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**Venous thromboembolism in Multiple myeloma – choice of prophylaxis, role of direct oral anticoagulants and special considerations**

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## **Abstract**

Multiple myeloma is associated with a significant risk of venous thromboembolism (VTE), causing substantial levels of morbidity and mortality. The thrombogenicity of myeloma is multifactorial, with disease- and treatment-related factors playing important roles. Immunomodulatory drugs (IMiDs) and high-dose dexamethasone, in particular, are known to enhance the thrombotic potential of myeloma. For this reason, assessment of the VTE risk has long been advocated prior to treatment initiation in patients with myeloma requiring IMiD-based regimens. However, despite routine use of thromboprophylaxis, these patients can still develop VTE and its sequelae. The optimum choice and dose of thromboprophylactic drug is not entirely clear, and with this, there is growing interest regarding use of the direct oral anticoagulants (DOACs) in this setting.

In this review we discuss the pathogenesis of thrombosis in multiple myeloma, its relation to some of the commonly used chemotherapeutic regimens, current risk stratification and the evidence supporting the different anticoagulants used as thromboprophylaxis. We propose an amended risk stratification, and consider management of challenging patients including those with renal impairment and recurrent thrombosis.

## **Introduction**

Risk of venous thromboembolism (VTE) is significantly increased in patients with cancer (4.3 fold increased incidence) (Blom, *et al* 2005), and VTE is the second commonest cause of death in these patients, other than the malignancy itself (Ambrus, *et al* 1975, Donati 1994, Khorana, *et al* 2007, Schoen, *et al* 2018). Amongst haematological malignancies, multiple myeloma confers an especially high risk with at least 10% of patients developing VTE during their disease history (Barlogie, *et al* 1999, Eby 2009, Falanga and Marchetti 2009, Kristinsson, *et al* 2010). A recent review of nearly 5000 myeloma patients showed VTE to be significantly associated with increased mortality at two and five years after diagnosis, independent of other known prognostic factors (Schoen, *et al* 2018). Although VTE risk is highest with active myeloma, it also extends to some degree to those with monoclonal gammopathy of uncertain significance (MGUS). A large retrospective study of over 4 million US veterans found a threefold increased risk of VTE in MGUS cases, and a nine-fold increased risk in myeloma cases (Kristinsson, *et al* 2008). As VTE is associated with an increased mortality (Sanfilippo, *et al* 2014), appropriate identification of VTE risk factors and subsequent stratification of patients is of paramount importance in the optimal care of patients with myeloma.

Our aim was to review the pathophysiology of thrombosis in myeloma, how this is affected by common anti-myeloma treatments, and the efficacy of the thromboprophylactic agents available. Finally, we propose practical algorithms for assessment of thrombotic risk, choice of prophylaxis, and management of VTE recurrence. MEDLINE, EMBASE, and NHS EVIDENCE were searched systematically for publications in English using the key words 'thrombosis', 'anticoagulation' and 'multiple myeloma'. References from relevant publications were also searched. Editorials, studies with <8 cases and letters were excluded. Conference abstracts have been included if deemed to be of particular relevance.

### Pathogenesis of thrombosis in Myeloma

Several disease-related, treatment-based and patient-related factors can lead to thrombosis in myeloma (Amrani 1990, Auwerda, *et al* 2007, Bellotti, *et al* 1989, Dong, *et al* 2018, Elice, *et al* 2006, Esmon 2001, Gado, *et al* 2000, Guo, *et al* 2018, Kotlin, *et al* 2008, Mechtcheriakova, *et al* 1999, O'Kane, *et al* 1994, Palumbo, *et al* 2004, Stirling, *et al* 1998, Thiagarajan, *et al* 2000, Yagci, *et al* 2003, Yasin, *et al* 1999, Zangari, *et al* 2003). The effect of plasma cell neoplasms on thrombotic risk is paramount and the various ways they can promote clot formation is given in Table 1. Risk of VTE is well documented to be increased during the active phase of disease, particularly during the first six months of treatment. This risk can be further augmented by certain therapeutic agents, in particular the immunomodulatory drugs, and especially in combination with high doses of corticosteroids and chemotherapy.

Table 1. **Thrombotic risk factors in plasma cell neoplasms**

Disease-related	Treatment-related	Patient-related
<p>Immunoglobulin dependent</p> <ul style="list-style-type: none"> <li>Hyperviscosity eg. serum viscosity &gt;4 cp (serum IgG usually <math>\geq 40</math> g/l, or IgA <math>\geq 60</math> g/l)*(Zangari, <i>et al</i> 2003)</li> <li>Defective fibrin polymerisation and fibrinolysis (Kotlin, <i>et al</i> 2008, O'Kane, <i>et al</i> 1994, Thiagarajan, <i>et al</i> 2000, Yagci, <i>et al</i> 2003)</li> <li>Lupus anticoagulant activity (LAC) of the paraprotein, antibodies against Protein S and C, acquired Activated Protein C (APC) resistance (Bellotti, <i>et al</i> 1989, Yasin, <i>et al</i> 1999)</li> </ul> <p>Immunoglobulin independent</p> <ul style="list-style-type: none"> <li>Elevated PAI-1 (plasminogen activator inhibitor-1)</li> <li>Increased proinflammatory cytokines IL-6 and VEGF (Amrani 1990, Gado, <i>et al</i> 2000, Mechtcheriakova, <i>et al</i></li> </ul>	<p>Drugs</p> <ul style="list-style-type: none"> <li>Thalidomide/Lenalidomide</li> <li>Dexamethasone</li> <li>Multiagent chemotherapy</li> <li>Proteasome inhibitors- bortezomib exerts a protective effect, carfilzomib is a risk factor for VTE</li> <li>Erythropoietin stimulating agents</li> <li>Indwelling central catheters (Palumbo, <i>et al</i> 2008)</li> </ul>	<ul style="list-style-type: none"> <li>Fractures and other causes of immobility</li> <li>Severe infections</li> <li>Elevated body mass index</li> <li>Comorbidities eg. cardiac disease, chronic renal failure, diabetes mellitus, inflammatory bowel disease, autoimmune disease</li> <li>Surgery, anaesthesia, trauma</li> <li>History of VTE or inherited thrombophilias (not myeloma-specific) (Palumbo, <i>et al</i> 2008)</li> </ul>

<p>1999, Stirling, <i>et al</i> 1998)</p> <ul style="list-style-type: none"> <li>• Increased endothelial TF (tissue factor) expression (Dong, <i>et al</i> 2018)</li> <li>• Elevated FVIII, VWF and fibrinogen levels (Auwerda, <i>et al</i> 2007, Stirling, <i>et al</i> 1998)</li> <li>• Increased cell surface phosphatidylserine expression (Dong, <i>et al</i> 2018, Guo, <i>et al</i> 2018)</li> <li>• Acquired APC resistance due to reduced levels of thrombomodulin (TM) (Elice, <i>et al</i> 2006, Esmon 2001)</li> </ul>		
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*\*IgM myeloma is uncommon. Hyperviscosity predisposing to increased risk of thrombosis is more likely to occur if serum IgM is >30g/l.*

#### *Dexamethasone*

Corticosteroids have been associated with VTE in different diseases including myeloma (Johannesdottir, *et al* 2013). High doses of dexamethasone have been shown to stimulate increased expression of tissue factor (TF), cellular adhesion molecules (ICAM-1, VCAM-1 and E-selectin) and von Willebrand factor (VWF), and decreased expression of thrombomodulin (TM) and plasminogen activator inhibitor-1 (PAI-1) by HUVEC cells *in vitro* (Kerachian, *et al* 2009), with similar **antifibrinolytic** effects seen in rats (van Giezen and Jansen 1992). Dexamethasone may act indirectly, by sensitizing cells to cytokine stimulation eg. tumour necrosis factor alpha (TNF- $\alpha$ ), but there is limited definitive data available to confirm its mode of action. Indeed, at low doses, glucocorticoids may even have a protective effect against inflammation and thrombosis. In the context of orthopaedic surgery, administration of hydrocortisone pre-operatively was associated with a significant reduction in markers of thrombin generation, and a non-significant increase in fibrinolysis markers (McLawnhorn, *et al* 2015).

