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ORIGINAL REPORT

# Aspirin, Warfarin, or Enoxaparin Thromboprophylaxis in Patients With Multiple Myeloma Treated With Thalidomide: A Phase III, Open-Label, Randomized Trial

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## ABSTRACT

### Purpose
In patients with myeloma, thalidomide significantly improves outcomes but increases the risk of thromboembolic events. In this randomized, open-label, multicenter trial, we compared aspirin (ASA) or fixed low-dose warfarin (WAR) versus low molecular weight heparin (LMWH) for preventing thromboembolism in patients with myeloma treated with thalidomide-based regimens.

### Patients and Methods
A total of 667 patients with previously untreated myeloma who received thalidomide-containing regimens and had no clinical indication or contraindication for a specific antiplatelet or anticoagulant therapy were randomly assigned to receive ASA (100 mg/d), WAR (1.25 mg/d), or LMWH (enoxaparin 40 mg/d). A composite primary end point included serious thromboembolic events, acute cardiovascular events, or sudden deaths during the first 6 months of treatment.

### Results
Of 659 analyzed patients, 43 (6.5%) had serious thromboembolic events, acute cardiovascular events, or sudden death during the first 6 months (6.4% in the ASA group, 8.2% in the WAR group, and 5.0% in the LMWH group). Compared with LMWH, the absolute differences were +1.3% (95% CI, −3.0% to 5.7%; $P = .544$) in the ASA group and +3.2% (95% CI, −1.5% to 7.8%; $P = .183$) in the WAR group. The risk of thromboembolism was 1.38 times higher in patients treated with thalidomide without bortezomib. Three major (0.5%) and 10 minor (1.5%) bleeding episodes were recorded.

### Conclusion
In patients with myeloma treated with thalidomide-based regimens, ASA and WAR showed similar efficacy in reducing serious thromboembolic events, acute cardiovascular events, and sudden deaths compared with LMWH, except in elderly patients where WAR showed less efficacy than LMWH.

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## INTRODUCTION

In patients with cancer, the incidence of venous thrombosis is more than 7%[1] but remains an underdiagnosed and undertreated condition.[2] Myeloma is associated with the highest risk of thromboembolism.[3]

Cancer chemotherapy amplifies the prothrombotic effect of cancer cells and damages vessel walls directly.[4] The combination of melphalan, prednisone, and thalidomide is now a standard of care for the initial treatment of elderly patients with myeloma.[5-7] However, thalidomide significantly increases the risk of thromboembolism.[8-10]

Small studies have evaluated the clinical benefits of single-agent antithrombotic prophylaxis (aspirin [ASA], warfarin [WAR], or low molecular weight heparin [LMWH]). Results of ASA and low-dose WAR are conflicting.[11-14] In a meta-analysis of 1,051 patients, the relative risk of thromboembolism in patients treated with thalidomide and LMWH was still 1.54 times higher than in patients not receiving thalidomide.[10] The American Society of Clinical Oncology guidelines recommend prophylaxis with LMWH or adjusted-dose WAR in patients receiving thalidomide.[15] At present, no randomized study has directly compared the clinical benefits of ASA, WAR, and LMWH as thromboprophylaxis for

patients with myeloma treated with thalidomide. This multicenter, randomized, open-label study compared the efficacy and safety of ASA or fixed low-dose WAR with LMWH in preventing thromboembolism in untreated patients with myeloma who received thalidomide-containing regimens.

## PATIENTS AND METHODS

### Study Design and Treatment

This open-label, phase III, randomized study was conducted at 84 centers in Italy during May 2006 to January 2009 as a common substudy of two simultaneous chemotherapy phase III trials using thalidomide-based regimens in previously untreated patients with myeloma.[16,17] The aim of this study was to compare the effectiveness of ASA and WAR with LMWH as antithrombotic prophylaxis. The study was approved by the institutional review board at each of the participating centers. All patients gave written informed consent before entering the study, which was performed in accordance with the Declaration of Helsinki. The study was designed by the investigators, who were also responsible for the data collection. The data analysis was performed by the investigators in conjunction with an independent statistical office.

