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Thrombosis in Patients with Myeloma Treated in the Myeloma IX and Myeloma XI Phase III Randomized Controlled Trials

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Abstract:
Newly diagnosed multiple myeloma (NDMM) patients treated with immunomodulatory drugs (IMiDs) are at high venous thrombosis (VTE) risk, but data are lacking from large prospective cohorts. We present thrombosis outcome data from Myeloma IX (n=1936) and Myeloma XI (n=4358), phase III randomized controlled trials for NDMM, treating transplant-eligible and ineligible patients before and after publication of thrombosis prevention guidelines. In Myeloma IX, compared to CTD (cyclophosphamide, thalidomide and dexamethasone), transplant-eligible patients randomized to CVAD induction (cyclophosphamide, vincristine, doxorubicin and dexamethasone) had higher VTE risk (22.5%(n=121/538) vs 16.1%(n=89/554), aHR:1.46,95%CI:1.11-1.93). For transplant-ineligible patients, compared to MP (melphalan and prednisolone), patients randomized to CTDa (attenuated CTD) induction had higher VTE risk (16.0%(n=68/425) vs 4.1%(n=17/419), aHR:4.25,95%CI:2.50-7.20). In Myeloma XI, there was no difference in VTE or arterial thrombosis risk between transplant-eligible pathways, CRD (cyclophosphamide, lenalidomide and dexamethasone) and CTD (VTE:12.2%(n=124/1014) vs 13.2%(n=133/1008), aHR:0.92,95%CI:0.72-1.18; arterial events:1.2%(n=12/1014) vs 1.5%(n=15/1008), aHR:0.80,95%CI:0.37-1.70). For transplant-ineligible patients, there was no difference in VTEs between CRDa (attenuated CRD) and CTDa (10.4%(n=95/916) vs 10.7%(n=97/910), aHR:0.97, 95%CI:0.73-1.29). However, arterial risk was higher with CRDa than CTDa (3.1%(n=28/916) vs 1.6%(n=15/910), aHR:1.91,95%CI:1.02-3.57). Thrombotic events occurred almost entirely within 6m of treatment initiation. Thrombosis was not associated with inferior progression-free or overall survival (OS), apart from inferior OS for patients with arterial events (aHR:1.53, 95%CI:1.12-2.08) in Myeloma XI. The Myeloma XI trial protocol incorporated IMWG thrombosis prevention recommendations and compared to Myeloma IX, more patients were on thromboprophylaxis (80.5% vs 22.3%) with lower VTE rates for identical regimens (CTD:13.2% vs 16.1%, CTDa:10.7% vs 16.0%). However, thrombosis remained frequent in spite of IMWG-guided thromboprophylaxis, suggesting new approaches are needed.

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Key Points

1. VTE risk is high for newly diagnosed Myeloma patients receiving treatment and only modestly reduced by IMWG-guided thromboprophylaxis.
2. VTE risk is equivalent for thalidomide and lenalidomide regimens, and in these clinical trials VTE was not associated with reduced PFS or OS.

Abstract

Newly diagnosed multiple myeloma (NDMM) patients treated with immunomodulatory drugs (IMiDs) are at high venous thrombosis (VTE) risk, but data are lacking from large prospective cohorts. We present thrombosis outcome data from Myeloma IX (n=1936) and Myeloma XI (n=4358), phase III randomized controlled trials for NDMM, treating transplant-eligible and ineligible patients before and after publication of thrombosis prevention guidelines. In Myeloma IX, compared to CTD (cyclophosphamide, thalidomide and dexamethasone), transplant-eligible patients randomized to CVAD induction (cyclophosphamide, vincristine, doxorubicin and dexamethasone) had higher VTE risk (22.5%(n=121/538) vs 16.1%(n=89/554), aHR:1.46,95%CI:1.11-1.93). For transplant-ineligible patients, compared to MP (melphalan and prednisolone), patients randomized to CTDa (attenuated CTD) induction had higher VTE risk (16.0%(n=68/425) vs 4.1%(n=17/419), aHR:4.25,95%CI:2.50-7.20). In Myeloma XI, there was no difference in VTE or arterial thrombosis risk between transplant-eligible pathways, CRD (cyclophosphamide, lenalidomide and dexamethasone) and CTD (VTE:12.2%(n=124/1014) vs 13.2%(n=133/1008), aHR:0.92,95%CI:0.72-1.18; arterial events:1.2%(n=12/1014) vs 1.5%(n=15/1008), aHR:0.80,95%CI:0.37-1.70). For transplant-ineligible patients, there was no difference in VTEs between CRDa (attenuated CRD) and CTDa (10.4%(n=95/916) vs 10.7%(n=97/910), aHR:0.97, 95%CI:0.73-1.29). However, arterial risk was higher with CRDa than CTDa (3.1%(n=28/916) vs 1.6%(n=15/910), aHR:1.91,95%CI:1.02-3.57). Thrombotic events occurred almost entirely within 6m of treatment initiation. Thrombosis was not associated with inferior progression-free or overall survival (OS), apart from inferior OS for patients with arterial events (aHR:1.53, 95%CI:1.12-2.08) in Myeloma XI. The Myeloma XI trial protocol incorporated IMWG thrombosis prevention recommendations and compared to Myeloma IX, more patients were on thromboprophylaxis (80.5% vs 22.3%) with lower

VTE rates for identical regimens (CTD:13.2% vs 16.1%, CTDa:10.7% vs 16.0%). However, thrombosis remained frequent in spite of IMWG-guided thromboprophylaxis, suggesting new approaches are needed.

Introduction

Venous thrombosis (VTE) has a well-established association with cancer and is one of the leading causes of death in cancer patients.[1] In addition to mortality risk, VTE is an important cause of long-term morbidity, impaired quality of life, adverse psychological impact and is a burden on health care resources.[2,3] Multiple myeloma (MM) is the second most common blood cancer and is associated with a high VTE risk.[4-7] A recent review of nearly 5,000 myeloma patients showed those with VTE to be at an increased risk of mortality at two and five years after diagnosis, independent of other known prognostic factors.[8]

A large retrospective study of over four million US veterans demonstrated a nine-fold increased deep vein thrombosis (DVT) risk in those with myeloma and a three-fold increased DVT risk in patients with Monoclonal Gammopathy of Uncertain Significance (MGUS).[9] Another large retrospective population-based study from Sweden demonstrated an increased VTE risk for patients with MM (adjusted hazard ratio (aHR) of 7.5, 4.6 and 4.1 at 1, 5 and 10 years respectively after MM diagnosis), and to a lesser extent, patients with MGUS (aHR 3.4, 2.1 and 2.1 at 1, 5 and 10 years respectively). Of interest, this group also showed an increased risk of arterial thrombosis for patients with MM (aHR 1.9, 1.5 and 1.5 at 1, 5 and 10 years respectively) and with MGUS (aHR 1.7, 1.3, 1.3 at 1, 5 and 10 years respectively).[7]

The pathogenesis of VTE in MM is complex and only partially understood; patients can develop thrombosis at any stage in the disease trajectory with the highest risk being in the first year from diagnosis.[6,9] The plasma cell cancer, its treatment and patient-related factors all contribute to the mechanism of thrombosis in MM.[5,10] Treatments for MM have improved over the last decade with the introduction of immunomodulatory drugs (IMiDs) e.g. thalidomide, lenalidomide and pomalidomide. However, these drugs further increase

VTE risk, as do corticosteroids which are included in most treatment regimens.[11,12] Newly diagnosed MM (NDMM) patients receiving initial treatment with IMiD and high-dose corticosteroid are at high thrombotic risk, but there is a vast range of reported incidences from heterogeneous studies and a lack of data from large prospective patient cohorts. In addition, it is not known whether the two most commonly used IMiDs in induction therapy combinations, thalidomide and lenalidomide, have the same thrombotic risk as they differ in potency and side effect profile. Recently, myeloma specific VTE risk assessment scores have been developed and validated (IMPEDE VTE and SAVED).[13-15] These scores help stratify VTE risk and may help identify patients who warrant thromboprophylaxis. The ability of the IMWG guidelines to discriminate VTE risk has been demonstrated in both the IMPEDE VTE and SAVED publications.

