# Low Molecular Weight Heparins for Thromboprophylaxis during Induction Chemotherapy in Patients with Multiple Myeloma

## Nízkomolekulární hepariny v tromboprofylaxi během indukční chemoterapie u pacientů s mnohočetným myelomem

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## Summary

***Backgrounds:*** Patients with multiple myeloma have a high risk of venous thromboembolism (VTE), especially during the induction chemotherapy. The aim of our observational study was to determine the impact of prophylaxis with low molecular weight heparin (LMWH) on the incidence of thromboembolic complications. ***Patients and Methods:*** We analyzed the incidence of thromboembolic events in 258 patients treated with induction chemotherapy containing vincristin, doxorubicin or idarubicin, and dexamethasone, followed by stimulation chemotherapy with cyclophosphamide and G-CSF, and high-dose chemotherapy with melphalan. Two groups of these patients were compared based on the practice of thromboprophylaxis. Patients in the first group (Control, n = 140) were either not treated or treated with a short duration of anticoagulation therapy while the patients in the second group (Prophylactic, n = 118) underwent standard prophylaxis with LMWH throughout the entire period of induction chemotherapy. A total of 102 patients were selected for a close monitoring of the prophylactic effect of different LMWH doses and to be compared to patients without treatment. ***Results:*** Standard prophylaxis with LMWH significantly ($p < 0.007$) lowered a risk of VTE when compared to patients without such prophylaxis (3.4% versus 12.9%, respectively). Furthermore, analysis of the subgroup of 102 patients revealed that higher LMWH doses (> 70 IU/kg per day) achieved full prophylaxis in 28 patients while lower doses were less effective leading to DVT in 3 (7.7%) out of 39 patients. In contrast, VTE was diagnosed in 5 (14.3%) out of 35 patients without any LMWH prophylaxis. ***Conclusion:*** Prophylaxis with LMWH leads to a significant reduction of the risk of thromboembolic complications during the induction chemotherapy in patients suffering from MM. The prophylactic effect of LMWH is dose-dependent.



## Key words

multiple myeloma – venous thromboembolism – prevention – low-molecular-weight heparin



## Souhrn

***Východiska:*** Pacienti s mnohočetným myelomem mají vysoké riziko tromboembolické nemoci (TEN), zejména během indukční chemoterapie. Cílem studie bylo zjištění vlivu profylaxe nízkomolekulárním heparinem (LMWH) na incidenci tromboembolických komplikací. ***Pacienti a metody:*** Analyzovali jsme incidenci tromboembolických příhod u 258 pacientů léčených indukční terapií obsahující vinkristin, doxorubicin nebo idarubicin a dexametazon, následovanou stimulační chemoterapií cyklofosfamidem a G-CSF, a vysokodávkovanou chemoterapií melfalanem. Byly porovnány dvě skupiny těchto pacientů podle praktikované tromboprofylaxe. Pacienti v první skupině (kontrolní, n = 140) buď nebyli léčeni, nebo byli léčeni antikoagulační terapií jen po krátkou dobu, zatímco pacienti ve druhé skupině (profylaktická, n = 118) dostávali standardní profylaxi LMWH po celou dobu indukční chemoterapie. U 102 pacientů byl vyhodnocen profylaktický účinek různých dávek LMWH a porovnán s pacienty bez léčby. ***Výsledky:*** Standardní profylaxe LMWH významně ($p < 0,007$) snížila riziko TEN ve srovnání s pacienty bez této profylaxe (3,4 % vs 12,9 %). V analýze podskupiny 102 pacientů bylo zjištěno, že vyšší dávka LMWH (> 70 IU/kg denně) vedla k 100% účinné profylaxi u 28 pacientů, zatímco nižší dávky byly méně efektivní, 3 pacienti z 39 (7,7 %) prodělali hlubokou žilní trombózu. Naproti tomu TEN byla diagnostikována u 5 z 35 (14,3 %) pacientů bez profylaxe. ***Závěr:*** Profylaxe LMWH vede k významné redukci rizika tromboembolických komplikací během indukční chemoterapie u pacientů s mnohočetným myelomem. Profylaktický efekt LMWH je závislý na dávce.



