**Apixaban vs. LMWH or aspirin as Thromboprophylaxis in Newly diagnosed Multiple Myeloma (TiMM) – an open label, randomised control feasibility clinical trial**

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**Abstract (200 words)**

*Background*

Routine thromboprophylaxis (TP) in newly-diagnosed multiple myeloma (NDMM) patients currently comprises either aspirin for standard risk patients or low molecular weight heparin (LMWH) for high risk patients. To date, no work has been published exploring the use of direct oral anticoagulants (DOACS) in this setting. The aim of this feasibility clinical trial was to establish the foundations for creating a multicentre trial and identify any safety concerns with apixaban in this setting.

*Methods*

NDMM patients were stratified according to VTE risk and randomised to either standard TP or apixaban 2.5mg BD and followed every 3-4 weeks throughout their chemotherapy.

*Results*

Ten patients were recruited, 2 were classed as high risk and received apixaban and 8 standard risk; 4 of which were randomised to aspirin and 4 to apixaban. Patients were well motivated to participate in this study and there were no major bleeding or VTE events.

*Conclusion*

Our study did not observe any serious bleeding events or adverse drug reactions. This provides preliminary evidence for the safety of apixaban to support further evaluation as an alternative to aspirin and LMWH in the myeloma cohort in a multicentre trial. A trial of thromboprophylaxis is acceptable to patients.

***Keywords:*** *multiple myeloma, DOACs, apixaban, venous thromboembolism, thromboprophylaxis, aspirin, enoxaparin, clinical trial*

**Introduction**

It is well recognised that myeloma patients have an increased risk of venous thromboembolism (VTE) (1). The reasons for this are often described as being patient-, disease- and treatment-related (2). The British Society of Haematology (BSH) guidelines suggest a risk assessment model for the prevention of VTE in myeloma patients treated with thalidomide or lenalidomide (3). The BSH guidance also stipulate that myeloma patients not receiving thalidomide or lenalidomide may be considered at risk and thromboprophylaxis should be considered on a case-by-case basis. The exact duration of thromboprophylaxis remains unclear but should be guided by bleeding and VTE risk factors such as active disease(4). Thromboprophylaxis is often prescribed for the first 4-6 months or until disease control is achieved and de-escalated or discontinued unless there are ongoing significant risk factors (5).

There is wide variation in thromboprophylaxis practice across hospitals but also within the same departments (6), demonstrating the lack of evidence base underpinning the VTE prevention process in this population. Patient-related factors that increase the risk of VTE are heterogeneous. For example, if a patient has had a previous VTE event or a thrombophilia, the risk stratification is straightforward. However, if a patient has a raised BMI, this is considered a weak risk factor. Disease- and treatment-related factors are also treated very differently. With the advent of newer agents to treat myeloma there have not been robust studies to assess their thrombotic risk. The proteasome inhibitor carfilzomib, for example, has a questionable thrombotic risk (7), which has led to variation in thromboprophylaxis. ASPIRE was a multicentre, open label trial that randomised patients to either receive lenalidomide with dexamethasone or lenalidomide, dexamethasone and carfilzomib. There was mandatory use of thromboprophylaxis in this trial as it contained an immunomodulator drug (IMiD) (8), but if an IMiD is not used in combination with carfilzomib, for example, in the CARDAMON study (NCT02315716), thromboprophylaxis guidelines were not clear.

The evidence for the use of DOACs in the cancer cohort is gradually expanding. Recent evidence has demonstrated that edoxaban is non-inferior to subcutaneous dalteparin (9) for the treatment of VTE. Select-D, which compares DOACS and LMWH for the treatment of VTE in patients with cancer, has recently reported that rivaroxaban has a very low VTE recurrence rate at 6 months (10). There are a number of other studies that are soon to report on this including the CANVAS study (NCT02744092) which is comparing DOACs and LMWH or warfarin. DOACs are also routinely used as thromboprophylaxis after hip and knee surgery and in stroke prevention (11) but currently there are no published studies on DOACs as thromboprophylaxis in the myeloma population.