The optimal thrombosis prevention strategy for patients with MM at high VTE risk remains controversial. Data from randomized trials suggest aspirin, LMWH and therapeutic warfarin reduce risk with an acceptable bleeding risk, but it is not clear which of these strategies is better.[16-25] Emerging data suggest Apixaban thromboprophylaxis may be an option but this has not yet been compared to conventional approaches in a randomised trial.[10,26-28]

In 2008, the International Myeloma Working Group (IMWG) published guidance on the prevention of IMiD-associated thrombosis in myeloma.[12] These guidelines recommended that all patients should be risk assessed and offered LMWH thromboprophylaxis if they have ≥2 thrombosis risk factors or if receiving concurrent IMiD and high-dose corticosteroid, whereas those with ≤1 risk factors be offered aspirin. More recent guidelines have made consistent recommendations.[29,30] However, it is recognised that the guidelines are based on limited evidence and the expected risk reduction if they are implemented is unknown.[30] It is also unclear how deliverable the recommendations are in the "real world", for example whether daily LMWH injections are acceptable to patients and the logistics of initiating heparin is achievable for health care providers.

The MRC Myeloma IX and NCRI Myeloma XI trials are the largest randomized trials using IMiD and corticosteroid regimens for NDMM patients published to date. Myeloma IX

recruited patients before the IMWG thrombosis prevention guidance and Myeloma XI recruited afterwards. Here, we present the thrombotic outcome data from both trials.

Methods

Trial design and treatment

Myeloma IX and XI are phase III, UK-based, multicentre, open label, parallel group, randomized controlled trials for NDMM patients. Myeloma IX (ISRCTN684564111) recruited patients between May 2003 and November 2007. Myeloma XI (ISRCTN49407852) recruited patients between May 2010 and April 2016. The trials were approved by the national ethics review board (National Research Ethics Service, London, UK), institutional review boards of the participating centres, and the competent regulatory authority (Medicines and Healthcare Products Regulatory Agency, London, UK), and were undertaken according to the Declaration of Helsinki and the principles of Good Clinical Practice as espoused in the Medicines for Human Use (Clinical Trials) Regulations. All patients provided written informed consent. Inclusion criteria were similar in both trials and included adult patients with newly diagnosed and histologically confirmed symptomatic MM.

Both trials had pathways for transplant-eligible and transplant-ineligible patients with pathway choice made by individual physician/patient based on patient's performance status and co-morbidities, without age restrictions. Methods and results from both trials have been published previously.[31-35] In brief, transplant-eligible patients in Myeloma IX were randomized between cyclophosphamide, thalidomide and dexamethasone (CTD) or cyclophosphamide, vincristine, doxorubicin and dexamethasone (CVAD) prior to autologous stem cell transplant (ASCT). Transplant-ineligible patients were randomized between attenuated CTD (CTDa) or melphalan plus prednisolone (MP) induction chemotherapy. After initial therapy, there was a randomization between thalidomide maintenance and observation in both pathways. All patients were also randomized to receive a bisphosphonate, either sodium clodronate or zoledronic acid.

Transplant-eligible patients in Myeloma XI were randomized between CTD and cyclophosphamide, lenalidomide and dexamethasone (CRD). There was a second randomization for patients achieving a partial or minimal response between intensification with cyclophosphamide, bortezomib and dexamethasone (CVD) or no further therapy prior to ASCT. Patients with stable or progressive disease underwent intensification therapy prior to ASCT whilst patients with a very good partial response or complete response proceeded directly to ASCT. Transplant-ineligible patients were randomized between CTDa and attenuated CRD (CRDa). Transplant-ineligible patients also underwent the intensification randomization. Patients in both pathways were randomized between lenalidomide (+/- vorinostat) and observation. The induction randomization of the transplant-eligible pathway of the Myeloma XI trial was amended in June 2013 to include a randomization between the response-adapted approach described above (CTD/CRD +/- CVD) and the quadruplet carfilzomib, cyclophosphamide, lenalidomide and dexamethasone (KCRD).

VTE prophylaxis

The Myeloma IX trial protocol did not include specific thrombosis prevention recommendations, although it was stated that anticoagulation should be considered in those at high-risk for VTE with either warfarin or LMWH. In contrast, the Myeloma XI trial protocol incorporated IMWG thrombosis prevention guidance and specified that all patients should receive thromboprophylaxis for at least the first three months of treatment.[12] It was recommended that low-risk patients should receive aspirin whereas high-risk patients should receive LMWH and definition of high VTE risk followed IMWG guidance. [12]

Collection of VTE and arterial events

The objectives of this secondary analysis of Myeloma IX and XI were: to estimate the frequency, incidence and types of thrombosis events occurring on trial according to baseline

characteristics, trial pathway and treatment; to investigate the thromboprophylaxis received prior to thrombosis events according to treatment and thrombosis risk category prior to the event; and to estimate the median progression-free survival (PFS) and overall survival (OS) according to thrombosis occurrence.

In Myeloma IX, thrombotic events were collected from the adverse events (AE) case report form (CRF) and follow-up CRFs which included a thromboembolism section. In Myeloma XI, thrombotic events were collected from a specific thromboembolism CRF. Treatment CRFs also included indication of the occurrence of thromboembolism. For both trials, thrombosis events categorised as 'other' site were reviewed by a clinician to determine if they were venous or arterial events.

Statistical analysis

Analyses were carried out separately for each trial and pathway. In Myeloma IX, only VTEs were analysed due to the very low frequency of arterial events recorded (n=11). In Myeloma XI, both venous and arterial thrombosis were analysed. Analysis of patients receiving KCRD in Myeloma XI was performed using only patients contemporaneously randomized to CTD and CRD and included only VTE.

Analyses were conducted using the safety population, which included all patients who received at least one dose of study treatment. This population classifies patients according to the treatment that they have received rather than to which they were randomized to receive.

Baseline characteristics were compared between those experiencing and not experiencing a thrombosis event. Continuous baseline variables were evaluated with a two-sample t-test and categorical baseline variables were evaluated with a chi-squared test; the non-parametric equivalent was used where appropriate.

The Fine and Gray competing risks regression model compared the hazard of thrombosis events by treatment group accounting for the minimisation factors, excluding recruiting centre (Myeloma IX: haemoglobin, corrected serum calcium, serum creatinine and platelets; Myeloma XI: β_2 microglobulin, haemoglobin, corrected serum calcium, serum creatinine and platelets), with unrelated death, defined as death without a preceding thrombosis event, specified as a competing risk.

Person-years on trial was calculated as the sum of all patients, receiving at least one dose of study treatment, time in years from randomization to death or last date known to be alive. The incidence was calculated with the number of events as the numerator and the number of person-years on trial as the denominator. Confidence intervals for incidence were calculated using approximations to the Poisson distribution.

Cumulative incidence function (CIF) curves of thrombosis events split by treatment group were estimated by non-parametric maximum likelihood estimation and compared by Gray's test, accounting for unrelated deaths as a competing risk.

Site of thrombosis, thrombosis risk and thromboprophylaxis were summarised in those who had an event. Thromboprophylaxis was also assessed in patients who had not had an event in Myeloma IX; this data was not available for Myeloma XI.

PFS and OS were compared between those who did and did not experience a thrombosis event using the Kaplan-Meier method and Cox regression models and hazard ratios were estimated, accounting for the minimisation factors, excluding recruiting centre.

Statistical analyses were performed using SAS (version 9.4). All reported p values are two-sided and considered significant at the 5% significance level.

Results

The median follow-up after randomization for this analysis was 71 months (IQR:60-83 months) in Myeloma IX and 60 months (IQR:48-77 months) in Myeloma XI. In both trials, the majority of the events occurred during induction (96.2% and 83.8% of events in Myeloma IX and Myeloma XI, respectively). The median time to first VTE in Myeloma IX was 2.2 months (IQR:1.31-3.44 months) and in Myeloma XI was 2.9 months (IQR:1.59-4.73 months).