What is known however, is that clinically, the addition of steroids, particularly at higher doses, is associated with a significant elevation in thrombosis risk. Rajkumar *et al.* reported a comparison between lenalidomide with high- or low-dose dexamethasone. In this study, high-dose was referred to as 40 mg dexamethasone on days 1-4, 9-12 and 17-20 of a 28 day cycle, versus low-dose where 40mg of dexamethasone was administered once weekly. The total dose of dexamethasone received in the 'high-dose' group was 480mg/month, in line with the IMWG's later definition of 'high-dose'

glucocorticoids (Palumbo, *et al* 2008). In the initial part of the study, VTE prophylaxis was recommended but not mandated. Of the first 266 enrolled patients, 18.2% developed VTE in the high-dose group and 3.7% in the low-dose group, after which thromboprophylaxis became mandatory (Rajkumar and Blood 2006). At one year from study initiation, the VTE rate in the high-dose group was over double that of the low-dose group (26% vs 12%), providing substantial supportive evidence for the thrombogenic potential of high-dose dexamethasone (Rajkumar, *et al* 2010).

### *Immunomodulatory agents*

Thalidomide is the first in the class of immunomodulatory drug (IMiD) used for myeloma treatment. Its mode of action is multifactorial, affecting angiogenesis, adhesion of myeloma plasma cells, and regulation of the immune system (Palumbo and Palladino 2012). VTE can be associated with single-agent thalidomide use, but is seen more often when thalidomide is combined with glucocorticoids, and is a frequent complication of treatment with high-dose dexamethasone or combination chemotherapy (Barlogie, *et al* 2001, Bennett, *et al* 2002, Li, *et al* 2017, Rajkumar, *et al* 2002, Tosi, *et al* 2002, Weber 2002). Rates of VTE seen with thalidomide with the addition of dexamethasone range from 2-17% (Cavo, *et al* 2004, Dimopoulos, *et al* 2001, Rajkumar, *et al* 2006) while with combination chemotherapy, rates of 10-58% have been reported (Barlogie, *et al* 2006, Baz, *et al* 2005, Schutt, *et al* 2005, Zangari, *et al* 2002, Zervas, *et al* 2004). The highest incidence (58%) was reported by Baz *et al.* in their trial evaluating the use of thalidomide in association with doxorubicin, vincristine and dexamethasone (Baz, *et al* 2005). Thrombosis rates are higher in newly diagnosed patients than those with relapsed/refractory disease (2-15% vs 3-34%) although the exact reasons for this difference is unclear (Palumbo, *et al* 2008). The incidence is maximal during the first three months of treatment and decreases after about 12 months (Zangari, *et al* 2004a, Zangari, *et al* 2002), possibly due to release of prothrombotic factors from apoptotic myeloma cells when burden of disease is at its highest (Zangari, *et al* 2003). *In vitro* studies have shown that application of thalidomide to endothelial cells damaged by doxorubicin exposure leads to altered Protease activated receptor-1 (PAR-1) expression, indicating endothelial dysfunction (Baz, *et al* 2005). This may in part explain the extremely high rate of thrombosis seen by Baz *et al.* Association studies have also suggested a link between IMiDs and increased endothelial TF expression (Li, *et al* 2017). A transient reduction in levels of soluble TM was reported during the first month of therapy in a group of 13 relapsed refractory patients, one of whom developed VTE (Corso, *et al* 2004). Interestingly, IMiDs themselves have not been shown to cause endothelial damage (Streetly, *et al* 2005). The thrombogenicity of thalidomide may therefore be potentiated by endothelial damage from combination chemotherapy, and dexamethasone-induced sensitization of cells to cytokine stimulation, which is known to be upregulated by IMiDs.

Lenalidomide is a second-generation immunomodulatory agent with increased *in vitro* efficacy compared with thalidomide, and less toxicity in data pooled from different trials (no head-to-head comparison of thalidomide and lenalidomide exists in the literature). Like thalidomide, single agent

lenalidomide has a modest thrombogenic potential (reported incidence 4%) (Richardson, *et al* 2009) which is enhanced by the addition of glucocorticoids, particularly high-dose dexamethasone (VTE 26% versus 12% high ie. 480mg/month versus low-dose dexamethasone) (Dimopoulos, *et al* 2007, Rajkumar, *et al* 2010, Weber, *et al* 2007, Zonder, *et al* 2005), and combination chemotherapy (14% when used with cyclophosphamide and 9% with doxorubicin) (Baz, *et al* 2006, Knop, *et al* 2006, Morgan, *et al* 2007). VTE rates are again higher in newly diagnosed patients. A meta-analysis of 125 patients enrolled in three clinical trials stratified the patients into high and low-VTE risk groups based on the concomitant dose of dexamethasone administered (40 mg weekly, or 40mg on 12 days/month, total 480mg/month). Most of the patients (110) received thromboprophylaxis, which in the majority was 325 mg aspirin once daily. The VTE rate was 12% for the high-dose dexamethasone group, 6% in the low-dose group, 7% in those on aspirin and 13% in those not receiving thromboprophylaxis. 7/10 VTE episodes occurred during the initial six months of therapy in keeping with the known increased thrombogenic potential associated with high disease burden (Menon, *et al* 2008). Consistent with these results, the Greek Myeloma Study Group analysed 212 relapsed refractory patients treated with lenalidomide and low-dose dexamethasone outside of clinical trials, and reported a similar VTE incidence of 5.7% overall (Katodritou, *et al* 2014).

There is less evidence again regarding the third-generation immunomodulatory agent, pomalidomide. A small phase I study of 24 relapsed refractory patients receiving single agent pomalidomide reported VTE in 17% without thromboprophylaxis (Schey, *et al* 2004). Subsequent studies have incorporated varying doses of thromboprophylaxis into treatment regimens. Of 60 relapsed-refractory patients receiving pomalidomide with low-dose weekly dexamethasone, only one thromboembolic event was reported (1.6%). All patients were thromboprophylaxed with a high dose of aspirin (325mg), therapeutic dose LMWH or warfarin with a target INR of 2-3 (of note, none of these thromboprophylaxis strategies would be routinely chosen in current clinical practice) (Lacy, *et al* 2009). A recent study of pomalidomide in combination with low-dose dexamethasone and bortezomib in 50 patients reported a higher VTE rate of 10%, despite using the high doses of thromboprophylactic agents detailed in the previous study (Paludo, *et al* 2017).

### *Proteasome inhibitors*

The first in-class proteasome inhibitor is bortezomib which reversibly inhibits the 20S subunit of the 26S proteasome. Downstream suppression of nuclear factor  $\kappa$ B (NF- $\kappa$ B) mediated transcription factor production results in enhanced expression of the natural anticoagulant endothelial TM via induction of Kruppel-like transcription factors. Bortezomib can also prevent TM downregulation by inflammatory cytokines (Hiroi, *et al* 2009, Lonial, *et al* 2008, Nayak, *et al* 2014). Data relating to bortezomib use suggests a far lower, or possibly even absent, thrombogenic potential. Addition of bortezomib to melphalan-prednisolone in the phase 3 VISTA trial was not associated with increased VTE rates (San Miguel, *et al* 2008). The APEX trial of single-agent bortezomib versus high-dose dexamethasone in

relapsed patients reported differential VTE rates of 0.6% for bortezomib versus 2.7% in the dexamethasone arm (Lonial, *et al* 2008). Addition of bortezomib to the DT-PACE regimen (dexamethasone, thalidomide, cisplatin, doxorubicin, cyclophosphamide and etoposide) was associated with a significant reduction in thrombotic episodes, from 10% to 0% (Zangari, *et al* 2004b). In the frontline setting, Zangari *et al.* reviewed phase 3 trials of bortezomib and/or immunomodulatory agent-based therapy. Regimens including bortezomib had overall VTE rates of  $\leq 5\%$  whereas IMiD-based treatment without bortezomib was associated with higher rates, further corroborating the low thrombogenicity associated with bortezomib (Zangari, *et al* 2011).

A small study involving 10 patients with relapsed multiple myeloma described *in vivo* effects of bortezomib on routine coagulation tests and impairment of platelet function. Platelet aggregation with different agonists was decreased after bortezomib infusion with statistically significant results with ADP on days one, (20% decrease,  $p=0.033$ ) and four (29% decrease,  $p=0.009$ ). Similar results were also obtained with epinephrine-induced platelet aggregation and ristocetin-induced agglutination. Expression level of the platelet surface marker, P-selectin, which has roles in adhesion and thrombosis, was also decreased after bortezomib treatment (Zangari, *et al* 2008). This anti-platelet effect and alteration in adhesion properties may explain the low VTE rates seen with proteasome inhibition.