The aims of this study were to assess the safety of apixaban as thromboprophylaxis in patients who are newly diagnosed with multiple myeloma and to establish the feasibility of a multicentre trial assessing the use of apixaban as thromboprophylaxis in multiple myeloma.

**Patients and Methods**

***Study design and oversight***

King’s College Hospital NHS Foundation Trust is one of the largest teaching hospitals in London and includes 2 main sites; King’s College Hospital, London and Princess Royal University Hospital (PRUH). There are over 1000 beds with tertiary services in cardiology, neurology, haematology and liver (12). Every year, at King’s it was estimated that 75 patients are newly diagnosed with myeloma, with the majority classed as high risk of VTE.

We conducted a randomised, open label phase IV feasibility clinical trial comparing the safety and efficacy of apixaban 2.5mg twice a day with the standard thromboprophylactic agents (figure 1); enoxaparin 40mg administered as a subcutaneous (SC) injection daily if a patient was classified as high risk of VTE, and aspirin 75mg orally (PO) daily if considered standard risk of VTE according to the Palumbo risk assessment model (3). NDMM patients were identified and referred by the myeloma team who also performed the VTE risk stratification. Eligible patients were given a patient information sheet (PIS) and written, informed consent was obtained from all recruited patients. Block randomisation was conducted following risk stratification. Patients were followed up for 6-months or until their disease was in remission (whichever occurred first).

The primary end points were bleeding which required cessation of prophylactic therapy or an objectively diagnosed VTE event such as a pulmonary embolism (PE) or a deep vein thrombosis (DVT). Data was also collected on the number of doses missed due to either medical advice or being forgotten by the patient.

Patients could withdraw from the study at any time for any reason. The investigator also had the right to withdraw patients from the study in the event of intercurrent illness, adverse events (AE), serious adverse events (SAE), suspected unexpected serious adverse reaction (SUSAR), protocol violations, administrative reasons or other reasons. The specific reasons for withdrawal were formally recorded.

An independent data monitoring and ethics committee (DMEC) was held to ensure the safety of the patients.

***Patients***

Inclusion criteria were patients with newly diagnosed with multiple myeloma requiring chemotherapy, age >18 years and able to give informed consent. Exclusion criteria included pregnancy or breastfeeding, established use of an anticoagulant or antiplatelet, and contraindications to the active substances or excipients being used, or any concomitant systemic treatment with strong inhibitors of both CYP3A4 and P-gp, and HIV protease inhibitors.

***Outcome Measures***

The trial specifically assessed the safety of apixaban as a thromboprophylaxis modality in the newly diagnosed myeloma population, whether patients would consent to a randomised controlled study following a recent diagnosis of myeloma where one of the comparator arms is an injectable agent and estimate the event rate for the different thromboprophylaxis modalities. A further aspect of the trial was to evaluate whether there should be any refinements to how patients are stratified as standard or high risk of VTE for a potential further multi-centre clinical trial.

***Surveillance and Follow-Up***

Thromboprophylaxis was started on the same day as chemotherapy. Before initiation, patients were asked about any current symptoms of VTE or bleeding. Bleeding symptoms were recorded according to the ISTH Bleeding Assessment Tool (BAT) (13). Patients were educated on the importance of monitoring for these through their chemotherapy.

After starting chemotherapy, patients were reviewed at 1 week to check adherence to thromboprophylactic medication and reassessed for bleeding and VTE symptoms. The next visit was at 3 weeks into their treatment, with ongoing 3 weekly reviews coinciding with chemotherapy visits, until 6 months (or remission obtained) (see table 1).