## Klíčová slova

mnohočetný myelom – tromboembolická nemoc – prevence – nízkomolekulární heparin


## Backgrounds

Multiple myeloma (MM) is associated with a moderate risk of venous thromboembolism (VTE) [1–4]. Similar risk of VTE has also been observed in patients suffering from monoclonal gammopathy of undetermined significance, which is a precancerous plasma cell disorder [5,6]. The problem has generated much attention in the recent years because of the high incidence of thromboembolic complications in patients treated with thalidomide-containing combination regimens [2,4,7]. It is generally accepted that MM patients are at a high risk of VTE and the risk is further increased by the treatment with agents such as dexamethasone, thalidomide, lenalidomide, or doxorubicin [7–11]. Several factors may play an important role in the pathogenesis of hypercoagulability, including hyperviscosity, high levels of von Willebrand Factor and Factor VIII, decreased levels of protein S [12,13] as well

**Tab. 1. Incidence of thromboembolic events in multiple myeloma patients receiving first-line treatment.**

| Regimen | Incidence of thromboembolism | Reference |
|---|---|---|
| Thalidomide 200–800 mg | 3–4% | Weber 2002, Rajkumar 2003 |
| Thalidomide + Melphalan + Prednisone | 20% | Palumbo 2005 |
| Thalidomide 100–400 mg + Dexamethasone | 18–26% | Cavo 2002, Rajkumar 2004 |
| Thalidomide + anthracyclin-based chemotherapy | 26–34% | Zangari 2004 |
| Lenalidomide + high dose Dexamethasone | 26% | Rajkumar 2009 |
| Lenalidomide + low dose Dexamethasone | 12% | Rajkumar 2009 |

**Tab. 2. Incidence of thromboembolic events in multiple myeloma patients receiving treatment for relapsed or refractory disease.**

| Regimen | Incidence of thromboembolism | Reference |
|---|---|---|
| Thalidomide 100–800 mg | 2–3% | Barlogie 2001, Tosi 2002, Kumar 2003 |
| Thalidomide 100–400 mg + Dexamethasone | 2–7% | Dimopoulos 2001, Palumbo 2004 |
| Thalidomide + chemotherapy | 4.2% | Moehler 2002 |
| Thalidomide + anthracyclin-based chemotherapy | 16% | Zangari 2002 |
| Lenalidomide + Dexamethasone | 4.5% | Chen 2009 |

as acquired protein C resistance [14,15]. The risk is higher during the first-line treatment as compared to the second-line treatment [9]. Such risk is also enhanced by previous history of VTE, immobility, central venous catheter, nephrotic syndrome, acute infection, or thrombophilia.

The incidence of VTE during various types of antineoplastic treatment for MM is shown in tab. 1 and 2. Therefore, it was not surprising that MM patients profited from the prophylactic administration of low molecular weight heparin (LMWH) [16]. The association of antiangiogenic therapy with arterial thrombosis is probably less common. However, it has recently been reported [17].

We have observed a significant incidence of VTE in randomized controlled trials conducted by the Czech Myeloma Group, where patients received induction chemotherapy regimens consisting of vincristin, doxorubicin (or idarubicin), and dexamethasone. In the 4W clinical trial (1996–2002), the incidence of VTE was 10.5%. There were 30 cases of VTE episodes (incidence of 11.9%) among the first 253 patients enrolled in the CMG 2002 clinical trial. Moreover, four sudden deaths likely related to arterial or venous thromboembolism were found. The majority of the thrombotic events occurred before transplantation (Fig. 1). All VTE cases occurring during the stem cell harvest were associated with the presence of femoral vein catheter.

Given the high incidence of VTE in the first 253 patients, we have amended the CMG 2002 study protocol to implement routine prophylaxis with LMWHs (dalteparin, nadroparin, or enoxaparin) for patients undergoing induction treatment. We have selected 50–100 anti-Xa IU/kg of LMWH once daily during the four cycles of induction chemotherapy until the start of stimulation chemotherapy.

Here we summarize the results of antithrombotic prophylaxis in 258 of these patients treated in 13 centers.

