various anticoagulants. However further standardisation of the test and reagents are required before its use in clinical practice.

The greater TG reduction of rivaroxaban would also support the results of the 4 phase III clinical trials (RECORD 1-4) which involved >12,500 patients (Eriksson *et al*, 2008;Kakkar *et al*, 2008;Lassen *et al*, 2008;Turpie *et al*, 2009). These studies demonstrated that rivaroxaban at 10 mg od was significantly more effective for the prevention of VTE than enoxaparin 40 mg od (RECORD 1-3) (Eriksson *et al*, 2008;Kakkar *et al*, 2008;Lassen *et al*, 2008) and enoxaparin 30 mg twice daily dose (RECORD 4) (Turpie *et al*, 2009). Clearly, one of the main concerns when prescribing chemical thromboprophylaxis in the first 24 hours post-operatively, and thereby reducing TG, is the bleeding risk. In the current study there were no clinical bleeding episodes but the size of the study is too small for us to draw any conclusions regarding its risk in general. It is worth mentioning, nonetheless, that according to the four RECORD studies the major bleeding risks between rivaroxaban (starting 6-8 hours post-operatively) and LMWH were similar. Furthermore, in the RECORD 2 study, despite rivaroxaban being given for 3 weeks longer than enoxaparin, the incidence of major bleeding at 5 weeks was similar in both groups (0.1%) (Kakkar *et al*, 2008).

Rivaroxaban prolongs PT in a dose dependent manner (Kubitza *et al*, 2005). In our study the PT values, between 15-18 hours after rivaroxaban administration, were within the normal ranges.

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This is explained by the low plasma rivaroxaban levels (median 0.03µg/ml) and the thromboplastin reagent (Innovin) used. In the *in vitro* study performed by Samama and colleagues (2010) the concentration of rivaroxaban required to double the PT, when Innovin is used, was 0.7µg/ml; compared with other thromboplastin reagents (Neoplastin, Neoplastin plus, Recombiplastin, Thromborel S and TriniClot) this concentration was the highest, indicating that Innovin is the least sensitive PT-reagent.

In conclusion, TG (**performed on platelet poor plasma using calibrated automated thrombogram and 1pM tissue factor),** increases during orthopaedic surgery to a similar extent between total hip and knee replacement surgery. The effect of dalteparin on TG can be highly variable between different individuals at ~24 hours after major orthopaedic surgery. Rivaroxaban showed more TG consistency in its effect across individuals, and also inhibited *in vivo* (F1+2 and TAT) and *ex vivo* TG more than dalteparin post-operatively.

Disclosures

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Table 1. Patient demographic

	Dalteparin (n = 25)	**Rivaroxaban** (n = 26)
Age	72 (60-88)	68 (51-86)
Female/Male	17/8	19/7
Body Mass Index (BMI) *Normal/Overweight/Obese	6/9/9	6/7/13
Previous medical history		
Osteoarthritis	23	24
Rheumatoid arthritis	1	2
****THR/TKR**	11/14	13/13
¶Previous THR or TKR	4	1
Smokers	4	5
Creatinine (μmol/L)	70 (56 – 88)	64 (50 – 78)
GFR (mL/min)	87 (69 – 90)	90 (71 – 90)

Data is presented as a median with the 25th and 75th percentiles in parenthesis
THR, total hip replacement; TKR, total knee replacement; GFR, glomerular filtration rate
*Normal BMI = 18.5- 24.9; Overweight = 25-29.9; Obese ≥ 30; **All hip and knee replacement surgeries were unilateral; ¶ **All previous THR or TKR surgeries were performed > 6 months ago and were not on the same joint.**