VTE required objective diagnosis using either duplex ultrasonography for suspected DVT or a ventilation/perfusion (V/Q) scan or computerised tomography of pulmonary arteries (CTPA) if suspected pulmonary embolus. Any bleeding events were classified according to the ISTH definitions of major bleeding, clinically relevant non-major bleeding (CRNMB) or minor bleeding (14).

***Data Management***

An electronic case report form (eCRF) was created and validated by the database provider (KCL CTU). This system was regulatory compliant (GCP, 21CRF11, EC Clinical Trial Directive). Source data was entered by the lead researcher (ZS). Participants were identified on the study database using a unique code and initials.

***Statistical Analysis***

The sample size for this study was considered with reference to estimating the recruitment rate standard deviation (SD) of continuous outcomes and event rate. The aim was to recruit for 1 year. Assuming the true recruitment rate was 60%, we estimated the recruitment percentage with a 95% confidence interval width of +/- 11 percentage points. Thus it was anticipated 40 patients would be recruited to the trial. Having 20 patients per arm would be sufficient for us to estimate the standard deviation for a larger multi-centre clinical trial. This study was designed as a feasibility study and not powered for statistical significance. The results are descriptive and displayed as means (or median where appropriate) with standard deviations.

**Regulatory approvals**

This protocol and related documents were submitted for review to London Central Research Ethics Committee (REC) (15/LO/131), and to the Medicines and Healthcare Products Regulatory Agency (MHRA) (40945/0003/001-0001) for Clinical Trial Authorisation.

**Results**

***Study Patients***

The TiMM trial was open for recruitment from 12th April 2016 until 21st April 2017. During this time, 29 patients with newly diagnosed multiple myeloma at KCH were assessed for eligibility to the trial. Eighteen patients did not meet the eligibility criteria as outlined in table 2. The predominant reason for exclusion was the concomitant use of antiplatelets or anticoagulants (n=11). The other main reason included the concurrent myeloma clinical trial in place - the CARDAMON trial, withdrawing authorisation of concurrent supportive trial participation if patients were enrolled in CARDAMON (n=4). Ten of a possible 11 patients consented to the TiMM trial with one patient declining to take part (who also refused taking part in a myeloma chemotherapy trial). The characteristics of the 10 patients who consented are outlined in table 3. Figure 2 shows the assignment and follow up and outcomes of these patients. Three were withdrawn from the aspirin arm, compared with only 1 from the apixaban arm.

***Efficacy***

No VTE events occurred. There were 2 superficial venous thrombotic events during the course of the trial. Both events were associated with the use of a peripheral cannula which was required for chemotherapy administration on the day as part of the CARDAMON trial. One occurred on apixaban and one on aspirin. Both patients had been risk assessed to the standard risk arm of the trial.

***Safety and omitted doses***

Table 3 outlines the adverse events that occurred on the trial. There were 3 bleeding events in the TiMM trial, 2 in the aspirin arm (both classified as standard risk of VTE), 1 in the apixaban arm (classified as high VTE risk). All reported bleeding was CNRMB. Any adverse events experienced by patients were considered minor and unrelated to the agents under investigation (see table 4).

Table 5 outlines the number of doses omitted on medical advice and those that were forgotten by the patient. More doses were omitted due to medical advice than were forgotten by the patient themselves.

**Discussion**

The findings from our feasibility trial suggest that patients will consent to a supportive clinical trial evaluating thromboprophylaxis whilst being treated for myeloma. From the small sample we have reported, that there are no safety or efficacy issues related to the use of apixaban as evidenced by no increase in VTE events or bleeding associated with apixaban use.

As newly diagnosed myeloma patients are treated, their clinical course is varied (due to comorbidities) and can become complicated, for example with the development of sepsis, renal failure or bleeding, all which becomes barriers to continuing prophylaxis therapy so presenting a unique challenge to clinicians managing these patients, who continually need to bear these factors in mind.