### Patient Populations and Random Assignment

Previously untreated patients with myeloma who were enrolled onto one of two studies[16,17] were assessed for eligibility for the substudy. In one study, patients age $\leq$ 65 years were randomly assigned to bortezomib (1.3 mg/m$^2$ on days 1, 4, 8, and 11), thalidomide (200 mg/d), and dexamethasone (320 mg) or to thalidomide and dexamethasone in each 21-day cycle for three courses as induction therapy before autologous transplantation.[16] In the other study, patients age $\geq$ 65 years were randomly assigned to bortezomib (1.3 mg/m$^2$ on days 1, 8, 15, and 22), melphalan (9 mg/m$^2$ on days 1 to 4), prednisone (60 mg/m$^2$ on days 1 to 4), and thalidomide (50 mg/d) for nine courses followed by continuous therapy with bortezomib (1.3 mg/m$^2$ every 15 days) and thalidomide (50 mg/d) or to bortezomib, melphalan, and prednisone for nine courses without any further continuous treatment.[17] Patients randomly assigned to receive bortezomib, melphalan, and prednisone did not receive any antithrombotic prophylaxis. Patients receiving thalidomide-based regimens in both trials were eligible for the substudy. Exclusion criteria were allergy or intolerance to study drugs, clear indication or contraindication for a specific antiplatelet or anticoagulant therapy (eg, cardiac arrhythmia, cardiac ischemia, or previous history of arterial or venous thromboembolism), and active bleeding or high risk of bleeding.

A simple random assignment sequence was generated by a centralized computer. After registration in a centralized database through the Internet and validation of eligibility, patients were randomly allocated to treatments using an automated assignment procedure concealed to the investigators.

### Study Interventions and Clinical Follow-Up

Patients receiving thalidomide-based regimens were randomly assigned to receive one of the following: ASA 100 mg/d orally, WAR 1.25 mg/d orally, or LMWH (enoxaparin) 40 mg/d subcutaneously. The prophylaxis was administered during the three cycles of induction therapy in the younger patients[16] and during the first six cycles of induction therapy in the elderly patients.[17] The antithrombotic prophylaxis was discontinued in the event of deep vein thrombosis, pulmonary embolism, arterial thrombosis, acute cardiovascular event, bleeding event, or platelet count $\leq$ 50,000/$\mu$L. The international normalized ratio (INR) was measured on days 1 and 21 of every cycle of chemotherapy. For INR greater than 3, WAR was discontinued, and patients received adjusted doses of WAR to maintain INR less than 3. Patients attended study visits every 3 weeks during the treatment period to assess the toxicity and efficacy of treatment and subsequently at the physician's discretion to evaluate the incidence of thromboembolism in the absence of prophylaxis.

### Outcome Measures

The primary end point was a composite measure defined as the proportion of patients developing a first episode of objectively confirmed symptomatic deep vein thrombosis, pulmonary embolism, arterial thrombosis, any acute cardiovascular event (acute myocardial infarction or stroke), or sudden, otherwise unexplained death (presumed to be a result of pulmonary embolism, acute myocardial infarction, or stroke) during the first 6 months from random assignment. Secondary end points included the comparison of each component of the composite primary end point, long-term cumulative incidence of the primary end point, major and minor bleeding events, and any toxicity that required interruption of study prophylaxis. All adverse events were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (version 3). The diagnostic procedures and definitions of the conditions included in the composite end point are detailed in the Appendix (online only). Major bleeding was defined as fatal bleeding, symptomatic bleeding in a crucial area or organ, or bleeding causing a reduction in hemoglobin concentration of $\geq$ 2 g/dL or necessitating transfusion of $\geq$ two units of whole blood or RBC cells.[18] Minor bleeding was all other bleeding not meeting the criteria for major bleeding.

### Statistical Analysis

The statistical power and the minimum effect size detectable in this trial was determined according to the sample size of the two predefined chemotherapy phase III trials, which was 450 patients for the bortezomib, thalidomide, and dexamethasone versus thalidomide and dexamethasone trial[16] and 500 patients for the bortezomib, melphalan, prednisone, and thalidomide versus bortezomib, melphalan, and prednisone trial.[17] Overall, we expected approximately 700 patients treated with thalidomide-containing regimens to be randomly assigned, with a 1:1:1 allocation ratio between the three prophylaxis regimens (approximately 230 patients per group). The main planned comparisons were ASA versus LMWH and WAR versus LMWH during the first 6 months from random assignment. The expected rate of thromboembolic events in patients with newly diagnosed myeloma treated with thalidomide-containing regimens without any prophylaxis is approximately 20% to 30%,[10] and to be considered effective, any prophylaxis should at least halve this risk. For each comparison, a sample size of 230 patients per group reaches a statistical power ranging from 53% to 86% to detect an absolute decrease of 5% to 7%, respectively, between the groups, with $\alpha = .05$ (two tailed), assuming a value of 10% for the composite primary end point in the LMWH group. Because the two planned comparisons of the primary end point are true independent hypotheses, we did not adjust for multiplicity.[19] Two interim analyses were planned at 15% and 45% of enrollment, using the O'Brien and Fleming group sequential test design.[20]