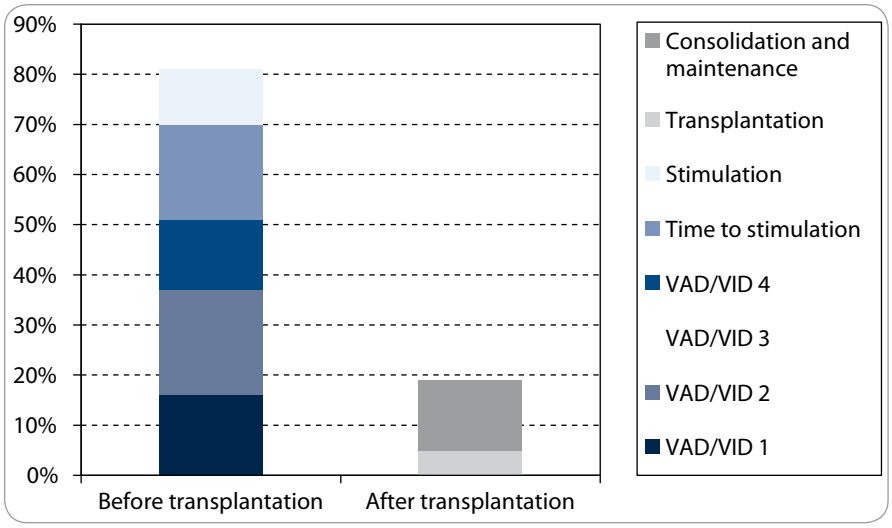


**Fig. 1. Occurrence of thromboembolic events in different phases of treatment.**

## Patients and Methods

A total of 258 patients with newly diagnosed MM were included in the CMG 2002 clinical trial. All patients underwent 4 cycles of induction chemotherapy VAD (vincristine 0,5 mg daily for 4 days, doxorubicin 9 mg per sq m daily for 4 days, and dexamethasone 40 mg daily on days 1 to 4, 10 to 13, and 20 to 23), or VID (vincristine 2 mg on day 1, idarubicin 10 mg per sq m daily for 4 days, and dexamethasone at the same dose, as in regimen VAD), stimulation chemotherapy with cyclophosphamide 2.5 g per sq m followed by G-CSF, and myeloablative chemotherapy with melphalan 200mg per sq m. The patients were subsequently randomized either to maintenance treatment with interferon alpha 3 million units three times weekly or to consolidation chemotherapy with CED (cyclophosphamide 300 mg to 400 mg per sq m on days 1 to 4, etoposide 30 mg to 40 mg per sq m on days 1 to 4, and dexamethasone 40 mg on days 1 to 4) in the 4th, 8th, 12th, and 16th month after autologous transplantations followed by interferon alpha in the same dose as above. The incidence of VTE and severe bleeding was calculated based on serious adverse event (SAE) reports. Patient baseline data were obtained from the CMG 2002 database. Data on thrombotic risk factors were gathered using an investigator-completed form that included items on past medical history, presence or absence of central venous catheter, and the circumstances of VTE. Out of the 340 enrolled (from April 2002 to June 2005), 258 patients received induction of chemotherapy and were fully evaluated. The LMWHs were used in prophylaxis during the 4 cycles of induction chemotherapy (once daily subcutaneously). Two groups of these patients

**Tab. 3. Baseline characteristics of patients who received antithrombotic prophylaxis during the entire induction chemotherapy (prophylactic group), and patients who did not receive any antithrombotic prophylaxis during the induction chemotherapy at all, or only during a part of it (control group).**

| | Prophylactic group (N = 118) | Control group (N = 140) | P |
|---|---|---|---|
| Gender (male/female) | 64 (54.2%) / 54 (45.8%) | 80 (57.1%) / 60 (42.9%) | 0.640 |
| Mean age (standard deviation) | 55.8 (7.3) years | 55.2 (7.6) years | 0.521 |
| Past medical history of thromboembolism | 6 (5.1%) | 1 (0.7%) | 0.030 |
| Central venous catheter | 17 (14.4%) | 32 (22.8%) | 0.086 |
| VAD/VID regimen | 105 (89.0%) / 13 (11.0%) | 111 (79.3%) / 29 (20.1%) | 0.035 |

were compared based on the practice of thromboprophylaxis. Patients in the first group (Control, n = 140) were either not treated or treated with a short duration of anticoagulation therapy while the patients in the second group (Prophylactic, n = 118) underwent standard prophylaxis with LMWH throughout the entire period of induction chemotherapy. The efficacy of LMWH prophylaxis was measured and compared between Prophylactic and Control group of patients. Furthermore, a more detailed analysis, focusing on LMWH dose response with respect to an incidence of confirmed VTE, was conducted on a subgroup of 102 patients from a single center. Of these 102 patients, 35 did not receive LMWH, while 39 patients were put on LMWH prophylaxis in a dose lower than 70 IU/kg daily, and 28 patients in a dose higher than 70 IU/kg daily.