***Recruitment***

Although we did not reach our recruitment target, recruitment to the TiMM trial was good. Patients appeared to be interested and motivated to take part, as evidenced by 10 of a possible 11 consenting to the trial. However, the main issues that led to not reaching the recruitment target appeared to stem from the eligibility criteria. Eleven patients who were referred for eligibility assessment were on an alternative anticoagulant or anti-platelet agent which precluded them from the TiMM trial. Furthermore, during the time the trial was open for recruitment, the number of patients newly diagnosed was significantly less than had been anticipated.

Seven patients were co-recruited to TiMM and the CARDAMON study – no patient declined co-recruitment. However, due to regulatory approvals, 4 patients who would have been candidates for the TiMM study were not eligible due to already being enrolled into another study. Myeloma trials are numerous, and the drugs trialled are rapidly evolving in terms of their mechanism of action leaving unanswered questions about their thrombotic risk. To improve recruitment, future trials of thromboprophylaxis should form a supportive arm of the main chemotherapy trials. This would enable new chemotherapy drugs to be trialled alongside thromboprophylaxis, as it would be offered in routine clinical practice. As each chemotherapy drug is given in different cycle numbers of different durations, it would allow thromboprophylaxis plans to be made alongside chemotherapy decisions.

***Newer myeloma agents and their associated risk assessment***

Risk assessment of myeloma patients is by no means homogenous. Despite availability of expert group guidance being in place, there is wide variation in the interpretation and thus practice differs both between clinicians and between hospitals, partly because guidelines lag behind advances in myeloma treatment. If a strong VTE risk factor such as previous VTE the clinical approach seems clear. However, weak risk factors such as obesity are interpreted variably. Updated thromboprophylactic guidelines are needed which take newer drugs into account. Carfilzomib, which was used as part of the CARDAMON study did not have clear data on thrombotic risk which has led to a lack of consensus regarding the role of VTE risk assessment within the myeloma community. These issues should be factored into future studies in order to maximise recruitment. A placebo arm could be considered in future trials if there is uncertainty about VTE risk associated with chemotherapy regimens used. Full engagement of the myeloma community is the only way to ensure this is achieved. Now may be the time to consider revising the current guidelines on thromboprophylaxis and having a supportive arm in a multicentre chemotherapy study is the ideal way of achieving this.

***Safety of Apixaban***

There are 2 main studies that have assessed the use of thromboprophylactic agents in myeloma and both involved the use of IMiD based therapy which has an irrefutable risk of thrombosis when used in combination with steroids or chemotherapy (17,18). The first compared aspirin (100mg/day) or fixed, low-dose warfarin (1.25mg/day) with LMWH (enoxaparin 40mg/day) in myeloma patients treated with thalidomide. This study concluded that all drugs had similar efficacy except in the elderly population, where warfarin was found to be less effective than LMWH (15). A further study compared the effectiveness and safety of aspirin (100mg/day) and LMWH (enoxaparin 40mg/day) as thromboprophylaxis in 342 previously untreated patients receiving lenalidomide based induction and consolidation chemotherapy. It concluded that aspirin could be an effective and less-expensive alternative to LMWH as thromboprophylaxis (16). Despite these studies, the optimal thromboprophylactic agent is unknown and the role of aspirin is not clearly defined, particularly with modern combination therapies. Recent work in the orthopaedic population has highlighted aspirin as being as effective as rivaroxaban in preventing VTE in patients following total hip or total knee arthroplasty after 5 days of rivaroxaban prophylaxis which may herald a new era for aspirin thromboprophylaxis (19).

There is a single study evaluating tolerability apixaban as thromboprophylaxis in cancer patients, including those with myeloma. It concluded that apixaban was well tolerated so supporting a further phase 3 study (20). A number of studies are currently investigating the use of DOACs in cancer patients (21). Evaluation of apixaban in prevention of thromboembolic disease in patients with myeloma treated with IMiDs (MYELAXAT) study (NCT02066454) is currently assessing the safety of apixaban in the myeloma cohort. As IMiDs have a known thrombotic risk, the findings from this study may not be applicable to alternate drugs being trialled in the newly diagnosed myeloma cohort.