The statistic test used to compare the difference between proportions was the two-sided $z$ test, with pooled variance. A subgroup analysis of the primary composite end point was planned according to the three thalidomide-containing regimens. To compare the incidence of the composite primary end point through the entire follow-up, taking into account the competing risk of dying from any other cause, the cumulative incidence, adjusted for competing risks, was compared between groups with the Gray's test. The hazard ratios (HRs) with 95% CIs were estimated using the Fine and Gray's proportional hazard model.[21,22] All efficacy and safety analyses were performed according to the intent-to-treat principle and included all randomly assigned patients who received at least one dose of the study drug. Times of observation were censored on September 30, 2009. Time-to-event and continuous variables are expressed as median with interquartile range (IQR). The post hoc analysis concerning the association of thromboembolic events with potentially prognostic baseline factors (age, performance status, presence or absence of comorbidities, high International Staging System stage, dose of corticosteroids, and bortezomib association) was performed accounting for competing events.[21,22] Interactions between treatment groups and covariates were assessed in the model.

## RESULTS

Of 991 patients assessed for eligibility, 734 had been randomly assigned to thalidomide-containing regimes and 257 had been assigned

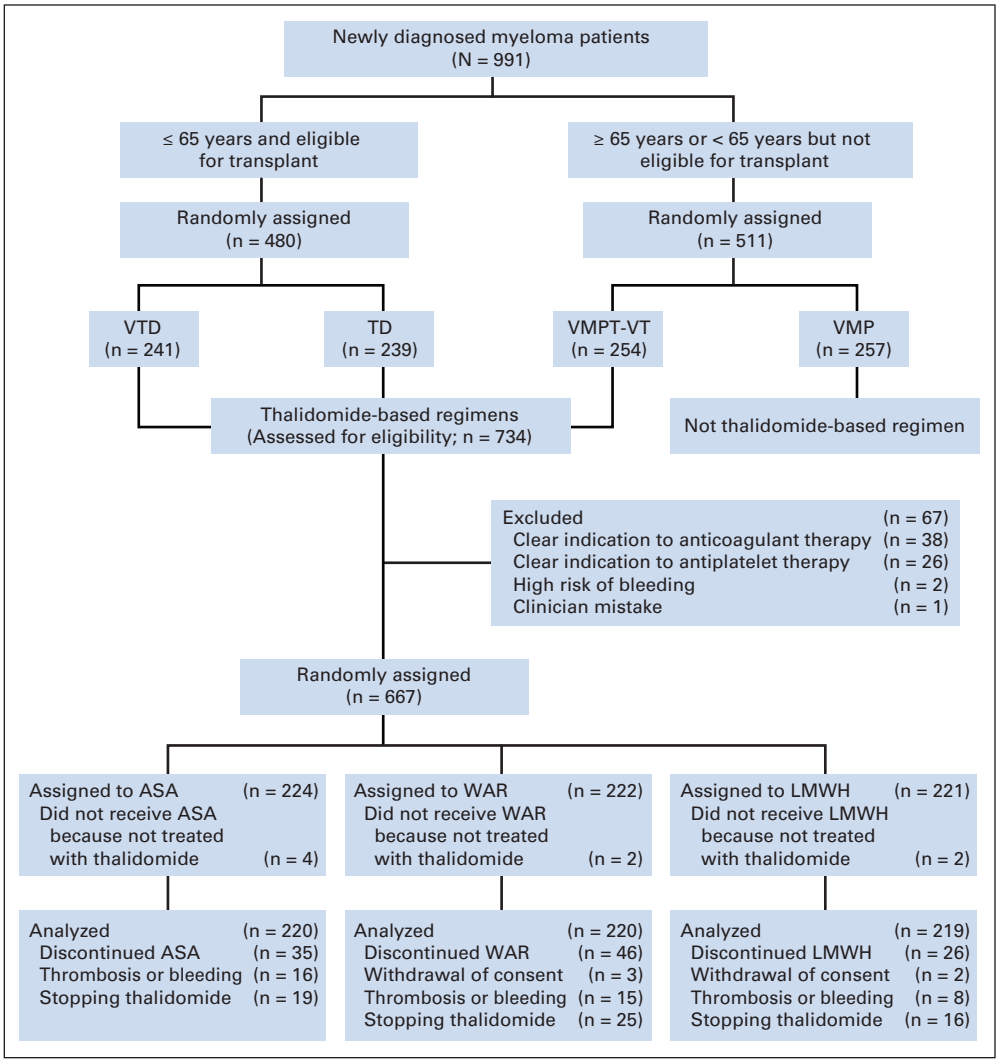


**Fig 1.** CONSORT diagram of patients in the trial. VTD, bortezomib, thalidomide, and dexamethasone; TD, thalidomide and dexamethasone; VMPT-VT, bortezomib, melphalan, prednisone, and thalidomide followed by continuous therapy with bortezomib and thalidomide; VMP, bortezomib, melphalan, and prednisone; ASA, aspirin; WAR, fixed low-dose warfarin; LMWH, low molecular weight heparin.