There is less available data on the second-generation proteasome inhibitor carfilzomib, which unlike bortezomib, causes *irreversible* inhibition of the 26S proteasome. The phase 3 study ASPIRE compared the triplet of carfilzomib, lenalidomide and dexamethasone, with lenalidomide and dexamethasone. VTE incidence during the first year was 13% versus 6% against the carfilzomib arm (Stewart, *et al* 2015), with significant rates of carfilzomib-related cardiovascular disease (hypertension, arrhythmias, myocardial infarction, and congestive cardiac failure) noted in this and other studies. These effects, suspected to be a reflection of endothelial toxicity possibly related to the irreversible 26S proteasome inhibition, appear to be specific to carfilzomib and are not seen with bortezomib.

### **Prophylaxis – risk stratification**

Assessment of VTE risk in myeloma has been advocated for many years (Palumbo, *et al* 2008), the mainstay of which requires a thorough clinical history, with close attention being paid to the features described in Table 1. Re-assessment is suggested at diagnosis, relapse, or when otherwise clinically indicated eg. if the patient develops VTE, or at instigation of a new non myeloma-related therapy with increased thrombogenic potential.

Optimal choice of pharmacological prophylaxis and appropriate patient VTE risk-stratification in patients with myeloma requires ongoing attention. Recent results from the large, phase 3 Myeloma XI trial highlight this fact. The updated analysis showed an overall VTE rate of 12.4%, 11.1% of which was during the first 6 months of therapy, with no differences seen between the thalidomide and



lenalidomide-containing regimens. By far the majority of patients (87.6%) were on some type of thromboprophylaxis prior to VTE with only 12.4% of patients not receiving thromboprophylaxis. However, the types and doses of thromboprophylaxis were variable and not accounted for by the preceding VTE risk assessment. Over 10% were on therapeutic dose LMWH prior to their thrombotic event, further emphasising the strong prothrombotic potential of selected patients (Bradbury 2017, C. A. Bradbury 2018).

In 2008, The International Myeloma Working Group recommended a VTE risk assessment be performed in all multiple myeloma patients treated with thalidomide or lenalidomide. They suggested aspirin prophylaxis (dose 81-325mg once daily) for those with no or one risk factor, LMWH or therapeutic dose warfarin if two or more risk factors are present, and the same for those receiving high-dose dexamethasone, doxorubicin or multi-agent chemotherapy irrespective of preceding risk factors (Palumbo, *et al* 2008). The recommendations were provided with the caveat that they were based on the limited available data alongside expert opinion, and do not provide a definitive model for this issue. The British Society of Haematology guidelines on the supportive care of multiple myeloma, 2011, concur with this advice (Snowden, *et al* 2011), as do the 2016 National Institute of Clinical Excellence (NICE) guidelines, once again acknowledging the relative lack of rigorous evidence on the topic (NICE Clinical guidelines 2016). However, the most recent guidance from NICE in 2018, merely suggests that either aspirin or prophylactic dose LMWH may be considered equivalent for myeloma patients receiving chemotherapy with IMiDs and a corticosteroid (guidelines 2018).

Although risk assessment tools are available, there is evidence to suggest that clinicians are often stratifying patients according to personal perception of strength of certain risk factors, for example placing more weight on a family history than treatment with high-dose dexamethasone. The MELISSE study was a large, multicentric, observational study which sought to evaluate VTE incidence, risk assessment and prophylaxis chosen in real-life practice in France. Of 513 patients on lenalidomide- or thalidomide-based regimens, 47% were deemed to be at low VTE risk, 39% intermediate and 14% high. Patients were managed with either aspirin, LMWH or VKA. At 12 months follow-up, VTE rates were 7% for aspirin, 3% LMWH and 0% in the VKA-treated group with no statistical significance identified. However, risk stratification was not standardised. 47% of patients were thought to be low risk, however only 15% had fewer than 3 VTE risk factors. Choice of prophylaxis was also not standardised and did not follow current international recommendations (Palumbo, *et al* 2008), with 19% of high-risk individuals receiving low-dose aspirin, and LMWH or VKA only prescribed for 40% of intermediate- and high-risk patients. A lack of consensus and clarity appeared evident with respect to both risk stratification of patients and subsequent choice of thromboprophylaxis (Chalayer, *et al* 2016b, Leleu, *et al* 2013).

Attempts to improve VTE risk stratifications have been made and various groups are investigating markers of thrombosis that could be incorporated into practical, validated risk assessment tools. Elevated levels of soluble p-selectin, an adhesion protein which mediates interactions between

platelets, leucocytes and cancer cells, have been shown to be associated with an increased risk of VTE, and incorporated into the Vienna risk prediction model (Ay, *et al* 2008). Other markers under investigation include D-dimers, microparticles and tissue factor, which was shown to be associated with recurrence of VTE in the CATCH trial (Khorana, *et al* 2017). Very recently, a group analysed conventional clinical myeloma risk factors such as dexamethasone use, thalidomide, previous VTE, central venous catheter *in situ*, and obesity, and developed a new risk model (the myeloma clot score, MCS), which they validated (Kristen Marie Sanfilippo 2018).

Point of care tests of global hemostasis may play a future role in identifying patients with prothrombotic haemostatic profiles, and perhaps in highlighting those with features of resistance to heparin or other anticoagulation (see recurrent thrombosis section). Given their increasing importance in other areas such as management of major haemorrhage, it is likely they may be of use in this field also, however more research is required.

## **Prophylaxis – choice of agent**

### *Aspirin versus LMWH*

The IMWG have advised the use of aspirin in low VTE risk patients receiving IMiD-based regimens, concluding from the available evidence that it is of clinical utility in this subgroup (Palumbo, *et al* 2008). Due to its oral route and lack of monitoring, it is an appealing option for patients, however most of the current evidence is not based on randomized trials, and published results do not uniformly show benefit. A study of patients receiving combination chemotherapy with thalidomide, pegylated doxorubicin, vincristine and dexamethasone without pharmacological thromboprophylaxis yielded a VTE incidence of 58% which was reduced to 18% in subsequent patients by the addition of aspirin 81mg daily (Baz, *et al* 2005). A small study of 34 patients receiving lenalidomide, dexamethasone and aspirin reported a 3% VTE rate (Rajkumar, *et al* 2005). A subsequent, larger, randomized study of lenalidomide with high or low dose dexamethasone found the addition of low-dose aspirin reduced VTE rates from 23% to 14% for high-dose dexamethasone patients and from 14% to 5% for low-dose patients (Rajkumar, *et al* 2006). A study of melphalan, prednisolone and lenalidomide with aspirin 100mg reported a 5% VTE rate (Palumbo, *et al* 2007), and another of lenalidomide, doxorubicin and dexamethasone with 81mg aspirin reported a 9% rate (Baz, *et al* 2006).

More recently, 342 patients treated with lenalidomide-based induction and consolidation therapy (lenalidomide and low-dose dexamethasone induction, and melphalan-prednisolone-lenalidomide consolidation) were randomized between aspirin 100mg daily and enoxaparin 40mg daily. This prospective, open-label, randomized sub-study of a phase 3 trial showed that during the first 6 months post-randomisation, VTE incidence was 2.27% in the aspirin group and 1.20% in the LMWH group, with an absolute difference of 1.07% (95% confidence interval, -1.69-3.83; P = .452) in favour of enoxaparin. Importantly, high-risk patients were excluded including those with recent orthopaedic

surgery, vertebroplasty, immobilisation, thrombophilia, known ischaemic heart disease or previous atrial fibrillation, and none of the cohort had a past history of VTE (Larocca, *et al* 2012). Another larger randomised trial of 667 patients receiving thalidomide-based first-line myeloma therapy compared aspirin 100mg, fixed low-dose warfarin 1.25mg and enoxaparin 40mg. Reported rates of serious thromboembolic events, acute cardiovascular events or sudden death during the first 6 months were 6.4% for aspirin, 8.2% for warfarin and 5.0% for LMWH. Three major and 10 minor bleeding episodes were recorded. High risk patients were excluded in this trial. The authors concluded from their data that aspirin was an effective prophylactic agent in low-risk patients, although there was no placebo arm for comparison. Of note, in this trial, the risk of VTE was 1.38 times greater in patients treated with thalidomide without bortezomib (Palumbo, *et al* 2011).