The TiMM study suggests apixaban is not able to prevent cannula associated thrombotic events. Given that two occurred in a relatively small cohort, when chemotherapy combinations include intravenously-administered drugs, consideration needs to be given to the risk of thrombosis associated with an intravenous line and irritant chemotherapy and how this should feature in a risk assessment is uncertain. One other question raised is how, following a cannula-associated event, this influences their risk assessment going forward. One patient received LMWH for 6 weeks to treat a cannula-associated event, following which he was switched back to prophylactic aspirin. The management of cannula-associated thrombosis lacks consensus and warrants further research. The optimal duration of thromboprophylaxis is also uncertain.

A notable benefit of apixaban compared with aspirin is the greater flexibility relating to peri-procedural use as demonstrated by the ease of stopping and restarting this with fewer doses needing to be omitted.

***Limitations***

It is undoubtedly a limitation that no high-risk patients were randomised to LMWH as they both received apixaban. It would have been interesting to compare any potential VTE or bleeding events whilst on this medication too.

Lower recruitment than expected impacted on the ability to assess VTE rates. Relaxing the exclusion criteria of future studies could be considered with regard to pre-existing anticoagulation or antiplatelet therapy. For example, if receiving LMWH for VTE prophylaxis whilst an inpatient, an adaptive clinical trial might allow their inclusion.

***Conclusion***

NDMM patients are a dynamic population. They suffer a whole host of complications throughout their treatment that requires in- and out-patient care which then influences the thromboprophylactic agent of choice. This needs to be reflected in the study design of thromboprophylaxis studies in the future. Ideally, a thromboprophylactic study (supportive clinical trial) would feature alongside a chemotherapy trial. It may be prudent to consider the use of other thromboprophylactic agents such as edoxaban and rivaroxaban if this was to become a larger trial so that local use of DOACs could be taken into account.

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**Tables**

Table 1: Trial visits

|  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | Baseline\* | Visit 1 | Visit 2 | Visit 3 | Visit 4 | Visit 5 | Visit 6 | Visit 7 | Visit 8 | Visit 9 |
| Weeks post chemotherapy | 0 | 1 | 3 | 6 | 9 | 12 | 15 | 18 | 21 | 24 |

Table 2: Reasons patients did not meet the eligibility criteria for TiMM

|  |  |
| --- | --- |
| **Reason for Exclusion** | **Number of Patients (n=)** |
| Thrombocytopenia (<50x10^9) | 1 |
| Creatinine clearance <30ml/min | 1 |
| Already prescribed anticoagulant or antiplatelet*In-patient on enoxaparin**Out-patient on enoxaparin**Warfarin**Clopidogrel**Apixaban**Rivaroxaban**Aspirin* | 11*4**1**1**2**1**1**1* |
| In another clinical trial without permission for co-recruitment | 4 |
| Unable to consent | 1 |