to thalidomide-free regimens (Fig 1). A total of 667 patients were enrolled onto the substudy, of whom 659 received at least one dose of the study treatment and were included in the efficacy and safety analyses (ASA, n = 220; WAR, n = 220; LMWH, n = 219; Fig 1). Sixty-seven patients were not enrolled onto the study (Fig 1). Patient characteristics were similar in all three groups (Table 1).

During the treatment period, symptomatic deep vein thrombosis, pulmonary embolism, arterial thrombosis, any acute cardiovascular event, or sudden death (composite primary end point) occurred in 14 patients (6.4%) in the ASA group, 18 patients (8.2%) in the WAR group, and 11 patients (5.0%) in the LMWH group (Table 2). The absolute differences were +1.3% (95% CI, −3.0% to 5.7%; $P = .544$) between the ASA and LMWH groups and +3.2% (95% CI, −1.5% to 7.8%; $P = .183$) between the WAR and LMWH groups (Table 3). The risk of composite end point was similar in patients who received ASA or LMWH and were treated with the different induction regimens (Table 4). This risk was also similar in the younger patients who received WAR or LMWH and were treated with thalidomide and dexamethasone or bortezomib, thalidomide, and dexamethasone; WAR was less effective than LMWH in the elderly patients treated with bortezomib, melphalan, prednisone, and thalidomide (absolute difference, +11.3%; 95% CI, 3.4% to 19.2%; $P = .006$; Table 4). The incidence of thromboembolic events, acute cardiovascular events, and sudden deaths was 5.4% in patients receiving thalidomide and bortezomib and 7.2% in patients receiving thalidomide without bortezomib ($P = .60$). In the thalidomide-bortezomib patients, the absolute differences were +1.5% (95% CI, −3.9% to 7.1%; $P = .56$) between the ASA and LMWH groups and +4.4% (95% CI, −1.5% to 10.7%; $P = .13$) between the WAR and LMWH groups. In the thalidomide patients, the absolute differences were +1.0% (95% CI, −7.9% to 9.8%; $P = .81$) between the ASA and LMWH groups and +0.8% (95% CI, −8.0% to 9.5%; $P = .84$) between the WAR and LMWH groups.

The most frequent complications were thromboembolic events; these occurred in 13 patients (5.9%) in the ASA group, 18 patients (8.2%) in the WAR group, and seven patients (3.2%) in the LMWH group in the first 6 months (Table 2). Symptomatic pulmonary embolism occurred in eight patients in the first 6 months, including four patients in the ASA group (one of whom died) and four patients in the WAR group. No pulmonary embolism was reported in the LMWH group. The absolute differences for serious thromboembolic events were +2.7% (95% CI, −1.2% to 6.6%; $P = .173$) between the ASA

  