In terms of lenalidomide, a systematic review of over 1126 patients found overall VTE occurrence rates of 10.7% in patients receiving aspirin prophylaxis versus 1.4% for those on LMWH. The highest risk was in patients taking lenalidomide with high-dose steroids (26.6%), compared with low-dose dexamethasone (10.3%) or melphalan, lenalidomide, prednisolone (MPR) (4.1%). They concluded that aspirin may be insufficient for regimens incorporating high doses of dexamethasone but may be a safe option for lower risk treatments such as MPR (Al-Ani, *et al* 2016). In contrast to these findings, a large retrospective cohort study of 4892 multiple myeloma patients in whom 586 developed VTE did not find evidence that aspirin reduced the risk of VTE, after adjusting for risk factors including IMiD use and past history of VTE. They suggested that aspirin may be insufficient for patients on immunomodulatory agent-based treatments and also those with a personal history of VTE (Sanfilippo, *et al* 2017).

From an economic standpoint, the limited cost associated with low-dose aspirin is advantageous. Chalayer E *et al.* performed a cost-effectiveness analysis of LMWH versus aspirin in newly diagnosed multiple myeloma patients, based on Palumbo *et al.*'s work (Palumbo, *et al* 2011). In their model, aspirin use was associated with a higher frequency of VTE, stroke, major bleeding, but reduced incidence of acute myocardial infarction, and due to the difference in route of administration, a slightly higher quality-adjusted life years (QALY) than LMWH (0.300 versus 0.299). Over 6 months of treatment, using aspirin in place of LMWH was calculated to save 1245 Euros on average per patient, with a slight improvement in quality of life. These results of course do not apply to patients who develop VTE with its associated complications, and no assessment of VTE risk was made in this model (Chalayer, *et al* 2016a).

Data supports low-dose aspirin as a reasonable option for patients on IMiD-containing regimens who are otherwise at low-risk of thromboembolic complications, although the number of patients in this category is likely to be small. Given the conflicting results available, we would generally recommend offering prophylactic LMWH to all patients receiving initial Multiple Myeloma treatment with an IMiD in combination with corticosteroid or chemotherapy, at least during the initial 6 months of treatment when risk of thrombosis is at its highest. Aspirin could be considered beyond 6 months in the absence

of additional significant patient related VTE risk factors. However, these recommendations are not based on robust evidence or any formal guideline. Prophylactic dose LMWH confers the greatest protection out of the conventional agents available, and is therefore the drug of choice for 'high-risk' individuals. There is some evidence that it may be inadequate for particularly high-risk patients who may benefit from more intensive VTE prophylaxis. However, there is a lack of evidence that a higher dose of anticoagulation is effective and safe, and risk of thrombosis and haemorrhage must be balanced if intensification of anticoagulation is to be considered.

### *Warfarin*

The little data available on warfarin as thromboprophylaxis suggests that at therapeutic doses aiming for an INR between 2 and 3 it isn't superior to prophylactic dose LMWH (Palumbo, *et al* 2011), and that at low fixed doses eg.1-1.25mg daily, it has poor efficacy. One study of thalidomide, dexamethasone and low dose warfarin saw a VTE incidence of 25% (Weber, *et al* 2003), and another of thalidomide, dexamethasone and chemotherapy reported a rate of 31% with fixed dose warfarin prophylaxis versus 15% with 40mg enoxaparin (Zangari, *et al* 2004a). Warfarin also has the potential for drug interactions and of course the need for frequent blood tests. Fluctuations in the INR due to issues with absorption (from vomiting and other GI issues), drug interactions, low albumin, systemic illnesses and interruptions for procedures can make warfarin a less attractive option. An **additional** practical issue to consider is the fluctuating thrombocytopenia which often develops in patients on proteasome inhibitors. The increased bleeding risk associated with a platelet count  $<50 \times 10^9/l$  also needs consideration in these patients.

### **The role of DOACs**

The direct oral anticoagulants (DOAC), either inhibitors of factor Xa (apixaban, rivaroxaban, edoxaban, betrixaban) or IIa (dabigatran), are an attractive option for VTE prophylaxis in myeloma, requiring no monitoring at routine doses, and sparing patients from daily subcutaneous injections. None of the DOACs are currently licensed for this use. A meta-analysis of trials comparing DOACs to VKAs for treatment of acute VTE in over 27,000 patients, without a specific diagnosis of myeloma, reported overall lower rates of VTE recurrence, major bleeding including fatal bleeds and intracranial haemorrhage, and clinically relevant non-major bleeds. Subgroup analysis of participants with cancer reported a hazard ratio of 0.57 for VTE recurrence in favour of the DOACs (van Es, *et al* 2014). There is also evidence for the use of DOACs in the setting of secondary VTE prevention, at reduced, prophylactic doses. This is provided by EINSTEIN CHOICE, where low dose rivaroxaban (10mg) was superior to aspirin (100mg) at prevention of VTE recurrence with equally low rates of bleeding (Weitz, *et al* 2017), and by AMPLIFY EXT which found 2.5mg twice daily apixaban to be as effective as 5mg twice daily, without increased bleeding compared with placebo (Agnelli, *et al* 2013).

Two recent trials have evaluated use of a DOAC in cancer patients for the treatment of VTE, one comparing edoxaban to dalteparin and the other rivaroxaban to dalteparin (Hokusai and SELECT-D respectively). Both studies obtained similar results. The HOKUSAI trial reported a 12-month VTE recurrence rate favouring edoxaban (7.9% versus 11.3), but with a slight increase in major bleeding (6.9% versus 4%). Similarly, the SELECT-D saw a reduction in 6-month VTE recurrence with rivaroxaban (4% versus 11%), a slight increase in major bleeding (6% versus 4%) and a significant increase in clinically significant non-major bleeding events in the DOAC arm (13% versus 4%). A significant proportion of bleeds were upper gastrointestinal in source, and more common amongst patients with gastric tract malignancies (Raskob, *et al* 2018, Young, *et al* 2018), which would be of limited relevance in the setting of myeloma. These studies did include some myeloma patients, however numbers were very small eg. one patient in the DOAC arm in SELECT-D. They also did not address the issue of VTE prophylaxis in cancer.

Data regarding prophylactic use of the DOACs in the cancer setting is presently sparser, and based mainly on small case series and case reports, but with promising results seen. A retrospective review of patients on IMiD-based regimens receiving therapeutic dose warfarin (16 patients) or therapeutic or prophylactic doses of dabigatran, rivaroxaban or apixaban (21 patients) as thromboprophylaxis reported four non-major bleeds in the DOAC group versus a total of six bleeds in the warfarin group, two of which were major, and no VTE events in either group (Man, *et al* 2017). A larger review of 70 patients receiving apixaban 2.5mg BD during front-line therapy with IMiD-containing regimens reported no episodes of VTE within the first 6 months, one ischaemic stroke, one NSTEMI in a patient with known ischaemic heart disease and one episode of major bleeding in a patient with concomitant severe thrombocytopenia. VTE risk assessment scores for the cohort are not available, however two patients had previous PE, two had a history of stroke or transient ischaemic attack and three had documented prior MI (Storrar, *et al* 2018). A prospective randomized controlled trial of apixaban 2.5mg BD versus placebo in myeloma patients on IMiD-based therapy, is ongoing (NCT02958969), and a large, multi-centre study comparing DOACs, LMWH and warfarin in VTE prophylaxis in cancer patients (CANVAS trial, NCT02744092) is also in recruitment.

Lack of routine monitoring at prophylactic doses is an attractive quality for patients, however may be an issue in patients where GI absorption is altered (eg. chemotherapy-induced vomiting and diarrhoea), when drug clearance is reduced in renal failure, or when drug interactions with chemotherapeutic agents and supportive treatments are unknown. Drug level monitoring may be a solution to these problems but isn't currently widely available and there is no evidence to guide thromboprophylaxis drug level targets for this indication, or dose alterations based on drug levels. In addition to this, in comparison with solid cancers, bleeding risk in myeloma is likely to be higher due to older age of the patients, co-existing thrombocytopenia and higher prevalence of renal dysfunction. Currently, a reversal agent is only available for dabigatran but not yet for rivaroxaban, apixaban or edoxaban. Bleeding episodes related to the direct anti-Xa inhibitors require treatment with pro-haemostatic products (eg; prothrombin complex concentrate).

The problems which may arise with DOAC use is presented in the table 2.