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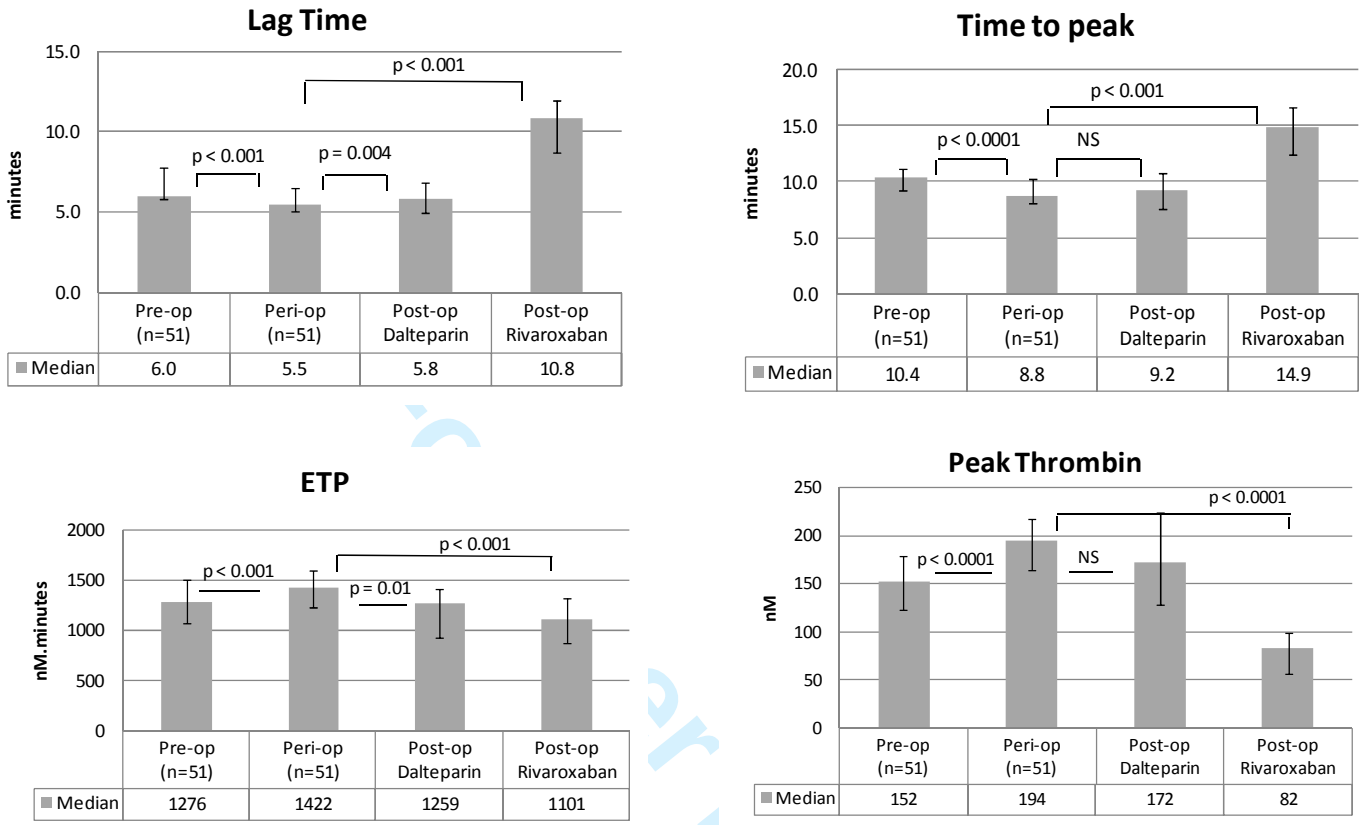
Figure 1. Thrombin generation during the pre-, peri- and post-operative period using 1pM Tissue Factor



ETP, endogenous thrombin potential; NS, not significant; **I** = interquartile range.

Table 2. Comparison of thrombin generation parameters between dalteparin and rivaroxaban patients

	Pre- to Post-operative Median % change					**Peri- to Post-operative** Median % change				
	Lag time	**ttP**	**Peak thrombin**	**ETP**	**Velocity-index-rate**	**Lag time**	**ttP**	**Peak thrombin**	**ETP**	**Velocity-index-rate**
Dalteparin (n = 21)	**0.0**	**-2.0**	**+13.0**	**- 4.1**	**+ 41**	**+12.7**	**+6.5**	**-3.7**	**-10.1**	**- 17**
Rivaroxaban (n = 26)	**+55.6**	**+38.5**	**-38.6**	**-14.9**	**- 46**	**+80.8**	**+71.0**	**-58.2**	**-23.5**	**- 64**
Dalteparin vs. Rivaroxaban	p <0.0001	p = 0.002	p =0.0001	NS	p = 0.001	p < 0.0001	p <0.001	p <0.0001	- p = 0.04	p = 0.0003