**Table 1.** Baseline Demographics and Clinical Characteristics of Study Populations

| Demographic or Clinical Characteristic | ASA (n = 220) | | WAR (n = 220) | | LMWH (n = 219) | |
|---|---|---|---|---|---|---|
| | No. of Patients | % | No. of Patients | % | No. of Patients | % |
| Age, years | | | | | | |
| Median | 61 | | 60 | | 62 | |
| IQR | 55-66 | | 54-66 | | 55-66 | |
| ≤ 55 | 54 | 25 | 61 | 28 | 55 | 25 |
| 56-65 | 103 | 47 | 100 | 45 | 102 | 47 |
| 66-75 | 52 | 24 | 43 | 20 | 50 | 23 |
| > 75 | 11 | 5 | 16 | 7 | 12 | 5 |
| Male | 117 | 53 | 115 | 52 | 130 | 59 |
| MM treatment | | | | | | |
| TD | 79 | 36 | 81 | 37 | 76 | 35 |
| VTD | 78 | 35 | 77 | 35 | 79 | 36 |
| VMPT-VT | 63 | 29 | 62 | 28 | 64 | 29 |
| ISS | | | | | | |
| I | 87 | 40 | 84 | 38 | 86 | 39 |
| II | 87 | 40 | 86 | 39 | 80 | 37 |
| III | 34 | 15 | 38 | 17 | 40 | 18 |
| Data missing | 12 | 5 | 12 | 5 | 13 | 6 |
| Creatinine, mg/dL* | | | | | | |
| Median | 0.98 | | 1.0 | | 0.96 | |
| IQR | 0.8-1.19 | | 0.8-1.19 | | 0.8-1.1 | |
| Glycemia, mg/dL* | | | | | | |
| Median | 94 | | 92 | | 93 | |
| IQR | 86-102 | | 85-102 | | 86-102 | |
| Data missing | 13 | 6 | 12 | 5 | 19 | 7 |
| Karnofsky performance status | | | | | | |
| ≤ 70% | 54 | 25 | 64 | 29 | 65 | 30 |
| Data missing | 8 | 4 | 12 | 5 | 8 | 4 |
| Diabetes | 10 | 5 | 9 | 4 | 8 | 4 |
| Cardiovascular disease | 35 | 16 | 48 | 22 | 38 | 17 |
| Hypertension | 29 | 13 | 44 | 20 | 33 | 15 |
| Acute myocardial infarction | 0 | 0 | 1 | 0.5 | 2 | 1 |
| Heart failure | 0 | 0 | 1 | 0.5 | 0 | 0 |
| Arrhythmia | 7 | 3 | 3 | 1 | 4 | 2 |
| Other | 0 | 0 | 0 | 0 | 1 | 0.5 |
| Orthopedic disease | 0 | 0 | 2 | 1 | 1 | 0.5 |
| Dyslipidemia | 4 | 2 | 7 | 3 | 4 | 2 |
| Prior thromboembolism | 2 | 1 | 2 | 1 | 1 | 0.5 |
| > two comorbidities | 7 | 3 | 10 | 5 | 4 | 2 |

Abbreviations: ASA, aspirin; WAR, fixed low-dose warfarin; LMWH, low molecular weight heparin; IQR, interquartile range; MM, multiple myeloma; TD, thalidomide and dexamethasone; VTD, bortezomib, thalidomide, and dexamethasone; VMPT-VT, bortezomib, melphalan, prednisone, and thalidomide followed by continuous therapy with bortezomib and thalidomide; ISS, International Staging System.

*Système International conversion factors: to convert serum creatinine to μmol/L, multiply by 88.4; to convert glucose to mmol/L, multiply by 0.0555.

and LMWH groups and +5.0% (95% CI, 0.7% to 9.3%; $P = .024$) between the WAR and LMWH groups (Table 3). The regression model showed a tendency toward a higher risk of developing thromboembolic events in the following patients: patients older than age 60 years (HR, 1.75; 95% CI, 0.84 to 3.62); patients with more than two comorbidities (HR, 1.43; 95% CI, 0.33 to 6.25); patients with a Karnofsky performance status less than 70% (HR, 1.47; 95% CI, 0.70 to 3.09); patients not receiving bortezomib (HR, 1.38; 95% CI, 0.66 to 2.89); and patients receiving higher doses of dexamethasone (HR, 1.97; 95% CI, 0.72 to 5.39).

After a median follow-up of 24.9 months (IQR, 18.4 to 32.0 months), 58 patients (8.8%) experienced one of the events included in the composite primary end point (Table 2). The cumulative proportions of thromboembolic events, acute cardiovascular events, and sudden deaths adjusted for competing risks at 18 months were 0.08 (95% CI, 0.05 to 0.12) in the ASA group, 0.10 (95% CI, 0.06 to 0.14) in the WAR group, and 0.08 (95% CI, 0.04 to 0.11) in the LMWH group ($P = .69$; Fig 2). The HRs for ASA and WAR versus LMWH, adjusted for competing risks, were 1.13 (95% CI, 0.59 to 2.17; $P = .716$) and 1.31 (95% CI, 0.70 to 2.47; $P = .397$), respectively. Any grade 3 or 4 thromboembolic events were reported in 17 patients (7.7%) in the ASA group, 21 patients (9.5%) in the WAR group, and 11 patients (5.0%) in the LMWH group (Table 2). No late pulmonary embolism was observed. Most grade 3 to 4 thromboembolic events (78%) occurred within the first 4 months; the median times to onset were 2.3 months (IQR, 1.4 to 3.1 months) in the ASA group, 2.3 months (IQR, 1.4 to 3.5 months) in the WAR group, and 4.5 months (IQR, 1.4 to 11.1 months) in the LMWH group. Overall, one patient died in the