In the Myeloma IX trial, VTE occurred in 15.2% of all patients receiving treatment (368 events in n=295/1936), 19.2% (n=210/1092) of transplant-eligible patients and 10.1% (n=85/844) of transplant-ineligible patients.

In the Myeloma XI trial, 13.7% of all patients receiving treatment suffered at least one thrombotic event ((746 events in n=599/4358), 12.2% (n=532) VTE and 1.8% (n=79) arterial thrombosis). Of note some patients suffered both VTEs and arterial events. Of transplant-eligible patients, thrombotic events occurred in 14.7% ((n=371/2532), 13.4% VTE (n=340) and 1.4% arterial (n=36)). Of transplant-ineligible patients, thrombotic events occurred in 12.5% ((n=228/1826), 10.5% VTE (n=192) and 2.4% arterial (n=43))**.**

There were a very small number of peri-transplant associated thrombotic events in both trials. In the 100 days after the administration of melphalan (autograft conditioning) there were 3 thrombotic events in Myeloma IX and 17 in Myeloma XI.

Baseline characteristics

The baseline characteristics for the safety population of patients within each trial and pathway are similar (**supplementary Table 1**). In both trials, transplant-eligible patients were younger than transplant-ineligible patients.

In Myeloma IX, sex, age and paraprotein type were significantly different between patients who did and did not experience a VTE; no other characteristics differed (**Table 1**)**.** Compared to patients who did not develop thrombosis, the patients developing thrombosis were younger, more likely to be female and more likely to have an IgG paraprotein. When the transplant-eligible and ineligible pathways were analysed separately, only paraprotein type differed in the transplant-eligible pathway and only sex differed in the transplant-ineligible pathway (**supplementary Table 2**).

In Myeloma XI, β_2 microglobulin and haemoglobin were significantly different between patients who did and did not experience a thrombosis event (**Table 1**). Compared to patients without thrombosis, the patients with thrombosis had a higher haemoglobin and lower β_2 microglobulin. When the transplant-eligible and ineligible pathways were analysed separately, sex, age, WHO performance status, β_2 microglobulin, calcium, haemoglobin and light chain type were significantly different according to thrombosis incidence within the transplant-eligible pathway (**supplementary Table 3**). No baseline characteristics differed according to thrombosis incidence within the transplant-ineligible pathway.

Thrombosis events according to treatment group

In the Myeloma IX transplant-eligible pathway, there was a higher VTE risk in patients receiving CVAD than CTD (22.5% (n=121/538) vs 16.1% (n=89/554), aHR: 1.46, 95%CI:1.11-1.93). For patients in the transplant-ineligible pathway, there was a higher VTE risk in patients receiving CTDa than MP (16.0% (n=68/425) vs 4.1% (n=17/419), aHR: 4.25, 95%CI:2.50-7.20). Within the maintenance phase, there were few thrombotic events and no difference in the number of patients with VTE between the thalidomide maintenance and the observation only groups (1.5% (n=6/391) vs 1.7% (n=7/402), p=0.82).

In the Myeloma XI transplant-eligible pathway, there was no difference in VTE risk between CRD and CTD (12.2% (n=124/1014) vs 13.2% (n=133/1008), aHR:0.92, 95%CI:0.72-1.18). In the KCRD treatment group, 16.3% (n=83/510) of patients experienced a VTE which was not significantly different to concurrently randomised patients receiving CRD (aHR:0.79, 95%CI:0.53-1.18) or CTD (aHR:1.02, 95%CI: 0.7-1.47). For patients in the transplant-ineligible pathway, there was no difference in VTE risk between CRDa and CTDa (10.4% (n=95/916) vs 10.7% (n=97/910), aHR:0.97, 95%CI:0.73-1.29).

In the Myeloma XI transplant-eligible pathway, there was no difference in risk of arterial thrombosis between CRD and CTD (1.2% (n=12/1014) vs 1.5% (n=15/1008), aHR:0.80, 95%CI:0.37-1.70). For patients in the transplant-ineligible pathway, there was a higher risk of arterial thrombosis in patients receiving CRDa than CTDa (3.1% (n=28/916) vs 1.6% (n=15/910), aHR:1.91, 95%CI:1.02-3.57).

Within the maintenance phase, significantly more patients had a VTE in the lenalidomide maintenance group than the observation group although the absolute incidence was very low (4.1% (n=44/1082) vs 0.6% (n=5/889), p<0.0001). Arterial events were also more frequent in those receiving lenalidomide maintenance than observation (1.3% (n=14/1082) vs 0.3% (n=3/889), p=0.022).

Incidence rate of thrombosis, comparison of equivalent treatment regimens in Myeloma IX and Myeloma XI trials

The VTE incidence rate for patients receiving CTD was slightly higher in Myeloma IX than Myeloma XI (5.4 events per 100 person-years (/100PY) (95%CI:4.5-6.5) vs 4.3 events/100PY (95%CI:3.7-5.0)). The VTE incidence rate for patients receiving CTDa was higher in Myeloma IX than Myeloma XI (7.6 events/100PY (95%CI:6.2-9.5) vs 4.2 events/100PY (95%CI:3.4-5.0)).

Cumulative incidence of thrombosis

Across both trials, and all treatments, the cumulative incidence of VTE increases most rapidly during the first 6 months post-randomization, after which it plateaus (**Figure 1**). All plots in Figure 1 have been cut at 60 months because all curves remain unchanged after this point.

In Myeloma IX, the 6-month VTE cumulative incidence was higher in the CVAD group than the CTD group (20.7% (95%CI:17.3%-24.1%) vs 15.0% (95%CI:12.0%-18.0%), Grey's test p=0.006). Additionally, the 6-month VTE cumulative incidence was higher in the CTDa group than the MP group (15.6% (95%CI:12.1%-19.0%) vs 2.2% (95%CI:0.76%- 3.55%), Grey's test p<0.0001).

In Myeloma XI, the 6-month VTE cumulative incidence was comparable between treatment groups (10.7% for CRD (95%CI:8.77%-12.6%), 11.7% for CTD (95%CI:9.69%-13.7%), Grey's test p=0.54). Additionally, there was no difference between the CIFs for KCRD, CRD and CTD (Grey's test p=0.46). This was also the case within the transplant-ineligible pathway (8.7% for CRDa (95%CI:6.83%-10.5%) and 8.7% for CTDa (95%CI:6.83%-10.5%), Grey's test p=0.82).

For arterial events, the 6-month cumulative incidence was similar between groups in the transplant-eligible pathway (0.7% for CRD (95%CI:0.18%-1.21%) and 0.9% for CTD (95%CI:0.31%-1.48%), Grey's test p=0.56), but in the transplant-ineligible pathway, the 6-month cumulative incidence of arterial events was greater in the CRDa group than the CTDa group (2.2% (95%CI:1.25%-3.16%) vs 0.9% (95%CI:0.28%-1.52%), Grey's test p=0.05) (**supplementary Figure 2**).

Thrombosis site

Within both trials and pathways, the most common sites of thrombosis were DVT and pulmonary embolism (PE) (**Table 2).** However, for patients randomized to CVAD, line associated VTE was the most common thrombosis site (37.1%, n=59/159 events), and line associated VTE was almost exclusively restricted to patients treated with CVAD (96.7% of all line associated VTEs in Myeloma IX). There were no other clear differences in the patterns of VTE presentations according to regimens.

Thromboprophylaxis prior to Thrombosis

In Myeloma IX, prior to the VTE event, 22.3% of patients received thromboprophylaxis (**Table 3**). Where thromboprophylaxis was given, treatment dose warfarin was given most frequently and patterns of thromboprophylaxis were similar between treatment groups. Of the patients who did not develop VTE, 19.7% received thromboprophylaxis, with therapeutic warfarin given most frequently.