LMWH prophylaxis was contraindicated in patients with platelet counts below 30 × 109/l, fibrinogen level below 1.0 g/l, or activated partial thromboplastin time longer than 1.5 times the upper limit of the reference interval. Platelet counts were checked within the first 14 days of LMWH administration in order to detect and avoid consequences of heparin-induced thrombocytopenia. Anti Xa activity was monitored 4 hours after LMWH injection in patients with renal impairment to ensure it was within the recommended range of 0.20–0.40 antiXa IU/ml.

The clinical diagnosis of deep vein thrombosis was confirmed by duplex ultrasonography or venography, the diagnosis of pulmonary embolism was based on CT angiography or ventilation-perfusion lung scintigraphy.

## Statistical Analysis

We used the Fisher's test to evaluate the statistical significance of differences between baseline characteristics of the two groups, including gender, age, past history of VTE, presence or absence of central venous catheter, and the use of VAD versus VID regimen. T-test was used to analyze the differences in age of the patients in the two groups. The level of statistical significance was set at p = 0.05.

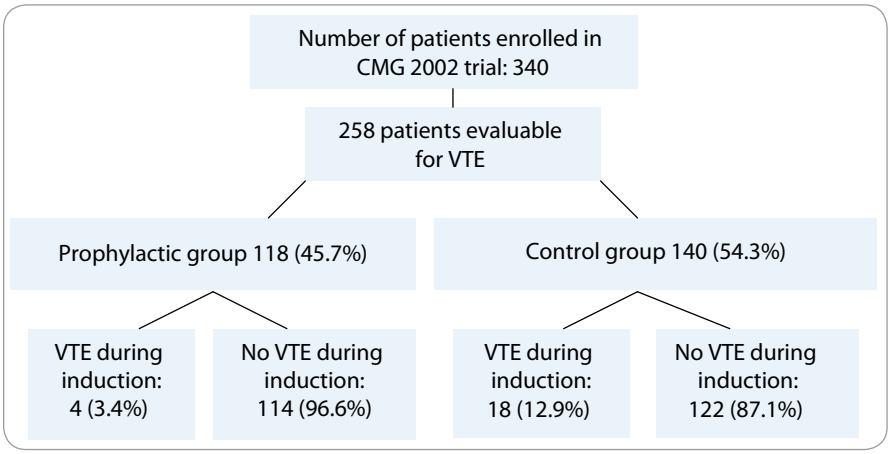


**Fig. 2. Summary of the results of prophylactic low molecular weight heparin treatment in patients with multiple myeloma receiving first-line chemotherapy.**

## Results

There were no differences between LMWH prophylactic and control groups regarding age, gender, and the application of the central venous catheter. However, more patients from the control group received the VID regimen, while more patients on LMWH prophylaxis suffered from VTE in their history (Tab. 3).

Patients in the LMWH prophylactic group had significantly (p = 0.007, absolute risk reduction 9.5%) lower incidence of VTE (4/118, 3.4%) as compared to patients in the control group (18/140, 12.9%) (Fig. 2). The incidence of bleeding SAE was similar in both groups (prophylactic – 1/118, 0.8% vs. control – 2/140, 1.4%, respectively.

In the subgroup of 102 patients treated at a single center in which data about the LMWH dosage were available, we found no statistically significant differences between subgroups of patients without and with LMWH prophylaxis at lower and higher dose of LMWH as to the age, past history of VTE, gender and MM stage at diagnosis. No thromboembolic events were observed in the group of 28 patients who received more than 70 IU/kg LMWH daily, while five of the 35 patients without prophylaxis developed VTE (0% vs. 14.3%, p = 0.002). Three out of the 39 (7.7%) patients receiving lower dose of LMWH (less than 70 IU/kg) developed VTE during the induction chemotherapy; the incidence was not significantly lower than in pa-

tients without LMWH prophylaxis (7.6% vs. 14.2%, p = 0.216). No hemorrhagic complications occurred within this subgroup of 102 patients.

## Discussion

Our study confirms an increased risk of VTE during an induction chemotherapy of MM with regimens such as VAD and VID, a finding previously reported in the literature. Although a number of authors report high incidence of VTE during treatment with regimens containing high-dose dexamethasone [8], the results are not unequivocal. For example, the incidence of VTE in the HOVON50/GMMG HD3 study was only 4% in 203 patients during three cycles of VAD chemotherapy and 8% during three cycles of thalidomide, doxorubicin, and dexamethasone (TAD) chemotherapy. While the study protocol did not require VTE prophylaxis in the VAD arm, patients in the TAD arm received obligatory prophylaxis with nadroparin [18]. Cavo et al reported only 2% incidence of grade 3–4 thromboembolic complications with the VAD regimen [19]. However, compared to our study, the dose of dexamethasone in their study was significantly reduced in alternate cycles. Furthermore, the higher proportion of stage III in our group of patients may contribute to the higher VTE incidence in our study.