ttP, time to peak; ETP, endogenous thrombin potential; NS, not significant

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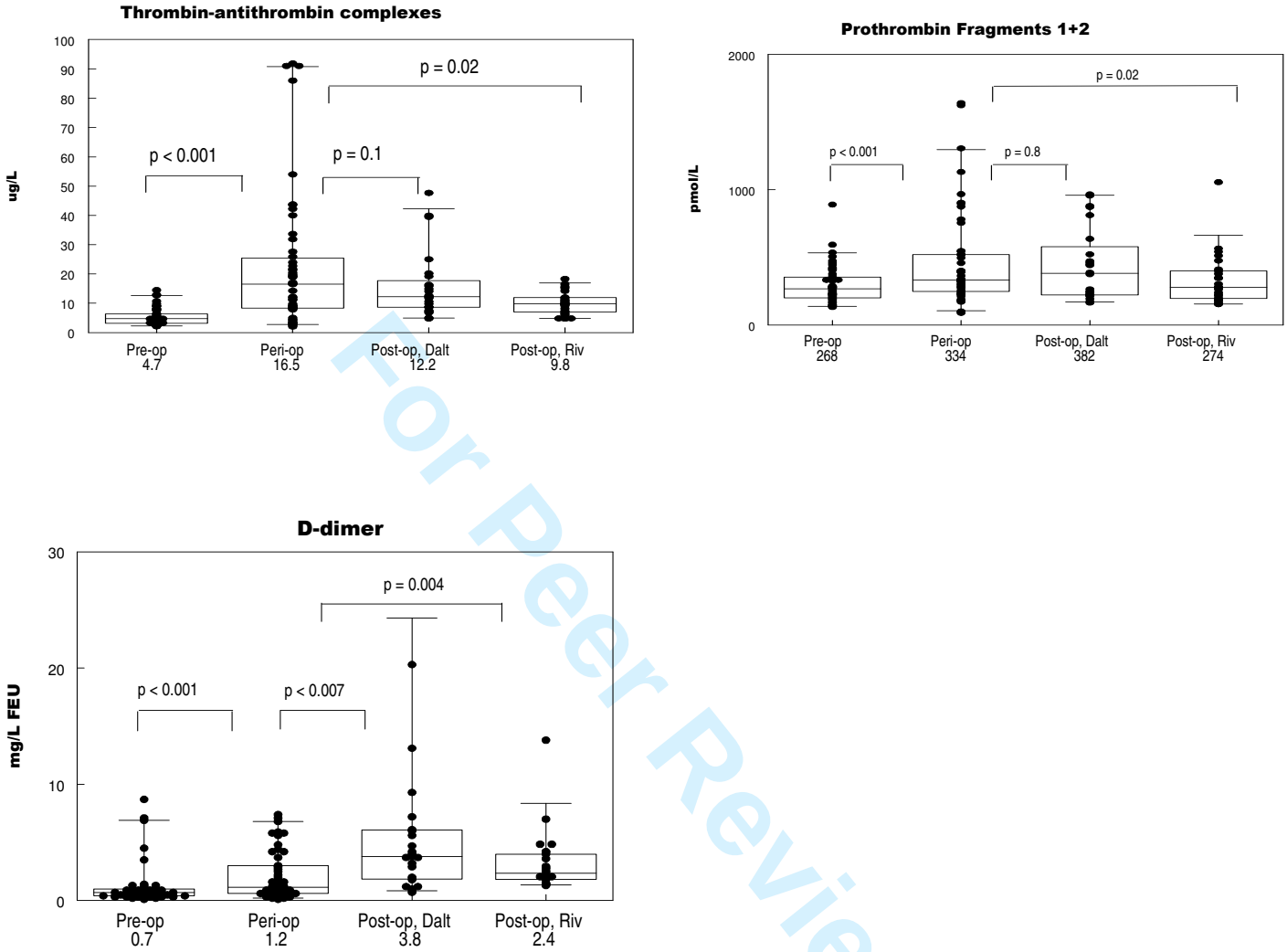
Figure 2. Haemostatic markers during the pre-, peri- and post- operative periods for dalteparin and rivaroxaban



Box-Whisker plots with median values beneath their respective time periods.

There were no significant differences between the data obtained from the pre-operative and peri-operative samples for the dalteparin and rivaroxaban groups, therefore these were pooled (n= 51).

Dalt, dalteparin; Riv, rivaroxaban

Normal reference ranges: Thrombin-antithrombin complexes: 1.0 – 4.1 µg/L; Prothrombin fragments 1+2: 69 – 229 pmol/L; D-dimer: < 0.5 mg/L FEU

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