In Myeloma XI, prior to the VTE event, 80.5% of patients received thromboprophylaxis (**Table 3**). Where thromboprophylaxis was given, LMWH was given most frequently. Patterns of thromboprophylaxis were similar between treatment groups.

VTE risk assessment prior to thrombosis

In Myeloma IX, prior to thrombosis, 21.0% of patients had been assessed as high VTE risk and 79.0% as low-risk, but the patterns of thromboprophylaxis were similar between these groups (**Table 4**).

In Myeloma XI, prior to VTE, 54.7% had been assessed as high VTE risk and 45.3% as low-risk. Thromboprophylaxis was not given to 13.7% of high-risk patients and 20.7% of low-risk patients. Where thromboprophylaxis was given, slightly more high-risk patients were on thromboprophylaxis and of these more received LMWH and fewer received aspirin than low-risk patients (**Table 4**).

Progression-free survival

There was no difference in PFS for patients developing VTE compared to those who did not in either trial (**Figure 2**) (IX aHR:0.92, 95%CI:0.80-1.05; XI aHR:0.92, 95%CI:0.83-1.03). There was also no difference in PFS for patients developing arterial thrombosis in Myeloma XI compared to those who did not (**supplementary Figure 3**) (aHR:1.12, 95%CI:0.86-1.47)**.**

Overall Survival

There was no difference in OS for patients developing VTE compared to those who did not in either trial (**Figure 3**) (IX aHR:0.87, 95%CI:0.74-1.02; XI aHR:0.90, 95%CI:0.78-1.04). In Myeloma IX, aHR for OS of patients with VTE remains virtually unchanged if results are adjusted for bisphosphonate allocation, zoledronate or clodronate (aHR of 0.88, (95%CI: 0.75-1.03). In Myeloma XI, there was no bisphosphonate randomisation and patients received bisphosphonate as standard of care.

In Myeloma XI, there was an increased mortality risk for patients developing arterial thrombosis (**supplementary Figure 4**) (aHR:1.53, 95%CI:1.12-2.08).

Discussion

Previous evidence from large retrospective cohorts has demonstrated that patients with myeloma are at increased risk of venous and arterial thrombosis, particularly in the first year after diagnosis.[7,9] NDMM patients receiving initial treatment with IMiD and corticosteroid are at particularly high thrombotic risk.[36] However, the range of reported incidences is very broad with unclear timing of risk, reflecting that the data arises from heterogeneous, relatively small studies. There is a need for data from large prospective cohorts to better define this risk. Myeloma IX and XI are the largest randomized trials for first line treatment of NDMM patients using regimens that include IMiD with corticosteroid and therefore add significant new data to the literature. In addition, Myeloma IX and XI

recruited patients before and after the IMWG VTE prevention guidance[12] respectively, allowing indirect evaluation of the impact of these recommendations by comparison of identical regimens used in both trials.

Both trials confirm and highlight the significant thrombosis risk for NDMM patients, with nearly all events occurring within 6 months of treatment initiation, regardless of treatment regimen. Data from Myeloma IX allows comparison between IMiD/corticosteroid containing induction to alternative regimens. For transplant-eligible patients, it is perhaps surprising that those treated without IMiD, using CVAD, had an even higher rate of thrombosis than those treated with CTD. The high thrombotic rate of CVAD for NDMM patients may in part relate to the high-dose dexamethasone and anthracycline chemotherapy (both known to contribute to VTE risk) but perhaps more importantly, the requirement of a long-term (3-6 months) central line for administration unlike the alternative "oral only" regimens. Of interest, in Myeloma IX, line related-VTEs were almost exclusively restricted to CVAD treated patients and represented 37.1% of VTE events in the CVAD group. For transplant-ineligible patients, as expected, thrombosis risk was far higher for the IMiD containing regimen, CTDa, than for MP, although even patients treated with MP, were at higher VTE risk than the expected background population (<1%/year).[37]

Thalidomide and lenalidomide are the most commonly used IMiDs for myeloma treatment. Although structurally similar, lenalidomide is more potent with a different side effect profile and it was not previously known whether the two drugs had equivalent thrombotic risk. A recent retrospective cohort (n=2397) suggested the risk of venous and arterial events was the same for both drugs when used for NDMM patients with very few of these patients (<20%) receiving thromboprophylaxis.[38] Data from Myeloma XI allows a direct comparison between lenalidomide and thalidomide treatment regimens for NDMM patients in a large prospective randomized NDMM patient cohort. In both transplant-eligible and ineligible patients, there was no difference in VTE risk between thalidomide and lenalidomide containing combination regimens and no difference in arterial event rate with CRD vs CTD. Patients receiving CRDa had a higher rate of arterial thrombosis than those treated with

CTDa but this needs to be interpreted with caution due to the low incidence of arterial events, which could also be affected by underreporting.

In the Myeloma IX trial, thalidomide maintenance did not increase the risk of thrombosis but in contrast, in Myeloma XI lenalidomide maintenance increased the risk of venous and arterial thrombosis. However, thalidomide maintenance was only delivered for a median of 7 months in Myeloma IX, as many patients stopped prior to progression due to (non-VTE) toxicity.[39] In contrast, within the lenalidomide maintenance phase of Myeloma XI, patients had a median of 18 cycles. Although lenalidomide increased the risk of thrombosis compared to observation, the absolute risk was low and far less than when used within induction as part of CRD or CRDa, probably due to the higher disease burden and additional corticosteroid in induction.

Previous data on large retrospective cohorts demonstrated that arterial and venous thrombosis were associated with inferior survival in myeloma.[40] In contrast to this, in both the Myeloma IX and XI trials, VTE events were not associated with an inferior OS. It is possible that this reflects differences between clinical trial and "real world" patient cohorts. Although both Myeloma clinical trials included a proportion of elderly patients with poor performance status within the transplant ineligible pathways, this may not reflect the full spectrum of frailty and comorbidity in non-trial patients. It is also important to recognise there may be other important adverse impacts of VTE such as chronic morbidity, impaired quality of life and psychological impact, but these have not been assessed in this study. In Myeloma XI, arterial events were associated with reduced OS, consistent with previous evidence. Thrombotic events (arterial or venous) did not adversely impact PFS, which suggests no meaningful reductions, delays or omissions of myeloma directed treatment resulted from the thrombotic events.

Myeloma IX recruited patients prior to the IMWG thrombosis prevention guideline[12] and accordingly there was no specific thrombosis prevention recommendation with only a

minority of patients on thromboprophylaxis, predominantly with warfarin. Myeloma XI recruited patients after the IMWG guidance and the trial protocol contained consistent recommendations, with the majority of patients receiving thromboprophylaxis prior to thrombosis, predominantly with LMWH and aspirin rather than warfarin. When identical treatment regimens were compared between trials (CTD and CTDa), the risk of VTE was less in Myeloma XI compared to Myeloma IX. However, in spite of implementation of IMWG guidance and widespread thromboprophylaxis, VTE incidence remained high with only a modest reduction between trials.

In both trials, patterns of thromboprophylaxis prior to VTE events did not significantly differ between treatment groups. Although in Myeloma XI, patients identified as high VTE risk prior to their event were more likely to be on preceding thromboprophylaxis, the differences in thromboprophylaxis patterns between high and low risk patients were surprisingly small. This suggests additional factors are considered when making thromboprophylaxis decisions, which may include patient and clinician choice, logistical difficulties with LMWH daily injections and bleeding risk.

Overall, these findings suggest that patients with NDMM remain at unacceptably high VTE risk in spite of implementation of IMWG-guided thromboprophylaxis. Therefore, new approaches are needed, particularly in the initial 6 months of treatment.