**Table 2: Practical issues with DOAC use in patients with myeloma**

- Dosing – We lack definitive evidence that prophylactic doses of DOACs are adequate in all patients who require thromboprophylaxis with myeloma. This is especially of concern since it is known that prophylactic doses of low molecular weight heparin do not prevent thrombosis in very high-risk patients. Escalated doses of DOACs are likely to reduce VTE recurrence rates, but possibly at the expense of increased haemorrhagic complications. Well-designed RCTs are needed to clarify this issue.
- Drug interactions –concomitant administration of DOACs with myeloma-specific treatment, and supportive medications (eg. azole antifungals etc.) is yet to be evaluated
- Extremes of body weight – Steroid use may cause weight gain in myeloma patients while cachexia may be an issue in some others. There is insufficient data for DOACs in extremes of body weight.
- Renal impairment – optimal dosing strategies depending upon severity of renal impairment are not yet known. The various DOACs have different licenses based upon creatinine clearance or eGFR threshold, and levels are further affected by hypoalbuminaemia. This is discussed further in the renal impairment section.

**Table 3: Primary experimental trials using IMiDs in multiple myeloma (meta-analyses excluded)**

Study- reference	Regimen and patients	Exclusions	Thromboprophylaxis	VTE rate
<b>Thalidomide</b> (Barlogie, <i>et al</i> 2001)	169 relapsed/refractory patients- single-agent thalidomide	Renal/liver impairment NOT excluded	Not described	<2%
(Tosi, <i>et al</i> 2002)	65 relapsed/refractory patients- single agent thalidomide (max 800mg daily)	None stated	None	1.5%
<b>Thalidomide-dexamethasone</b> (Cavo, <i>et al</i> 2004)	71 newly diagnosed patients, thalidomide with high-dose dexamethasone prior to ASCT	>65 yrs, history of thrombosis	1 <sup>st</sup> 19 patients- no thromboprophylaxis, remaining 52- 1.25mg prophylactic warfarin	26% without warfarin, 13% with warfarin
(Rajkumar and Blood 2006)	207 patients with newly diagnosed myeloma randomized to high dose dexamethasone +/- thalidomide	Severe renal impairment, liver impairment, cytopenias, or past/current thrombosis	None	17% in the thalidomide arm vs. 3% without
(Rajkumar, <i>et al</i> 2002)	50 patients with newly diagnosed myeloma-	Severe cytopenias, poor performance	None	Single agent arm 4%,

	thalidomide with dexamethasone at alternating high and low doses	status		combination 15%
(Weber, <i>et al</i> 2003)	28 newly diagnosed asymptomatic myeloma patents- single agent thalidomide (max dose 600mg), 40 patients- thalidomide with high-dose dexamethasone	Newly diagnosed patients. those with CRAB criteria were excluded	None given in single-agent arm, in combination arm, 1 <sup>st</sup> 24 patients received 1mg OD coumadin, remaining 16 received treatment dose LMWH or coumadin	34% vs 18% with or without thalidomide
<b>Thalidomide combination therapy</b> (Barlogie, <i>et al</i> 2006)	Newly diagnosed MM randomized to melphalan-ASCT+/- thalidomide	Adequate performance status, renal failure not excluded	1 <sup>st</sup> 162 patients did not receive thromboprophylaxis, remaining 163- prophylactic LMWH	without LMWH, 24% vs 15% with LMWH
(Baz, <i>et al</i> 2005)	105 Newly diagnosed or relapsed patients- thalidomide, peglylated doxorubicin and vincristine	Life-expectancy <3 months, severely deranged liver function, impaired LV function	Aspirin 81mg OD PO, from the start of treatment, after 1 cycle or not at all	VTE-19% (aspirin from the start), 15% (from cycle 2) and 58% (no aspirin)
(Palumbo, <i>et al</i> 2011)	667 patients treated with thalidomide-containing regimen: if <65 yrs, bortezomib, thalidomide, and dexamethasone, or thalidomide and dexamethasone with ASCT, if >65 yrs, melphalan, prednisolone, and thalidomide with maintenance, or bortezomib, melphalan, thalidomide and prednisolone without maintenance	Previous venous or arterial thrombosis or high risk of bleeding	Aspirin 100mg OD PO, warfarin 1.25mg OD PO, or enoxaparin 40mg OD s/c	VTE rates (at 6 months) 6.4% for aspirin, 5% for LMWH and 8.2% for warfarin
(Schutt, <i>et al</i> 2005)	31 patients received thalidomide 400mg with vincristine, epirubicin and dexamethasone +/- ASCT	None stated	Not specified	26%
(Zangari, <i>et al</i> 2004)	Comparison between 98 patients receiving DT-PACE and 68 receiving VDT-PACE in the UARK 2001-12 and 2003-33 trials respectively (VDT-PACE = velcade, dexamethasone, thalidomide, doxorubicin, cisplatin, Adriamycin, cyclophosphamide and etoposide)	None stated	Not specified	10% in DT-PACE trial vs. 0% for VDT-PACE
(Zangari, <i>et al</i>	192 relapsed/refractory	None stated	Not specified	DVT occurred

2002)	patients received DT-PACE and 40 received DCEP-T (same regime as DT-PACE without doxorubicin)			in 16.5% in the DT-PACE arm vs. 2.5% in the DCEP-T arm
(Zervas, <i>et al</i> 2004)	39 newly diagnosed patients received thalidomide (200mg), vincristine, liposomal doxorubicin and dexamethasone	None stated	Not specified	DVTs in 10%
<b>Lenalidomide</b> (Richardson, <i>et al</i> 2009)	222 relapsed refractory patients received lenalidomide 30mg days 1-21	Non-myeloma related severe cytopenias, severe renal impairment, liver enzymes >3 times ULN	Not specified	DVT 4% PE 1%
<b>Lenalidomide-dexamethasone</b> (Zonder, <i>et al</i> 2005)	12 newly diagnosed patients received 25mg lenalidomide with high-dose dexamethasone, and 9 received dexamethasone with placebo	None stated	No prophylaxis	LD arm 75% VTE rate, placebo 0%
(Weber, <i>et al</i> 2007)	177 relapsed refractory patients received lenalidomide 25mg days 1-21 with high dose dexamethasone, versus 176 patients on a placebo arm	Non-myeloma related severe cytopenias, severe renal impairment, liver enzymes >3 times ULN	Thrombo-prophylaxis-physician discretion	VTE 14.7% vs 3.4% in treatment arm vs placebo
(Dimopoulos, <i>et al</i> 2007)	351 Relapsed refractory patients received lenalidomide days 21 days per 28 day cycle and high-dose dexamethasone, or placebo/dexamethasone	Non-myeloma related severe cytopenias, Liver enzymes >2 times ULN, severe renal impairment	Not specified	11.4% VTE vs. 4.6% in lenalidomide-dex arm
(Rajkumar, <i>et al</i> 2005)	34 newly diagnosed patients received lenalidomide 25mg days 1-21 and high dose dexamethasone	Cytopenias, severe renal impairment, unanticoagulated VTE	Aspirin 80mg or 325mg at clinician's discretion OD PO	9%
(Rajkumar, <i>et al</i> 2010)	445 newly diagnosed patients were randomized to lenalidomide 25mg days 1-21 with either high or low dose dexamethasone +/- ASCT	Severe cytopenias, renal impairment or liver impairment, current or past thrombosis, poor performance status	Thrombo-prophylaxis was recommended initially then mandated after the 1 <sup>st</sup> 266 patients due to high VTE rates	26% in high dose dex arm and 12% in the low dose arm
<b>Lenalidomide combination therapy</b> (Baz, <i>et al</i> 2006)	62 Newly diagnosed or relapsed patients receiving lenalidomide, pegylated doxorubicin and vincristine	Life-expectancy <3 months, Non-myeloma related cytopenias, liver enzymes >2 times ULN, severe renal impairment, impaired LV	Aspirin 81mg OD PO	3%