**Table 2.** Incidence of Thromboembolic Events, Acute Cardiovascular Events, or Sudden Deaths and Bleeding by Treatment Group and Length of Follow-Up

| Analysis | ASA (n = 220) | | | | WAR (n = 220) | | | | LMWH (n = 219) | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | First 6 Months | | Entire Follow-Up | | First 6 Months | | Entire Follow-Up | | First 6 Months | | Entire Follow-Up | |
| | No. of Patients | % | No. of Patients | % | No. of Patients | % | No. of Patients | % | No. of Patients | % | No. of Patients | % |
| Efficacy analysis | | | | | | | | | | | | |
| Composite primary end point* | 14 | 6.4 | 19 | 8.6 | 18 | 8.2 | 22 | 10.0 | 11 | 5.0 | 17 | 7.8 |
| Any grade 3 or 4 thromboembolic event | 13 | 5.9 | 17 | 7.7 | 18 | 8.2 | 21 | 9.5 | 7 | 3.2 | 11 | 5.0 |
| Deep vein thrombosis | 8 | 3.6 | 12 | 5.5 | 14 | 6.4 | 17 | 7.7 | 6 | 2.7 | 10 | 4.6 |
| Pulmonary embolism | 4 | 1.8 | 4 | 1.8 | 4 | 1.8 | 4 | 1.8 | 0 | 0 | 0 | 0 |
| Arterial thrombosis | 1 | 0.5 | 1 | 0.5 | 0 | 0 | 0 | 0 | 1 | 0.5 | 1 | 0.5 |
| Acute cardiovascular events | 2 | 0.9 | 4 | 1.8 | 0 | 0 | 3 | 1.4 | 4 | 1.8 | 6 | 2.7 |
| Acute myocardial infarction | 0 | 0 | 2 | 0.9 | 0 | 0 | 1 | 0.5 | 3 | 1.4 | 4 | 1.8 |
| Stroke | 1 | 0.5 | 1 | 0.5 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0.5 |
| Sudden death | 1 | 0.5 | 1 | 0.5 | 0 | 0 | 2 | 0.9 | 1 | 0.5 | 1 | 0.5 |
| Safety analysis | | | | | | | | | | | | |
| Major bleeding | 3 | 1.4 | — | — | 0 | 0 | — | — | 0 | 0 | — | — |
| GI | 2 | 0.9 | — | — | 0 | 0 | — | — | 0 | 0 | — | — |
| Urinary tract | 1 | 0.5 | — | — | 0 | 0 | — | — | 0 | 0 | — | — |
| Minor bleeding | 6 | 2.7 | — | — | 1 | 0.5 | — | — | 3 | 1.4 | — | — |
| GI | 1 | 0.5 | — | — | 0 | 0 | — | — | 1 | 0.5 | — | — |
| Urinary tract | 2 | 0.9 | — | — | 0 | 0 | — | — | 0 | 0 | — | — |
| Nasal | 1 | 0.5 | — | — | 1 | 0.5 | — | — | 1 | 0.5 | — | — |
| Skin | 2 | 0.9 | — | — | 0 | 0 | — | — | 1 | 0.5 | — | — |

Abbreviations: ASA, aspirin; WAR, fixed low-dose warfarin; LMWH, low molecular weight heparin.
*The composite primary end point was the first episode of any objectively confirmed symptomatic deep vein thrombosis, pulmonary embolism, arterial thrombosis, acute cardiovascular event (acute myocardial infarction or stroke), or sudden otherwise unexplained death (presumed to be a result of pulmonary embolism, acute myocardial infarction, or stroke).

ASA group (pulmonary embolism), two patients died in the WAR group (acute myocardial infarction and cardiac arrest), and one patient died in the LMWH group (cardiac arrest; Table 2).

The median durations of prophylaxis were 2.6 months (IQR, 2.1 to 4.0 months) in the ASA group, 2.4 months (IQR, 2.1 to 3.5 months) in the WAR group, and 2.6 months (IQR, 2.1 to 4.5 months) in the LMWH group. Thirty-five patients (16%) in the ASA group, 46 patients (21%) in the WAR group, and 26 patients (12%) in the LMWH group discontinued prophylaxis prematurely, mainly because of thromboembolic, cardiovascular, or bleeding events, or because of thalidomide discontinuation for adverse events or progressive disease (Fig 1). There were no statistically or clinically significant differences among the three groups in terms of the incidences of any adverse events during the treatment or follow-up periods. Major bleeding occurred during the first 6 months in three patients (1.4%) who received ASA but in no patients who received either WAR or LMWH. Six patients (2.7%) in the ASA group, one patient (0.5%) in the WAR group, and three patients (1.4%) in the LMWH group had minor bleeding (Table 2).