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Author contributions

JAC, GHJ and GJM were chief investigators of the MRC Myeloma IX study. GHJ, FED and GJM were chief investigators of the NCRI Myeloma XI study. AH and AP coordinated the data collection and regulatory and governance requirements. ZC, DAC and CAB developed and carried out the statistical analysis plan. MFK, MTD, RGO and GJM coordinated the central laboratory investigations. GHJ, FED, CP, JRJ, MWJ, GC, MFK, RGO and GJM participated in recruitment of patients. MFK, MTD, RGO and GJM coordinated the central laboratory investigations. CAB, ZC, CP, GC and GHJ developed the first drafts of the manuscript. All authors contributed to the review and amendments of the manuscript for important intellectual content and approved this final version for submission.

Conflicts of interest

CAB reports consultancy fees, honoraria and speakers' bureau fees from BMS Pfizer and Novartis, Janssen, Ablynx and funds to attend conferences from Bayer, Novartis and Amgen

ZC reports grants and non-financial support from Celgene, Merck Sharpe & Dohme, Amgen and Takeda, during the conduct of the study.

GC has received consultancy fees, honoraria, research funding, and speakers' bureau fees from Takeda, Celgene Corporation, Janssen and Amgen; consultancy fees and honoraria from Glycomimetics and Bristol-Myers Squibb; and consultancy fees, honoraria, and speakers' bureau fees from Sanofi.

CP reports grants from Celgene, during the conduct of the study; and personal fees and non-financial support from Amgen, Takeda Oncology, Janssen and Celgene, outside the submitted work.

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AP declares no competing interests.

MWJ has received consultancy fees, honoraria, travel support, and research funding from Janssen; consultancy fees, honoraria, and travel support from Takeda and Amgen; consultancy fees, honoraria, and research funding from Celgene Corporation; and consultancy fees and honoraria from Novartis.

JRJ has received honoraria and research funding from Celgene Corporation.

MTD has equity ownership in, and is on the board of directors and advisory committee of Abingdon Health.

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Results Tables

Table 1. Myeloma IX and Myeloma XI baseline characteristics by VTE occurrence

	Myeloma IX				Myeloma XI			
Characteristic	**Thrombosis (n=295)**	**No thrombosis (n=1641)**	**Total (n=1936)**	**P**	**Thrombosis (n=599)**	**No Thrombosis (n=3759)**	**Total (n=4358)**	**P**
Sex								
Male	154 (52.2%)	996 (60.7%)	1150 (59.4%)	0.0063	373 (62.3%)	2178 (57.9%)	2551 (58.5%)	0.0458
Female	141 (47.8%)	645 (39.3%)	786 (40.6%)		226 (37.7%)	1581 (42.1%)	1807 (41.5%)	
Age								
Mean (SD)	61.8 (10.07)	65.0 (10.17)	64.5 (10.22)	<0.0001	65.5 (9.67)	65.7 (10.33)	65.7 (10.24)	0.5952
Median (Range)	62.0 (31.0, 87.0)	66.0 (31.0, 89.0)	65.0 (31.0, 89.0)		67.0 (37.0, 89.0)	67.0 (28.0, 92.0)	67.0 (28.0, 92.0)	
Ethnicity								
White	292 (99.0%)	1586 (96.6%)	1878 (97.0%)	0.4425	576 (96.2%)	3498 (93.1%)	4074 (93.5%)	0.2801
Black (black Caribbean, black African, other)	1 (0.3%)	26 (1.6%)	27 (1.4%)		6 (1.0%)	69 (1.8%)	75 (1.7%)	
Asian (Indian, Pakistani, Bangladeshi, other)	1 (0.3%)	14 (0.9%)	15 (0.8%)		5 (0.8%)	87 (2.3%)	92 (2.1%)	
Other	1 (0.3%)	15 (0.9%)	16 (0.8%)		4 (0.7%)	35 (0.9%)	39 (0.9%)	
Unknown	0 (0.0%)	0 (0.0%)	0 (0.0%)		8 (1.3%)	70 (1.7%)	78 (1.8%)	
WHO performance status								
0	79 (26.8%)	386 (23.5%)	465 (24.0%)	0.4739	187 (31.2%)	1359 (36.2%)	1546 (35.5%)	0.1610
1	134 (45.4%)	737 (44.9%)	871 (45.0%)		248 (41.4%)	1471 (39.1%)	1719 (39.4%)	
2	51 (17.3%)	313 (19.1%)	364 (18.8%)		102 (17.0%)	543 (14.4%)	645 (14.8%)	

	Myeloma IX				Myeloma XI			
Characteristic	Thrombosis (n=295)	No thrombosis (n=1641)	Total (n=1936)	P	Thrombosis (n=599)	No Thrombosis (n=3759)	Total (n=4358)	P
3	29 (9.8%)	169 (10.3%)	198 (10.2%)		28 (4.7%)	178 (4.7%)	206 (4.7%)	
4	1 (0.3%)	21 (1.3%)	22 (1.1%)		3 (0.5%)	19 (0.5%)	22 (0.5%)	
Missing	1 (0.3%)	15 (0.9%)	16 (0.8%)		31 (5.2%)	189 (5.0%)	220 (5.0%)	
β2 microglobulin (mg/l)								
Mean (SD)	5.7 (5.10)	6.1 (6.02)	6.0 (5.89)	0.3240	4.8 (3.48)	5.3 (4.37)	5.2 (4.26)	0.0167
Median (Range)	4.1 (0.2, 58.0)	4.4 (0.1, 114.1)	4.4 (0.1, 114.1)		3.7 (0.9, 33.9)	4.0 (0.0, 88.0)	4.0 (0.0, 88.0)	
Missing	27	135	162		221	1350	1571	
Creatinine (µmol/l)								
Mean (SD)	117.6 (68.15)	118.0 (61.70)	118.0 (62.70)	0.2553	98.6 (46.57)	101.1 (55.04)	100.7 (53.95)	0.8659
Median (Range)	97.0 (49.0, 495.0)	100.0 (2.4, 468.0)	100.0 (2.4, 495.0)		86.0 (32.0, 390.0)	86.0 (32.0, 609.0)	86.0 (32.0, 609.0)	
Missing	12	55	67		0	1	1	
Calcium (µmol/l)								
Mean (SD)	2.4 (0.26)	2.4 (0.70)	2.4 (0.65)	0.3303	2.4 (0.21)	2.4 (0.25)	2.4 (0.25)	0.0826
Median (Range)	2.4 (1.6, 3.5)	2.4 (1.3, 26.4)	2.4 (1.3, 26.4)		2.4 (1.6, 3.6)	2.4 (1.3, 4.9)	2.4 (1.3, 4.9)	
Missing	11	65	76		0	3	3	
Platelets (*10/l)								
Mean (SD)	254.0 (94.80)	247.5 (97.60)	248.5 (97.18)	0.2924	244.0 (95.22)	245.8 (96.87)	245.6 (96.64)	0.6221
Median (Range)	241.0 (43.0, 642.0)	235.0 (15.0, 825.0)	237.0 (15.0, 825.0)		234.0 (3.0, 1112.0)	235.0 (2.0, 1093.0)	234.0 (2.0, 1112.0)	
Missing	0	1	1		0	0	0	
Haemoglobin g/dl								
Mean (SD)	10.7 (1.86)	10.8 (3.43)	10.8 (3.24)	0.5868	11.1 (1.94)	10.7 (1.88)	10.8 (1.89)	0.0001
Median (Range)	10.7 (6.5, 17.8)	10.5 (4.0, 95.0)	10.6 (4.0, 95.0)		10.9 (5.2, 16.8)	10.7 (3.3, 17.4)	10.7 (3.3, 17.4)	
Missing	0	1	1		1	1	2	
Paraprotein type								
IgG	193 (65.4%)	962 (58.6%)	1155 (59.7%)	0.0430	372 (62.1%)	2296 (61.1%)	2668 (61.2%)	0.1563
IgA	59 (20.0%)	378 (23.0%)	437 (22.6%)		138 (23.0%)	938 (25.0%)	1076 (24.7%)	
IgM	0 (0.0%)	8 (0.5%)	8 (0.4%)		1 (0.2%)	15 (0.4%)	16 (0.4%)	