(Knop, <i>et al</i> 2006)	41 patients with relapsed refractory multiple myeloma received lenalidomide, adriamycin and dexamethasone	Adequate organ and bone marrow function required	Not specified	0%
(Larocca, <i>et al</i> 2012)	342 newly diagnosed patients received Melphalan, prednisolone and lenalidomide plus ASCT	Excluded if history of arterial thrombosis or VTE in past 12 months, contraindication to aspirin or LMWH, or active bleeding	Assigned to aspirin 100mg OD PO or enoxaparin 40mg OD s/c	2.27% in aspirin group, 1.2% in enoxaparin group
(Morgan, <i>et al</i> 2007)	21 heavily pre-treated relapsed refractory patients received lenalidomide 25mg OD days 1-21, cyclophosphamide weekly, and 40mg dexamethasone days 1-4 and 12-15	Not specified	Not specified	14%
(Palumbo, <i>et al</i> 2007)	54 newly diagnosed patients received oral mephehan and prednisolone days 1-4 and lenalidomide days 1-21	Creatinine clearance <20mls/min, severely deranged LFTs, severe cytopenias, amyloidosis, psychiatric illness	Aspirin 100mg OD PO	4.8%
(Stewart, <i>et al</i> 2015)	792 relapsed refractory patients received carfilzomib with lenalidomide and dexamethasone, or lenalidomide and dexamethasone (low-dose)	Moderate renal impairment, cytopenias, heart failure, grade 3-4 peripheral neuropathy	All patients received thromboprophylaxis-not specified	1 yr rate 13% in the carfilzomib arm vs. 6%
<b>Thalidomide or lenalidomide</b> (Bradbury 2017)	Cyclophosphamide, dexamethasone + thalidomide or lenalidomide +/- ASCT if eligible in 3838 newly diagnosed patients	Grade 2 or worse peripheral neuropathy, acute renal failure unresponsive to 72hrs of intravenous fluids	Thrombo-prophylaxis as per the IMWG 2008 guidelines	11.8%, no sig. difference between thal or len arms
<b>Pomalidomide</b> (Schey, <i>et al</i> 2004)	24 relapsed refractory patients received escalating doses of CC-4047 (pomalidomide)	Severe cytopenias, mod renal impairment	None	1 case- due to undiagnosed melanoma
(Streetly, <i>et al</i> 2005)	15 relapsed refractory patients received escalating doses of CC-4047 (pomalidomide)	None specified	None	20%
<b>Pomalidomide combination therapy</b> (Paludo, <i>et al</i> 2017)	50 relapsed refractory patients received pomalidomide 4mg days 1-21, weekly bortezomib and weekly dexamethasone 40mg	DVT not anticoagulated, poor performance status, pregnancy	325mg aspirin OD PO, or therapeutic LMWH or warfarin	10%

### **Pragmatic approach for VTE prophylaxis in myeloma**

Here we provide a pragmatic approach to managing a patient with myeloma who requires pharmacological thromboprophylaxis, taking into consideration the risk factors as proposed by the IMWG, current available evidence for the use of different anticoagulants in this setting, practicalities of managing the type of anticoagulant chosen, and situations where additional thrombotic risks may arise, such as the need for surgery, hospitalization and other reasons for poor mobility.

This approach is based on the available, albeit limited evidence, and would require future review and/or modification as new evidence becomes available. It represents the authors opinions only and not a formal guideline or recommendation.

We recommend risk stratification based on the IMWG model, with classification of patients into low- and high-risk groups. Since there are a group of patients who may fail standard dose thromboprophylaxis, we propose an additional group, which would be considered as very high-risk. This would include patients who have had a previous thrombosis, and those known to have antithrombin deficiency. The choice of anticoagulant would be (see Figure 1):

- Low-risk patients - prophylactic LMWH based on the current available data but aspirin may be chosen if patients do not prefer daily injections. Once evidence is available, aspirin may be substituted with a DOAC.
- High-risk patients - prophylactic weight-based LMWH or warfarin with an INR target of 2-3 are the drugs of choice. A prophylactic DOAC may be chosen in this group in the context of a clinical trial or according to patient wishes after appropriate counselling and consent regarding the unlicensed indication. If a DOAC is preferred, meticulous review of concomitant interacting medications and contraindications such as renal failure should be performed.
- Very high-risk patients - after assessment of bleeding risk and adjustment of any modifiable risk factors, a high prophylactic dose of LMWH (target anti-Xa of 0.4-.0.6 IU/ml) or therapeutic dose LMWH may be chosen until the period of greatest thromboembolic risk has passed. Given the evidence provide by Myeloma XI that the vast majority of VTEs occurred within the initial 6 month induction period, this may be a practical timeframe to apply (Bradbury 2017, C. A. Bradbury 2018).

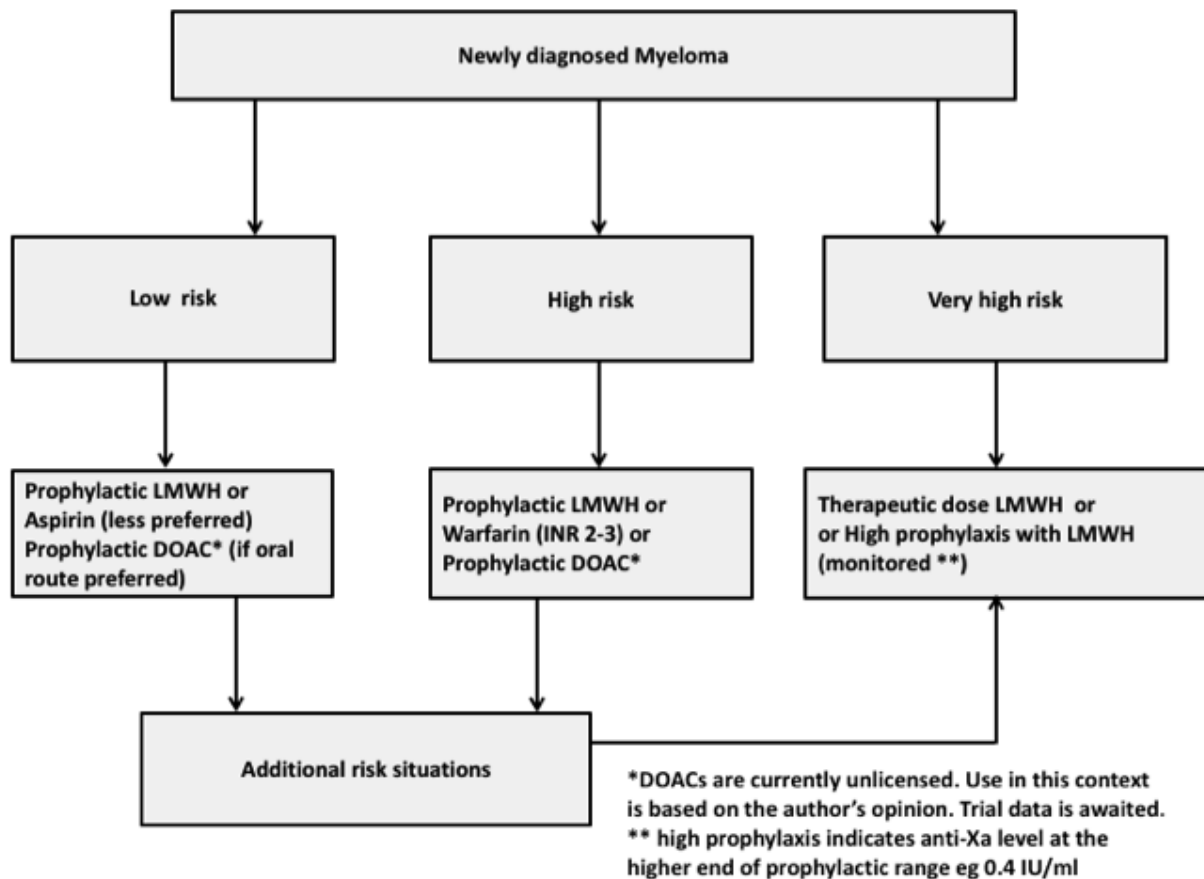


Figure 1. **Thrombosis risk assessment and anticoagulant choice in newly diagnosed multiple myeloma**

The duration of thromboprophylaxis has not been adequately studied but at least six months from the initial diagnosis is preferable. If IMiD-based treatment is being continued in the absence of high-dose dexamethasone or other chemotherapies, continued thromboprophylaxis should be discussed with the patient. This may be with aspirin, a DOAC or even continued prophylactic LMWH. In all cases, the dosing may need altering based on patient's initial risks of bleeding or thrombosis, and at regular intervals. For example, if the patient's mobility is restricted following myeloma-related fracture, a higher dose may need consideration, whereas renal impairment or thrombocytopenia may necessitate dose reduction.