## DISCUSSION

Our findings showed that, in patients with myeloma treated with thalidomide, the incidence of symptomatic deep vein thrombosis, pulmonary embolism, arterial thrombosis, any acute cardiovascular event, or sudden death was 6% during ASA, 8% during WAR, and 5% during LMWH thromboprophylaxis, without statistically significant

**Table 3.** Absolute Risk Difference of Thromboembolic Events, Acute Cardiovascular Events, or Sudden Deaths and Bleeding During the First 6 Months for ASA and WAR Compared With LMWH

| Event | ASA *v* LMWH | | | WAR *v* LMWH | | |
|---|---|---|---|---|---|---|
| | Absolute Difference (%) | 95% CI (%) | *P* | Absolute Difference (%) | 95% CI (%) | *P* |
| Composite primary end point | 1.3 | −3.0 to 5.7 | .544 | 3.2 | −1.5 to 7.8 | .183 |
| Any grade 3 or 4 thromboembolic event | 2.7 | −1.2 to 6.6 | .173 | 5.0 | 0.7 to 9.3 | .024 |
| Acute cardiovascular events | −0.9 | −2.7 to 0.9 | .313 | −1.4 | −2.9 to 0.2 | .082 |
| Major bleeding | 1.4 | −0.2 to 2.9 | .083 | 0.0 | −1.7 to 1.7 | 1.000 |
| Minor bleeding | 1.3 | −1.3 to 4 | .316 | −0.9 | −2.7 to 0.9 | .313 |

Abbreviations: ASA, aspirin; WAR, fixed low-dose warfarin; LMWH, low molecular weight heparin.

  

**Table 4.** Absolute Risk Difference of Thromboembolic Events, Acute Cardiovascular Events, or Sudden Deaths During the First 6 Months of Treatment for ASA and WAR Compared With LMWH, Stratified by Myeloma Treatment

| | ASA *v* LMWH (heterogeneity test, $P = .748$) | | | WAR *v* LMWH (heterogeneity test, $P = .077$) | | |
|---|---|---|---|---|---|---|
| Treatment | Absolute Difference (%) | 95% CI (%) | *P* | Absolute Difference (%) | 95% CI (%) | *P* |
| TD | 1.0 | −7.1 to 9.1 | .805 | 0.8 | −7.1 to 8.8 | .839 |
| VTD | 0.1 | −8.2 to 8.4 | .982 | −1.1 | −9.1 to 6.9 | .788 |
| VMPT-VT | 3.2 | −1.2 to 7.5 | .151 | 11.3 | 3.4 to 19.2 | .006 |

Abbreviations: ASA, aspirin; WAR, fixed low-dose warfarin; LMWH, low molecular weight heparin; TD, thalidomide and dexamethasone; VTD, bortezomib, thalidomide, and dexamethasone; VMPT-VT, bortezomib, melphalan, prednisone, and thalidomide followed by continuous therapy with bortezomib and thalidomide.

differences between the ASA or WAR groups compared with the LMWH group.

Without thromboprophylaxis, the incidence of thromboembolic events has been reported to be 14% to 26% in patients with myeloma receiving thalidomide plus dexamethasone[23,24] and 10% to 20% in patients receiving thalidomide plus melphalan.[23] In the ASA group, the incidence of thromboembolism was 6% over 6 months. In a previous study, the rate of thromboembolism with ASA prophylaxis was reported to be 11% to 18%.[14] In our study, 8% of patients had thromboembolic events during WAR therapy (6 months). In other studies of patients taking thalidomide, dexamethasone, and fixed low-dose WAR, the rate of thromboembolism has been reported to be 13% to 25%.[11,12,25] In our LMWH group, the incidence of thromboembolism was 3% (6 months), which is consistent with other trials including thalidomide plus LMWH (along with various combinations of dexamethasone, prednisone, and melphalan), where the rate of thromboembolism has been reported to be 0% to 9%.[5,12,26] In our study, the risk of thromboembolism was 1.38 times higher among patients receiving thalidomide without bortezomib, which may support the protective role of bortezomib against thromboembolism. Bortezomib alone or in combination with dexamethasone or chemotherapy did not increase the risk of thromboembolism,[27-29] whereas it seems to confer protection when administered with thalidomide.[16,30] The thalidomide analog lenalidomide is emerging as an interesting alternative in the first-line therapy of myeloma. Most recent trials have included thromboprophylaxis with ASA, which seemed to be effective.[31,32] The combination of lenalidomide-bortezomib-dexamethasone with ASA prophylaxis showed promising results, with a severe thromboembolism incidence of 5%.[33]