Characteristic	Myeloma IX				Myeloma XI			
	Thrombosis (n=295)	No thrombosis (n=1641)	Total (n=1936)	P	Thrombosis (n=599)	No Thrombosis (n=3759)	Total (n=4358)	P
IgD	9 (3.1%)	27 (1.6%)	36 (1.9%)		1 (0.2%)	34 (0.9%)	35 (0.8%)	
Non-secretor	6 (2.0%)	26 (1.6%)	32 (1.7%)		6 (1%)	20 (0.5%)	26 (0.6%)	
Light chain only	26 (8.8%)	220 (13.4%)	246 (12.7%)		81 (13.5%)	451 (12.0%)	532 (12.2%)	
Missing	2 (0.7%)	20 (1.2%)	22 (1.1%)		0 (0.0%)	5 (0.1%)	5 (0.1%)	
Light Chain Type								
Lambda	101 (34.2%)	519 (31.6%)	620 (32.0%)	0.4451	179 (29.9%)	1269 (33.8%)	1448 (33.2%)	0.0741
Kappa	172 (58.3%)	981 (59.8%)	1153 (59.6%)		411 (68.6%)	2455 (65.3%)	2866 (65.8%)	
Missing	22 (7.5%)	141 (8.6%)	163 (8.4%)		9 (1.5%)	35 (0.9%)	44 (1.0%)	

SD: Standard deviation, WHO: World Health Organization

Table 2. Myeloma IX and XI thrombosis by site

	Treatment received	Venous thrombosis								Arterial thrombosis				Total
		DVT below knee	DVT above knee	PE	Other VTE	Superficial thrombophlebitis	Line associated VTE	PE or DVT (Type unknown)	Location of recent operation	Stroke	TIA	Arterial thrombosis	MI	
Myeloma IX	**Transplant-eligible induction treatment**													
	CVAD	23 (14.5%)	22 (13.8%)	35 (22.0%)	9 (5.7%)	1 (0.6%)	59 (37.1%)	10 (6.3%)	NR					159 (100%)
	CTD	22 (20.4%)	26 (24.1%)	45 (41.7%)	3 (2.8%)	1 (0.9%)	2 (1.9%)	9 (8.3%)	NR					108 (100%)
	Total	45 (16.9%)	48 (18.0%)	80 (30.0%)	12 (4.5%)	2 (0.7%)	61 (22.8%)	19 (7.1%)	NR					267 (100%)
	Transplant-ineligible induction treatment													
	MP	2 (11.1%)	10 (55.6%)	6 (33.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	NR					18 (100%)
	CTDa	22 (26.5%)	15 (18.1%)	39 (47.0%)	1 (1.2%)	0 (0.0%)	0 (0.0%)	6 (7.2%)	NR					83 (100%)
	Total	24 (23.8%)	25 (24.8%)	45 (44.6%)	1 (1.0%)	0 (0.0%)	0 (0.0%)	6 (5.9%)	NR					101 (100%)
	Total	**69 (18.8%)**	**73 (19.8%)**	**125 (34.0%)**	**13 (3.5%)**	**2 (0.5%)**	**61 (16.6%)**	**25 (6.8%)**	**NR**					**368 (100%)**
Myeloma XI	**Transplant-eligible induction treatment**													
	CTD	37 (20.8%)	39 (21.9%)	78 (43.8%)	7 (3.9%)	1 (0.6%)	1 (0.6%)	NR	0 (0.0%)	8 (4.5%)	3 (1.7%)	2 (1.1%)	2 (1.1%)	178 (100%)
	CRD	49 (28.2%)	51 (29.3%)	51 (29.3%)	9 (5.2%)	1 (0.6%)	0 (0.0%)	NR	1 (0.6%)	6 (3.4%)	3 (1.7%)	1 (0.6%)	2 (1.1%)	174 (100%)
	KCRD	37 (30.1%)	28 (22.8%)	26 (21.1%)	18 (14.6%)	1 (0.8%)	3 (2.4%)	NR	1 (0.8%)	3 (2.4%)	3 (2.4%)	1 (0.8%)	2 (1.6%)	123 (100%)

Treatment received	Venous thrombosis								Arterial thrombosis				Total
	DVT below knee	DVT above knee	PE	Other VTE	Superficial thrombophlebitis	Line associated VTE	PE or DVT (Type unknown)	Location of recent operation	Stroke	TIA	Arterial thrombosis	MI	
Total	**123 (25.9%)**	**118 (24.8%)**	**155 (32.6%)**	**34 (7.2%)**	**3 (0.6%)**	**4 (0.8%)**	**NR**	**2 (0.4%)**	**17 (3.6%)**	**9 (1.9%)**	**4 (0.8%)**	**6 (1.3%)**	**475 (100%)**
Transplant-ineligible induction treatment													
CTDa	25 (19.7%)	30 (23.6%)	44 (34.6%)	11 (8.7%)	0 (0.0%)	0 (0.0%)	NR	1 (0.8%)	8 (6.3%)	7 (5.5%)	0 (0.0%)	1 (0.8%)	127 (100%)
CRDa	29 (20.1%)	22 (15.3%)	44 (30.6%)	20 (13.9%)	0 (0.0%)	0 (0.0%)	NR	0 (0.0%)	18 (12.5%)	8 (5.6%)	1 (0.7%)	2 (1.4%)	144 (100%)
Total	**54 (19.9%)**	**52 (19.2%)**	**88 (32.5%)**	**31 (11.4%)**	**0 (0.0%)**	**0 (0.0%)**	**NR**	**1 (0.4%)**	**26 (9.6%)**	**15 (5.5%)**	**1 (0.4%)**	**3 (1.1%)**	**271 (100%)**
Total	**177 (23.7%)**	**170 (22.8%)**	**243 (32.6%)**	**65 (8.7%)**	**3 (0.4%)**	**4 (0.5%)**	**NR**	**3 (0.4%)**	**43 (5.8%)**	**24 (3.2%)**	**5 (0.7%)**	**9 (1.2%)**	**746 (100%)**

MI: myocardial infarction, NR: Not recorded, TIA: transient ischaemic attack

Table 3. Myeloma IX and Myeloma XI thromboprophylaxis given prior to VTE and type of thromboprophylaxis received if given (by induction chemotherapy)

	Myeloma IX					Myeloma XI					
	CVAD	**CTD**	**MP**	**CTDa**	**Total**	**CTD**	**CRD**	**CTDa**	**CRDa**	**KCRD**	**Total**
Thromboprophylaxis given											
Yes	44 (27.7%)	18 (16.7%)	3 (16.7%)	17 (20.5%)	82 (22.3%)	130 (79.8%)	132 (82.0%)	93 (84.5%)	93 (80.9%)	85 (75.2%)	533 (80.5%)
No	114 (71.7%)	90 (83.3%)	15 (83.3%)	64 (77.1%)	283 (76.9%)	32 (19.6%)	27 (16.8%)	17 (15.5%)	21 (18.3%)	28 (24.8%)	125 (18.9%)
Missing	1 (0.6%)	0 (0.0%)	0 (0.0%)	2 (2.4%)	3 (0.8%)	1 (0.6%)	2 (1.2%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	4 (0.6%)
Total	**159 (100%)**	**108 (100%)**	**18 (100%)**	**83 (100%)**	**368 (100%)**	**163 (100%)**	**161 (100%)**	**110 (100%)**	**115 (100%)**	**113 (100%)**	**662 (100%)**
Thromboprophylaxis received (if given)*											
Aspirin	NR	NR	NR	NR	NR	39 (28.9%)	46 (34.3%)	42 (43.3%)	39 (41.1%)	19 (21.6%)	185 (33.7%)
Treatment dose warfarin	24 (54.5%)	9 (50.0%)	1 (33.3%)	13 (76.5%)	47 (57.3%)	5 (3.7%)	9 (6.7%)	3 (3.1%)	3 (3.2%)	2 (2.3%)	22 (4.0%)
LMWH	16 (36.4%)	9 (50.0%)	2 (66.7%)	4 (23.5%)	31 (37.8%)	88 (65.2%)	76 (56.7%)	51 (52.6%)	52 (54.7%)	64 (72.7%)	331 (60.3%)
Other	3 (6.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	3 (3.7%)	3 (2.2%)	3 (2.2%)	1 (1.0%)	1 (1.1%)	3 (3.4%)	11 (2.0%)
Missing	1 (2.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (1.2%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Total	**44 (100%)**	**18 (100%)**	**3 (100%)**	**17 (100%)**	**82 (100%)**	**135 (100%)**	**134 (100%)**	**97 (100%)**	**95 (100%)**	**88 (100%)**	**549 (100%)**