### **Special considerations**

#### ***Renal disease***

Renal disease in multiple myeloma is common and variable, ranging from patients with mild proteinuria, to the nephrotic syndrome, with or without renal impairment. Renal failure occurs in 50% of patients during the course of their disease (Clark, *et al* 1999), yet patients with end-stage renal failure are poorly represented in trials. It is a prothrombotic state, with a multifactorial aetiology, due to

prothrombotic changes in the vascular endothelium, increased levels of inflammatory procoagulant factors and alterations in platelet physiology (Hughes, *et al* 2014). In patients with myeloma, and especially those with AL amyloidosis, proteinuria can contribute to increased thrombotic tendency, and this is most marked in those with nephrotic-grade proteinuria. Bever *et al.* reviewed 929 patients with AL amyloidosis presenting to a single-centre over a 10-year period, of whom 7% had documented VTE (Bever, *et al* 2016). A non-significant increase in VTE risk was observed if serum albumin was 30-40 g/dl (hazard ratio 2.16, CI 0.80-5.81). Patients with serum albumin of less than 30 g/dl, however had a hazard ratio of 4.30 for the development of thrombosis which was statistically significant (CI 1.60-11.55, p=0.0038). Increasing levels of proteinuria were also associated with increased VTE risk, although this only reached statistical significance at levels of more than 8g per day. Of 382 cases with nephrotic-grade proteinuria, VTE rate was 9.7%. Serum albumin level is inversely correlated with urinary protein loss, not only of albumin but also important endogenous antithrombotic proteins, in particular antithrombin III (AT). Overall, the studies on AL amyloidosis patients have found similar rates of thrombosis to those seen in myeloma, with high associated mortality noted (1 month mortality 20% in 1 study) (Halligan, *et al* 2006, Srkalovic, *et al* 2005). Given the association between nephrotic-grade proteinuria and clinically significant antithrombin deficiency, assessment of urine is important in myeloma patients not purely for the detection of M-proteins and light chains. Patients with documented AT deficiency and thrombosis provide an even greater management challenge (they are at extremely high risk of thrombosis and may require LMWH dosing alterations, as LMWH works by potentiating AT). We would suggest AT deficiency is worth excluding in those with thrombosis in the context of significant proteinuria (Kumar, *et al* 2012), and concurrent AL amyloidosis should be considered in these patients. This is of additional relevance due to the haemorrhagic deficiencies seen in amyloidosis. These have been more extensively studied than the thrombotic issues, and involve defective vascular integrity, acquired factor X deficiency and acquired von Willebrand syndrome (Bever, *et al* 2016), and clearly have to be borne in mind when managing thrombotic risk in affected individuals.

Separate to proteinuria and the nephrotic syndrome, chronic renal impairment is not only a risk factor for thrombosis, but subsequent anticoagulation also poses challenges in this demographic, who are at greater risk of haemorrhagic complications (Parker *et al* 2018). Most bleeding risk assessment scores include renal impairment as a risk factor. Analysis of over 14,000 patients enrolled in the RIETE registry (Registro Informatizado de Enfermedad Trombo Embolica) reported that, of the 20% who had active cancer, rates of fatal pulmonary embolism (PE) and fatal bleeding were increased compared to patients without malignancy, and renal insufficiency was identified as one of several independent risk factors for mortality (Trujillo-Santos, *et al* 2009).

In relation to anticoagulant treatment in patients with cancer and co-existing renal impairment, data from the CLOT trial (Lee, *et al* 2003) was reviewed in patients with moderate (CrCl 30-60ml/min) or severe (CrCl<30ml/min) renal impairment. 24% of the total group had some degree of renal impairment, but only 2% met criteria for 'severe' impairment. Major and minor bleeding episodes

occurred in 20% in the dalteparin group versus 24% of VKA-treated patients with significantly more VTE recurrences in the VTE group (17% versus 3%). Although based on this data, LMWH was concluded to be superior to warfarin in patients with cancer and renal impairment; patients with a creatinine three times or more above the upper limit of normal were excluded from the study. If LMWH is chosen in this setting, it also needs to be borne in mind that the various LMWHs are not identical in terms of their pharmacokinetic profiles in renal insufficiency. Prophylactic doses of enoxaparin have been shown to accumulate in patients with  $\text{CrCl} < 30 \text{ ml/min}$ , whereas tinzaparin and dalteparin do not. For this reason, dose reductions or monitoring might be required if enoxaparin is chosen (Atiq, *et al* 2015). Monitoring using an anti-Xa assay calibrated to LMWH is essential and is recommended in all antithrombotic therapy guidelines, with a target trough level of 0.1-0.3 IU/ml and peak of 0.5-1.0 IU/ml for treatment, while a peak level of 0.1-0.3 IU/ml would be ideal for prophylaxis (Hughes, *et al* 2014).

VKAs are not renally excreted, being metabolised by cytochrome P450 enzymes. However, renal failure causes downregulation of enzymatic activity and can therefore still alter warfarin's pharmacokinetic profile (Limdi, *et al* 2010). This may partly explain the poor INR control seen in patients with severe renal failure on warfarin (Chaaban, *et al* 2015, Kai, *et al* 2017, Yang, *et al* 2017), providing additional evidence against the use of VKAs in this setting. Furthermore, alongside the evidence of inferiority to LMWH, meta-analysis of studies comparing DOACs to VKAs has shown fewer haemorrhagic complications with DOACs in patients with moderate renal impairment ( $\text{CrCl}$  30-50ml/min) (van Es, *et al* 2014).

The DOACs in common usage have different licenses with respect to treatment of VTE in renal impairment. This has recently been reviewed (Parker, *et al* 2018). Specifically in relation to myeloma, rivaroxaban and apixaban are highly protein-bound in circulation, and therefore affected by hypoalbuminaemia which may develop in renal failure patients with proteinuria or nutritional deficiency. Since patients with renal impairment may require other drugs in addition to those specific for myeloma, and the fact that all four DOACs are to some extent metabolized by cytochrome P450 enzymes, careful drug selection is required. If a DOAC is chosen, close attention to drug monitoring may be necessary in this setting (Parker, *et al* 2018). Betrixaban, the most recent anti-Xa inhibitor on the market has the lowest renal clearance at only 11% and is not metabolized by the CYP 450 system. It has been FDA-approved for VTE prophylaxis in those with  $\text{CrCl} \geq 15 \text{ ml/min}$  without severe liver impairment (Huisman and Klok 2018). It has not yet been approved for prophylaxis by the EMA, and while it offers a potentially attractive future option for use in patients with renal failure, it should be noted that its long half-life (approximately 37 hours) may be of concern in those with a high bleeding risk.

### *Recurrent thrombosis*

There is a paucity of data on how best to manage recurrent VTE in cancer patients, and even less in those with myeloma specifically. What is abundantly clear, is that patients with cancer have high

recurrence rates despite anticoagulation of any form eg. In the Hokusai trial, 7.9% of edoxaban or 11.3% of dalteparin patients suffered a further VTE (Raskob, *et al* 2018). These rates are similar to those seen in patients with unprovoked events who discontinue anticoagulation. Similar findings have been seen in myeloma trials. In a cohort of 256 newly diagnosed myeloma patients, where LMWH, (enoxaparin 40 mg daily) was instituted as DVT prophylaxis in the thalidomide-treated patients (n = 68), DVT recurred in four patients (11%) (Zangari, *et al* 2004a), and the majority of patients in Myeloma XI (over 4000 patients in all) were on thromboprophylaxis at the time of VTE (Bradbury 2017, C. A. Bradbury 2018). This means that prophylactic LMWH does not fully eliminate the thrombotic risk in myeloma. The ISTH issued recommendations for patients with malignancy who suffer recurrent thrombosis on anticoagulation, giving the following options - switching from a VKA to LMWH, increasing the dose of LMWH by 20-25% if already in use, or to consider insertion of an inferior vena cava filter (Farge, *et al* 2016). These recommendations were based on results of a small, 70 patient, retrospective cohort study of patients with VTE on anticoagulation, alongside expert opinion *in lieu* of robust evidence. In this study, those on warfarin or prophylactic dose LMWH switched to therapeutic dose LMWH, whereas those on treatment dose LMWH received a 20-25% dose escalation for at least 4 weeks. Despite this, 8.6% of the cohort had a further VTE during a minimum of only 3 months follow up, and it should be noted that the group's median survival was less than one year (Carrier, *et al* 2009). General measures including assessment of compliance to pharmacological thromboprophylaxis, consideration of other prothrombotic conditions for example heparin-induced thrombocytopenia, and presence of mechanical compression from tumour masses are also routinely advised (Romualdi and Ageno 2016). For those on oral agents, gastrointestinal absorption should be reviewed alongside possible interactions with other medications being administered.

Most of the available information with respect to 'failure of anticoagulation' pertains to VKAs and LMWH. The Hokusai (Raskob, *et al* 2018) and SELECT-D (Young, *et al* 2018) trials provide evidence in support of use of DOACs in the therapeutic setting but are not specific to myeloma, nor VTE recurrence. 9% of the Hokusai group had a prior history of VTE, but whether this was in the context of malignancy is not known, and patients on therapeutic anticoagulation at time of thrombosis are specifically excluded. A case report of successful management of a myeloma patient with VTE on prophylactic aspirin and erratic INR control on warfarin was recently published (Oka, *et al* 2017), and it is likely that DOACs are being used more frequently in clinical practice in this setting.