Table 3: Baseline characteristics

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  |  | **Aspirin** | **Apixaban** | **Total** |
| **Category** | **Characteristic** | **n = 4** | **n=6** | **n=10** |
| Gender | Male sex, no (%) | 2 (50) | 3 (50) | 5 (50) |
| VTE Risk | Standard  | 4 (100) | 4 (67) | 8 (80) |
|  | High  | 0 (0) | 2 (33) | 2 (20) |
| Mean age, years (sd) |  |  |  |  |
|  |  | 65.0 (8.6) | 61.0 (10.5) | 63.3 (8.6) |
| Ethnicity  |  |  |  |  |
|  | Black |  | 2(20) | 2 (20) |
|   | White | 4 (100) | 2 (80) | 8 (80)  |
| Weight kg - no (%) | <70  | 1 (25) | 1 (17) | 2 (20) |
| 70 - ≤ 90  | 2 (50) | 3 (50) | 5 (50) |
| > 90 | 1 (25) | 2 (33) | 3 (30) |
| Creatinine clearance, mL/min | ≥ 80, n(%) | 2 (50) | 4 (67) | 6 (60) |
|  | 50 - <80, n(%) | 2 (50) | 2 (33) | 4 (40 |
| Previous VTE (DVT/PE) |  |  |  | 0 (0) |
| Smoking status |  |  |  |  |
|  | Never smoker | 3 (75) | 6 (100) | 1 (10) |
|   | Ex-smoker | 1 (25) | 0 (0) | 9 (90) |
| Myeloma Treatment regimen, n(%) |  |  |  |
|  | Velcade/Thalidomide/Dexamethasone (VTD) | 1 (25) | 0 (0) | 1 (10) |
|  | Carfilzomib/Cyclophosphamide/ Dexamethasone (CCD) | 2 (50) | 5 (83) | 7 (70) |
|   | Velcade/Melphalan/Prenisolone (VMP) | 4 (100) | 6 (100) | 2(20) |
| Multiple myeloma classification, n(%) |  |  |  |
|  | Stage 1 | 2 (50) | 3 (50) | 5 (50) |
|  | Stage 2 | 1 (25) | 3 (50) | 4 (40) |
|   | Stage 3 | 1 (25) | 0 (0) | 1(10) |
| VTE risk factors, n(%) |  |  |  |  |
|  | Obesity (BMI>30) | 1 (25) | 3 (50) | 4 (40) |
|  | Recent surgery (<6 weeks) | 0 (0) | 1 (17) | 1 (10) |
|  | Acute stroke (< 4 weeks) | 0 (0) | 0 (0) | 0 (0) |

Table 4: Adverse events in all patients

|  |  |  |  |
| --- | --- | --- | --- |
|  | **Aspirin (n=)** | **Apixaban (n=)** | **Total (n=)** |
| **Thrombosis** |  |  |  |
|  Cephalic vein thrombosis | 1 | 1 | 2 |
| **Bleeding** |  |  |  |
|  PV bleeding post pessary removal | 0 | 1 | 1 |
|  Mild PR bleeding | 1 | 0 | 1 |
|  Bleeding post eye injection - (apixaban was omitted for 4 doses prior to this) | 0 | 1 | 1 |
| **Other Adverse Events** |  |  |  |
|  One episode of temperatureᶧ | 0 | 1 | 1 |
|  Myocardial infarction | 0 | 1\* | 1 |
|  Chromatopsia | 0 | 1 | 1 |
|  Constipation | 0 | 1 | 1 |
|  Light headedness | 0 | 1 | 1 |
|  Abnormal liver function tests/generally unwell | 1 | 0 | 1 |
|  Back ache | 1 | 0 | 1 |
|  Bilateral calf tenderness | 0 | 1 | 1 |
|  Diarrhoea | 0 | 1 | 1 |
|  Hyperglycaemia | 0 | 1\* | 1 |
|  Rash | 1\* | 0 | 1 |
|  Red blotches | 0 | 1 | 1 |
| **Total** | **5** | **12** | **17** |
| \*severe intensity events; all other events recorded as mild intensityᶧ As reported by patient*PV: per vagina* |

Table 5: Number of Doses Omitted

|  |  |  |
| --- | --- | --- |
| **Number of doses omitted:** | **Aspirin** | **Apixaban**  |
| **On medical advice:** | 28 | 12 |
|  *Deranged LFTs*  | *9* | *-* |
|  *Bleeding*  | *-* | *4* |
|  *Operation requiring LMWH*  | *19* | *-* |
|  *Day procedure*  | *-* | *8* |
| **Forgotten by the patient** | 4 | 1 |

**Figures**

Figure 1: Trial Protocol

Figure 2: Assignment of Patients and outcomes