* Not mutually exclusive

NR: Not recorded

Table 4. Myeloma IX and XI highest level of thromboprophylaxis given, by risk prior to VTE

	Myeloma IX			Myeloma XI		
Thromboprophylaxis received	High-risk (n=62)	Low-risk (n=233)	Total (n=295)	High-risk (n=291)	Low-risk (n=241)	Total (n=532)
Not given	42 (67.7%)	182 (78.1%)	224 (75.9%)	40 (13.7%)	50 (20.7%)	90 (16.9%)
Aspirin	NR	NR	NR	67 (23.0%)	80 (33.2%)	147 (27.6%)
Treatment dose warfarin	9 (14.5%)	29 (12.4%)	38 (12.9%)	11 (3.8%)	3 (1.2%)	14 (2.6%)
LMWH	9 (14.5%)	19 (8.2%)	28 (9.5%)	168 (57.7%)	100 (41.5%)	268 (50.4%)
Other	1 (1.6%)	1 (0.4%)	2 (0.7%)	4 (1.4%)	5 (2.1%)	9 (1.7%)
Missing	1 (1.6%)	2 (0.9%)	3 (1.0%)	1 (0.3%)	3 (1.2%)	4 (0.8%)

NR: Not recorded

Figure Legends

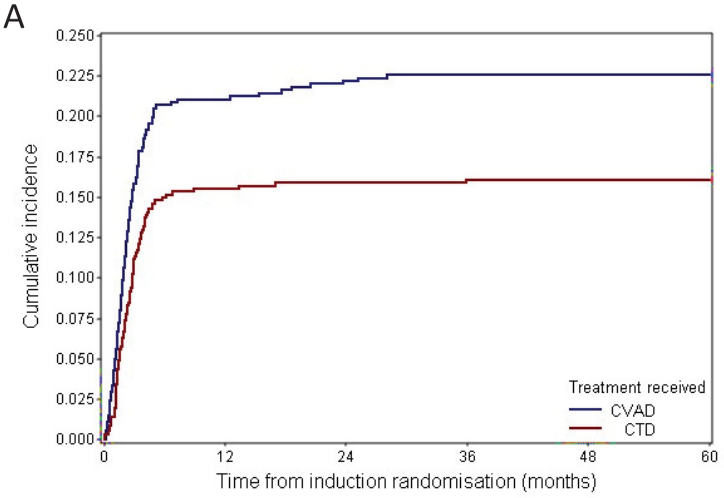
Figure 1. VTE CIF curves for Myeloma IX transplant-eligible (A) and transplant-ineligible (B) pathways and Myeloma XI transplant-eligible (C), transplant-eligible including KCRD (D) and transplant-ineligible (E) pathways

Figure 2. Progression free survival (PFS) by VTE occurrence in Myeloma IX (A) and Myeloma XI (B)

Figure 3. Overall survival (OS) by VTE occurrence in Myeloma IX (A) and Myeloma XI (B)