In general, the distribution of thromboembolic events during a therapy is to some extent determined by the thrombogenic effect of chemotherapy used in particular treatment phases. Indeed, in studies where thalidomide was used, the majority of VTE occurred during the induction phase. Thus, in the HOVON50/GMMG HD3 trial, 25 of 30 (83%) of thromboembolic events were observed during the induction treatment [20]. This notion is also supported by Zangari and collaborators [2] who evaluated the effect of 400 mg of thalidomide daily added to a combination chemotherapy, where all thromboembolic events occurred during the induction phase. The relatively high dose of thalidomide may be responsible for such thrombogenicity. Interestingly, the risk of VTE in our study is distributed more evenly thus supporting our recommendation to use LMWH in prophylactic doses throughout the first 6 months of induction treatment and stimulation chemotherapy until the autologous transplantation.

Only several non-randomized studies on the efficacy and safety of various approaches to VTE prophylaxis were published until March, 2011. For example, a low dose of warfarin appears to be ineffective, while a full anticoagulation dose is effective but carries a significant risk of bleeding [20,8,21]. Aspirin is not generally considered effective for VTE prophylaxis, as also supported by recent evidence [16]. However, some uncontrolled cohort studies [22,23] and one pooled data analysis [24] revealed low incidence of VTE in patients treated with lenalidomide-based regimens using aspirin as a thromboprophylaxis. This would suggest improved antithrombotic efficacy of aspirin, particularly in this group of patients. There are numerous published reports on the efficacy of LMWHs for this indication. For example, an addition of 40 mg of enoxaparin daily has decreased the incidence of VTE in patients treated with combination chemotherapy plus thalidomide from 34% to 15% [8]. In a GIMEMA study [25], the incidence of VTE in patients treated with melphalan, prednisone, and thalidomide was reduced from 20% to 3% after an addition of enoxaparin (40 mg daily). Prophylactic failure in two patients in the present study is understood to be due to termination of enoxaparin administration. In another study, nadroparin (in a dose of 2,850 antiXa IU, 5,700 antiXa IU in persons > 90 kg) was used as an obligatory VTE prophylaxis during thalidomide-doxorubicin-dexamethasone combination treatment [18], resulting in 8% incidence of VTE during the induction chemotherapy. Even though VTE has been shown to be less common in relapsed patients than in newly diagnosed patients, LMWH prophylaxis can reverse this ratio. Thus, VTE was observed in 11% of newly diagnosed MM patients receiving LMWH prophylaxis, whereas the VTE incidence rose to 24% in relapsing patients without anticoagulation [26]. A randomized trial comparing Aspirin, Warfarin or Enoxaparin for thromboprophylaxis in MM patients treated with thalidomide based regimen was recently published [27]. The primary outcome (Major VTE and/or acute cardiovascular event and/or sudden death) occurred in 5% patients treated with LMWH, in 6.4% treated with Aspirin and in 8.2% treated with warfarin, respectively. The differences were not statistically significant. The incidence of VTE in our study was significantly reduced (from 12.9% to 3.4%) with negligible incidence of bleeding at1.4% in patients on prophylaxis compared to 0.8% in patients without prophylaxis. The prophylaxis was 100% effective in a subgroup of patients treated with the dose of LMWH higher than 70 antiXa IU/kg daily.

The main weakness of our study is that different LMWHs were used. It is well known that the LMWHs are not identical. However, nadroparin, enoxaparin and dalteparin are commonly used in our hospitals and they are considered to be interchangeable when indicated for the prophylaxis of VTE. Therefore, our study reflects real clinical practice.

## Conclusions

The risk of VTE in MM patients receiving induction chemotherapy with VAD/VID regimens is high. Prophylactic effect of LMWH (in particular > 70 antiXa IU/kg daily) prevented VTE in our patients with MM throughout the induction chemotherapy until the initiation of high-dose chemotherapy. A proper randomized study is needed to validate such finding [28]. The use of aspirin prophylaxis has been recommended in myeloma patients with 1 or no additional risk factor of thrombosis and receiving thalidomide or lenalidomide, while LMWH prophylaxis has been recommended for patients with 2 or more risk factors [29]. Warfarin (INR 2–3) seems to be an appropriate alternative to LMWH for selected patients.

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