The ISTH set up an international registry to increase the available data regarding this issue. 212 cancer patients with a recurrence of VTE despite anticoagulation with either unfractionated heparin, LMWH, fondaparinux or a VKA were monitored for 3 months. A small proportion (8%) had leukaemia, lymphoma or myeloma. 70% of the cohort had been therapeutically or supra-therapeutically anticoagulated at the time of VTE. 11% had a further event during follow-up, 8% had major bleeding and 27% died. Increasing anticoagulation intensity had no beneficial effect on recurrence rate, or a

significant association with increased haemorrhagic complications. As seen previously, rate of recurrence was higher with VKAs than LMWH (Schulman, *et al* 2015).

Evaluation of whether anticoagulation is in the therapeutic range is traditionally achieved using standard laboratory investigations eg. the International Normalized Ratio (INR) for VKA and anti-Xa levels for LMWH. However, use of global measures of coagulation may provide further, relevant information regarding the patient's overall haemostatic state. One group used thromboelastography (TEG), thrombin generation test (TGT), thrombodynamics (TD) and some standard laboratory parameters such as D-dimer levels, fibrinogen, activated partial prothrombin time (APTT) and prothrombin time (PT) in MM patients at diagnosis, during stem cell mobilisation, and in remission (Gracheva, *et al* 2015). D-dimer was significantly elevated, and global haemostasis tests showed patients to be hypercoagulable compared with normal controls whether at diagnosis or in remission. However, there was significant heterogeneity of results with some patients also demonstrated to be hypocoagulable. Patients undergoing stem cell mobilisation received infusional unfractionated heparin as VTE prophylaxis. Importantly, in 22%, at least 2 of the global tests of haemostasis showed no hypocoagulable features despite APTT levels in the target range, and some remained hypercoagulable suggesting a significant proportion of the patients assessed had evidence of heparin-resistance. If this finding were reproduced in a larger sample size, particularly in patients receiving LMWH, it would provide concerning evidence of lack of efficacy of current thromboprophylactic measures, at least in a subset of patients, which may be contributing to ongoing rates of VTE despite anticoagulation. It is likely that anti-Xa levels may not be fully reflective of global haemostasis in patients with recurrent VTE despite seemingly therapeutic LMWH anticoagulation, and more information is required regarding the practical utility of global tests of haemostasis in managing these challenging patients.

The findings from the ISTH registry along with evidence of heparin resistance in a significant minority of patients, suggests that therapeutic doses of LMWH do not offer sufficient protection for a subset of myeloma patients, and that mere dose escalation may not be an adequate strategy. Our approach in these patients is summarized in Figure 2. with suggestions for patients who may have been on warfarin, LMWH or a DOAC. Since currently, no better approaches are available in patients who are on therapeutic doses of LMWH who developed recurrent clots; we would choose the split dose strategy (ie. The full weight-based dose divided into two doses, given at 12 hour intervals) in addition to modifying thrombotic risk factors (mobilization, temporary interruption of IMiDs etc). Some of the rare causes of recurrent thrombosis on anticoagulation include antiphospholipid syndrome, vasculitis, vascular malformations and hyperhomocystenemia, which require due consideration (Thachil 2012).

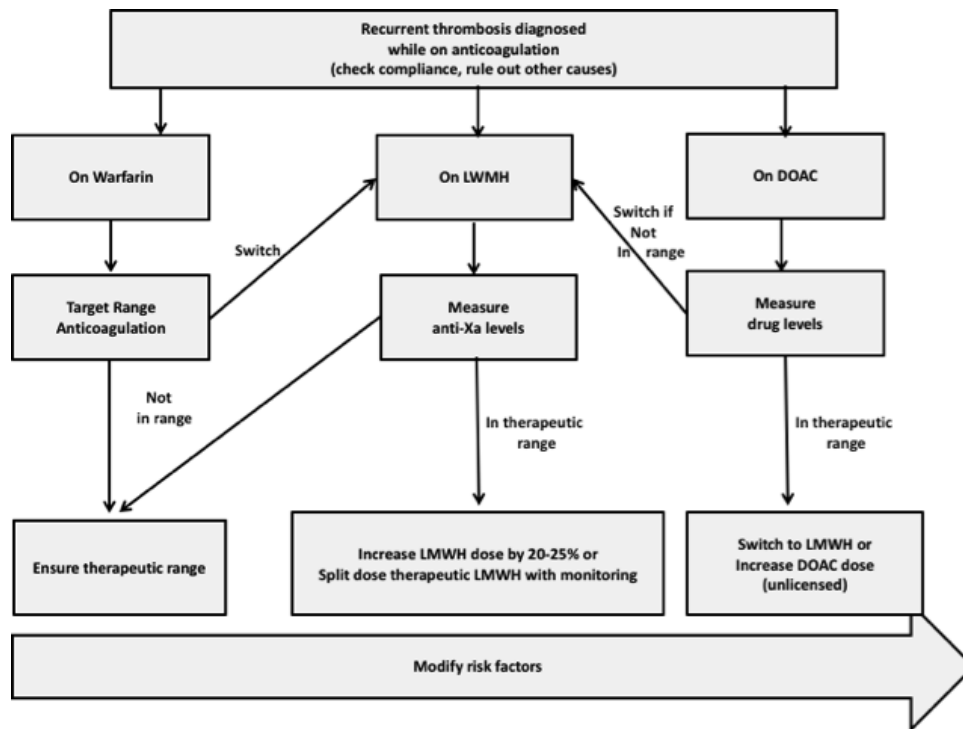


Figure 2. **Management of anticoagulation in recurrent thrombosis**

### *Spinal cord compression*

Spinal cord compression may occur in patients with myeloma as a result of vertebral lytic lesions or growth of compressive soft tissue masses. VTE risk in these patients is markedly increased by the combination of immobility, and need for surgical interventions, venous stasis due to loss of contraction of lower limb muscles, inflammatory prothrombotic changes stimulated by tissue damage, alongside all the usual myeloma-related risk factors. Reported rates of VTE in spinal cord injury are as high as 50% of patients (Teasell, *et al* 2009). Specific guidance relating to spinal cord compression in myeloma patients is lacking, however the NICE recommendations on management of metastatic spinal cord compression suggest mechanical thromboprophylaxis with thigh-high graduated compression stockings, unless contraindication eg. by sensory loss, or intermittent pneumatic compression devices with concomitant LMWH prophylaxis. Duration of thromboprophylaxis should be based on individual risk assessment, overall clinical condition, and whether the patient has regained normal mobility (NICE Clinical guidelines 2008).

### **Future directions**

Management of multiple myeloma has developed significantly in recent years with patients surviving for many years more than previously reported (Kumar, *et al* 2008). However, in this era of novel agents, patients are still dying from VTE-related complications, and despite current thromboprophylactic approaches, a significant proportion of patients are still expected to develop



thromboembolic disease as a sequelae of myeloma or its treatment, with those at highest risk not fully protected by the pharmacological agents administered as part of modern treatment protocols. The current recommendation for thromboprophylaxis in patients receiving IMiD-based regimens is low-dose aspirin if at low risk of thrombosis and LMWH if at high-risk, as per the IMWG 2008 model. If future models allow improved identification of those at the highest risk, either through use of novel thrombosis biomarkers, point of care testing, or presence of numerous clinical risk factors, thromboprophylaxis measures will need to adapt to reflect this, following confirmation of safety and efficacy in prospective RCTs. Data from the Hokusai trial suggests that DOACs may possibly confer greater protection than LMWH (Raskob, *et al* 2018), based on the reduction of VTE seen, however this evidence does not pertain to primary VTE prevention, nor is specific to myeloma, and further information is needed in order to improve management of these patients. Similarly more work can only provide us with better knowledge on how to deal with the special situations of renal impairment and spinal cord compression, where the risk of both thrombosis and haemorrhage are increased and carefully weighing the risks and benefits are crucial.

DS performed the literature review, wrote the first draft and made the edits for the final version. AR and CB critically reviewed the manuscript. JT conceived the review and critically reviewed the manuscript. All the authors approved the final version submitted

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Figure 1: Algorithm for risk stratification and choice of anticoagulants for patients with myeloma.  
LMWH- low molecular weight heparin; DOAC - direct oral anticoagulant

Figure 2 - Management of recurrent thrombosis while on anticoagulant therapy in patients with myeloma

LMWH- low molecular weight heparin; DOAC - direct oral anticoagulant