Figure 1

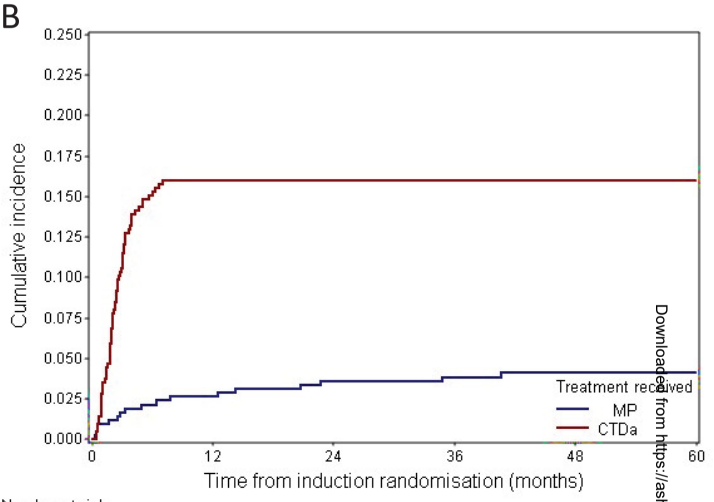
A



Number at risk

CVAD	538	364	316	281	236	167
CTD	554	409	372	334	299	198

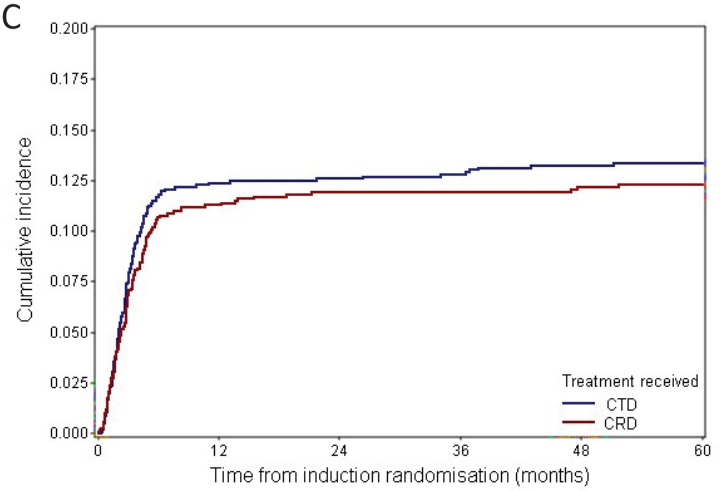
B



Number at risk

MP	419	308	243	168	116	65
CTDa	425	259	214	168	136	77

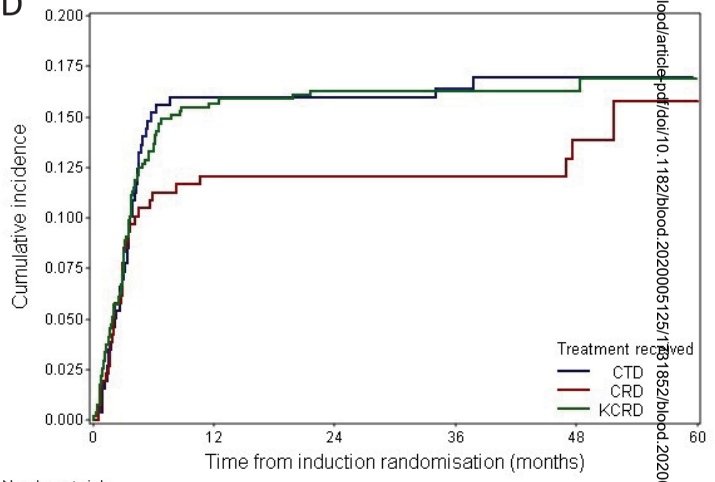
C



Number at risk

CTD	1008	807	727	618	486	366
CRD	1014	820	754	678	530	399

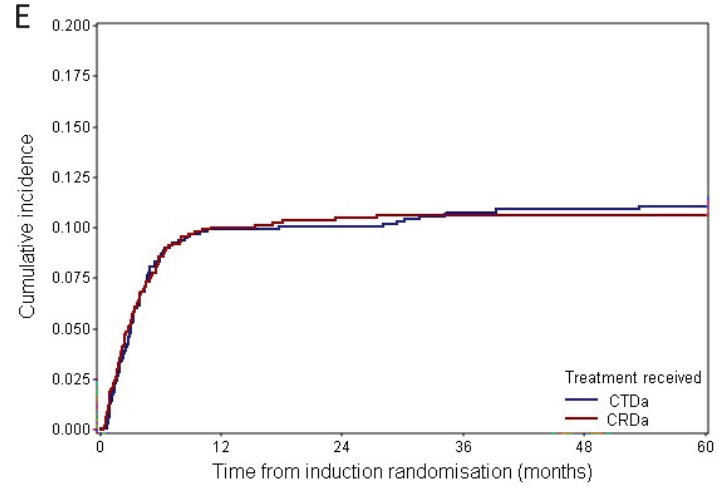
D



Number at risk

CTD	260	202	185	132	61	11
CRD	261	209	186	149	56	7
KCRD	510	410	376	305	122	10

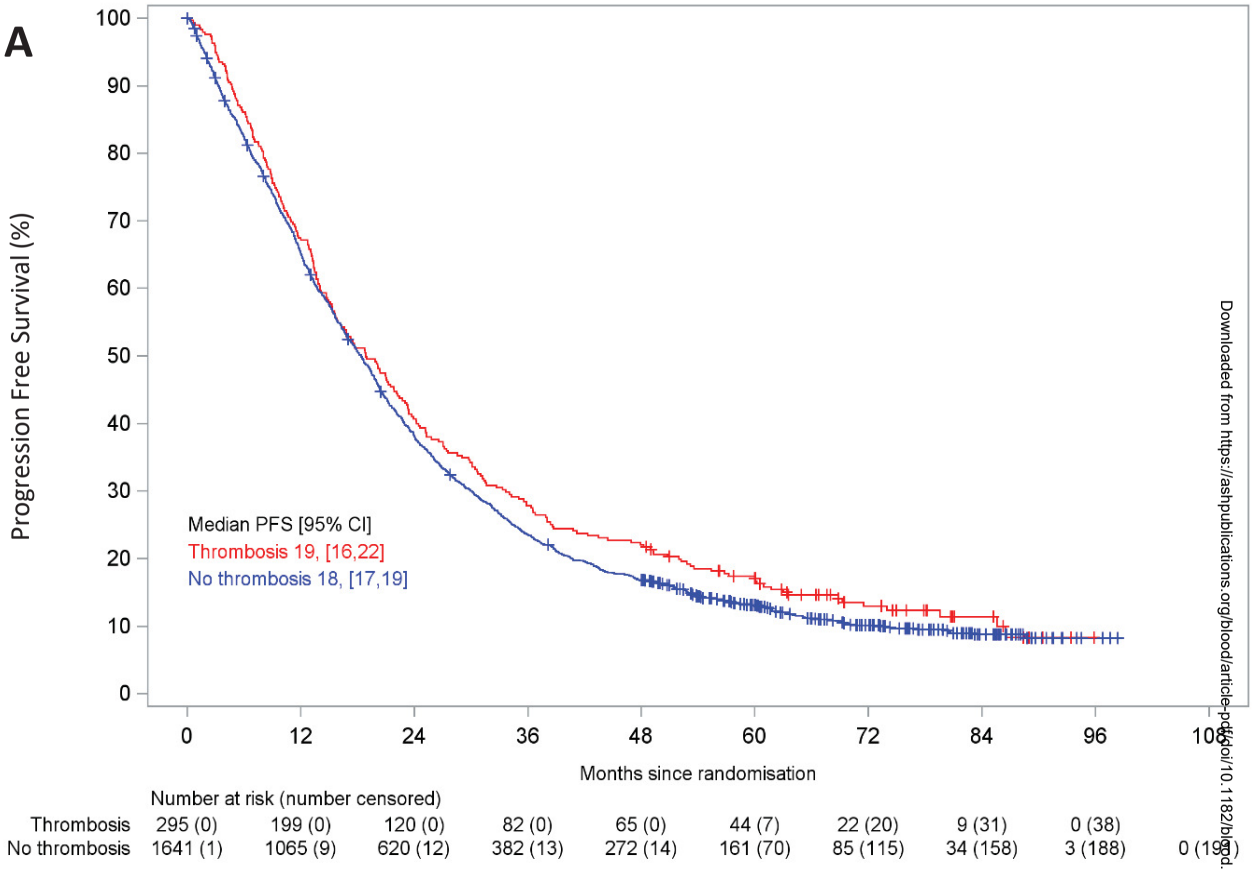
E



Number at risk

CTDa	910	637	536	431	302	176
CRDa	916	663	573	461	318	174

Figure 2



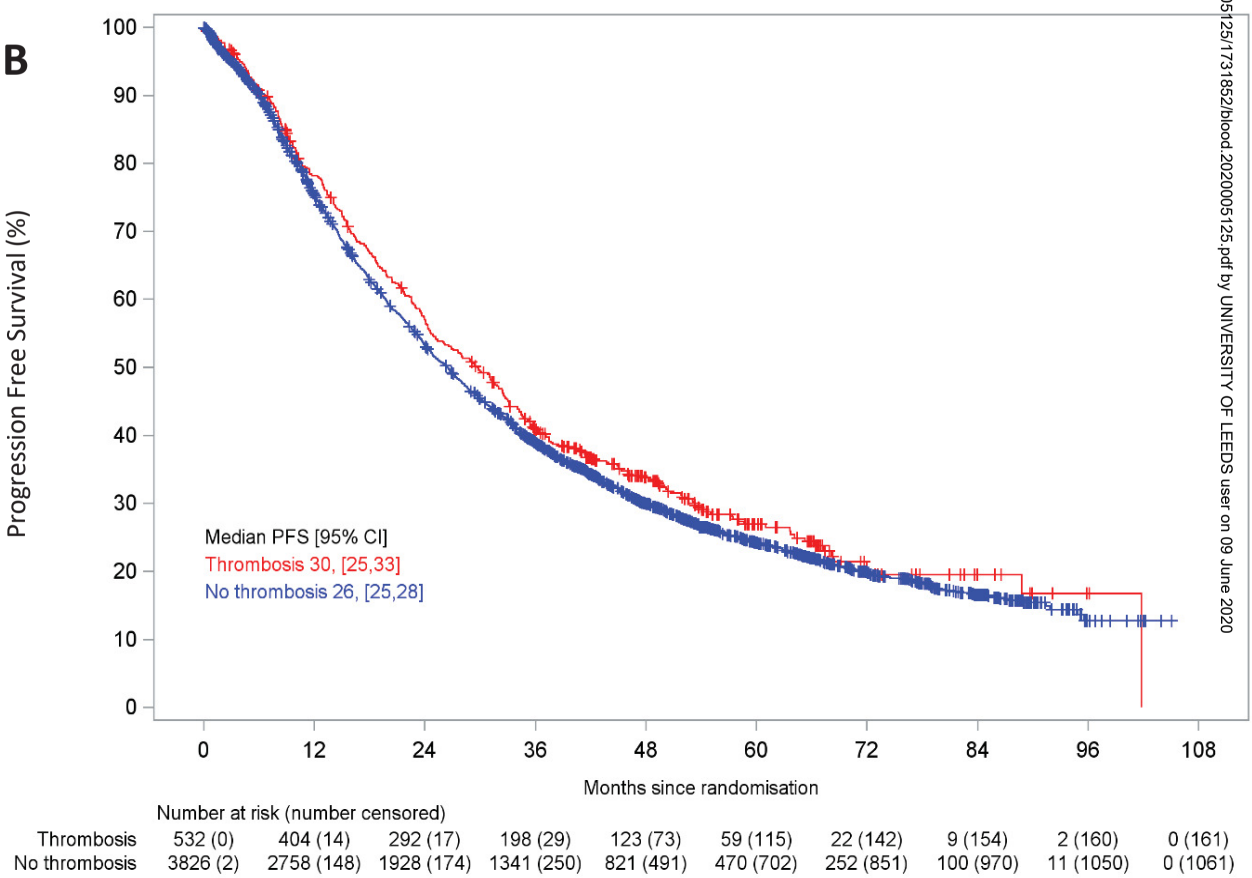


Figure 3