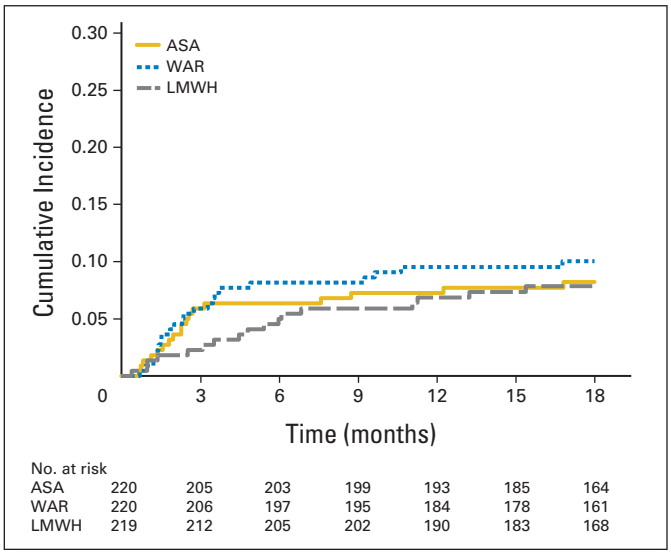


**Fig 2.** Cumulative incidence (proportion) of the primary composite end point, adjusted for competing risks (other causes of death) by treatment group. The follow-up end was defined at 18 months because no additional events occurred after this time. The cumulative incidences of the primary composite end point (thromboembolic events, acute cardiovascular events, or sudden deaths), adjusted for competing risks, at 18 months were 0.08 (95% CI, 0.05 to 0.12) in the aspirin (ASA) group, 0.10 (95% CI, 0.06 to 0.14) in the fixed low-dose warfarin (WAR) group, and 0.08 (95% CI, 0.04 to 0.11) in the low molecular weight heparin (LMWH) group (Gray's test $P = .69$).

Prevention of thromboembolic complications has a central role in the treatment of patients with cancer because the occurrence of thromboembolism may cause chemotherapy discontinuation, increases health expenditure, and requires anticoagulant treatment with a higher risk of complications. To date, only results from small phase II studies on single antithrombotic agents including ASA, WAR, or LMWH are available.[11-14,23,24,26] To our knowledge, our study is the first randomized trial to question which antithrombotic prophylaxis may be more effective. All three regimens were equally effective and safe in patients with standard risk of thromboembolism. LMWH was slightly superior to ASA and WAR, but some practical issues, such as costs and feasibility of self-injection, should be considered. Both ASA and WAR may be considered valid alternative options and are less expensive, are administered orally, and do not require constant monitoring.

In a recent meta-analysis, when thalidomide was used as maintenance after autologous transplantation, the incidence of thromboembolic events was 4% to 6%, and the risk of thromboembolism was 1.95 times higher than in patients who did not receive thalidomide.[10] The use of ASA for a longer period of time may reduce the risk of late thromboembolism, and future studies should address this question.

The rates of pulmonary embolism and bleeding were higher among patients receiving ASA than patients receiving LMWH. The risk of bleeding in the ASA group was comparable with that seen in other studies on thromboprophylaxis in patients with cancer.[34,35] If these increased risks are confirmed in a larger series of patients, they may outweigh the practical advantages of ASA versus LMWH.

Patients at high risk of thromboembolic events, such as patients with previous history of thromboembolism, severe cardiac disease, uncontrolled diabetes, infections, immobilization, or surgery, were not included in our analysis because they had a clear indication of anticoagulant or antiplatelet therapy. This is a major limitation of the

study. LMWH prophylaxis should remain mandatory in patients at high risk of venous thromboembolism for at least the first 6 months of therapy; thereafter, ASA may be considered to reduce the occurrence of late thromboembolic events when long-term thalidomide therapy is planned.

Further limitations of our study are the absence of a placebo group and the open-label design. However, the inclusion of a placebo arm would not have been ethical because all patients enrolled onto this study were treated with thalidomide-containing regimens and could have an increased risk of thromboembolic events.

To conclude, both ASA and WAR showed similar safety and efficacy in reducing thromboembolic complications when compared with LMWH in patients with myeloma treated with thalidomide-based regimens. Antiangiogenic agents may inhibit the healing of chemotherapy-induced endothelial injury, increasing the risk of thromboembolism.[36] Of note, defibrotide, which targets endothelial cell damage, may have a protective effect against thromboembolism, specifically induced by thalidomide.[37,38] New and effective antithrombotic agents with reduced drug interactions and without the need for constant monitoring could optimize patient care and eventually modify the indication for use and duration of thromboprophylaxis.

## AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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