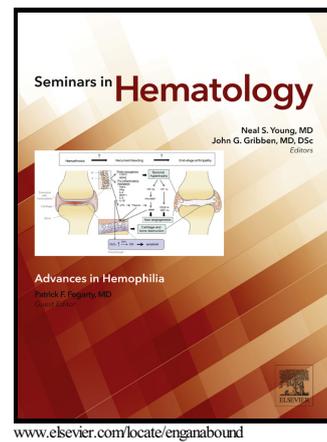


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Thromboprophylaxis in multiple myeloma

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ACCEPTED MANUSCRIPT

**Primary thromboembolic prevention in multiple myeloma patients: an
exploratory meta-analysis on aspirin use.**

Running head: thromboprophylaxis in multiple myeloma

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Multiple myeloma (MM) patients have high risk for venous thromboembolism (VTE).¹ Potent immune-modulatory drugs (IMiDs) are increasingly used to improve survival but VTE risk further increases.²⁻⁴ Observational and randomized controlled trials (RCTs) on IMiDs-treated MM patients reported thromboprophylaxis efficacy either with acetylsalicylic acid (ASA) or low-molecular-weight-heparin (LMWH).⁵⁻⁷ However, there is still no agreement about the best antithrombotic strategy.

We conducted an exploratory meta-analysis and a systematic literature review, following the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) statement,⁸ to better understand the role of ASA, as compared to LMWH or no antithrombotic therapy, in patients with MM, for VTE primary prevention.

Two investigators (GZ and LG) independently searched PubMed and Scopus, without language restriction, from database inception until 30 November 2016, for studies comparing ASA versus other interventions for thromboprophylaxis in patients with MM. In PubMed, we used the following search strategy: (multiple myeloma OR plasma cellular myeloma OR plasma cell myeloma) AND (aspirin OR heparin OR fondaparinux OR “unfractionated heparin” OR UFH OR placebo) AND (deep vein thrombosis OR VTE OR venous thromboembolism OR embolism OR thrombosis OR thrombotic).

RCTs, longitudinal and retrospective studies reporting on VTE frequency in patients with MM treated with ASA vs. other interventions (LMWH and no interventions) were included. Inclusion criteria were: (1) validated MM diagnosis, (2) data on ASA prevention vs. LMWH or no prevention, (3) data on VTE occurrence and (4) peer-review journal only. Studies not including clinical outcomes were excluded such as those that (1) measured only in vitro parameters or used animal models or (2) reported only laboratory data. Two authors (GZ and SG) independently extracted data using a standardized spreadsheet. The Newcastle Ottawa Scale was used to assess the

quality of longitudinal and retrospective studies,⁹ while the Jadad's score was used for RCTs quality assessment.¹⁰

Primary outcome was frequency of new VTE in patients treated with ASA vs. other or no antithrombotic treatments. Secondary outcomes were frequency of new bleeding, cardiovascular events, death or loss to follow-up.

The meta-analysis was performed using the Review Manager (RevMan) software, version 5.3 for Windows [Cochrane Collaboration, <http://ims.cochrane.org/revman>]. When combining studies, the random effects model was used to better account for pre-planned study heterogeneity.¹¹ Odds ratios (ORs) with their 95% confidence intervals (CIs) were calculated. Study heterogeneity was measured using chi-squared and I-squared statistics, with chi-squared $p \leq 0.05$ and I-squared $\geq 50\%$ indicating significant heterogeneity.¹² Publication bias was assessed by funnel plots inspections if more than 4 studies were included for each outcome.

The search identified 940 non-duplicate potentially eligible studies. After excluding 909 papers through title and abstract review and 21 after full text examination, 10 studies were included. These studies (6 longitudinal studies, 2 RCTs and 2 retrospective) included a total of 1,964 participants with MM (1,257 treated with ASA, 640 with LMWH and 67 with no thromboprophylaxis). Quality of the observational studies and RCT was deemed sufficient. In the observational studies, the most common source of bias was the poor assessment of exposure, while in RCTs the lack of appropriate blinding.

As shown in Figure and Table 1, three longitudinal studies including four cohorts^{5, 13, 14} - and one retrospective study¹⁵ - reported a significantly lower frequency of VTE in patients treated with ASA vs. no intervention (OR=0.20; 95%CI: 0.07-0.61, $p=0.005$; $I^2=41\%$). In the longitudinal studies¹⁶⁻¹⁸ comparing ASA vs. LMWH (Figure and Table 1), ASA was associated with higher VTE frequency (OR=2.60; 95%CI: 1.08-6.25; $p=0.03$; $I^2=0\%$). Two RCTs^{19, 20} and one retrospective study²¹ did not show any significant difference in VTE occurrence between patients taking ASA or LMWH (Table 1). Other outcomes of interest were reported in the two RCTs^{19, 20} as

shown in Table 1: bleedings, cardiovascular events, death, or loss at follow-up were similar among patients receiving LMWH, ASA or no interventions.

VTE prophylaxis has become a mainstay therapy in MM patients.²² Anticoagulation is very effective in counteracting thrombosis in many diseases.²³ However, it has been hypothesized that in MM patients the pro-thrombotic process behaves differently: instead of the classical coagulation cascade activation, endothelial cells injury (driven by chemotherapy) with endothelial inflammation and platelet aggregation may represent a possible explanation for ASA efficacy.^{24, 25} The present analysis, including almost 2,000 patients overall, shows that ASA reduces VTE risk by 80% when compared to no antithrombotic therapy. This result confirms the findings of the Eastern Cooperative Oncology Group²⁶ and the South-West Oncology Group:¹⁴ in these trials, investigators had to amend the study protocol by adding ASA for all patients because of exceeding number of VTE. However, a recent systematic review suggested that ASA had an unacceptable high VTE rate in IMiDs-treated MM patients (10.7% of the population).²⁷

Looking at the effect of ASA vs. LMWH, the findings were variable. One retrospective study²¹ and two RCTs^{19, 20} included in our meta-analysis did not show statistical difference in terms of efficacy, with a tendency for higher VTE with ASA. On the other hand, longitudinal studies showed that LMWH was associated with significantly fewer VTE¹⁶⁻¹⁸ and pulmonary embolism was observed only in patients treated with ASA. Only one longitudinal study reported bleeding events¹⁷ and found a similar rate in the two groups (9.3% vs. 9.1%, respectively). No significant differences in bleeding were seen in our meta-analysis of the RCT comparing ASA and LMWH (Table 1). Our main limitation is the low number of studies for each outcome, which prevented us to perform a meta-regression analysis and to stratify for some important confounders (i.e. cancer stage, VTE individual risk factors, LMWH regimens and chemotherapy treatments).

In conclusion, data in literature do not allow to draw definite conclusions on thromboprophylaxis strategies in MM patients. American guidelines suggest anticoagulant therapy in all IMiDs-treated patients²⁸ while European guidelines propose a risk-based approach to choose antithrombotic therapy:²⁹ these strategies are likely to be based on clinical practice and the assumption (yet to be validated) that ASA is safer and less potent than LMWH or warfarin. ASA can be considered as an alternative to no antithrombotic treatment in patients with known contraindications for LMWH. Well powered, large trials are warranted to draw firm conclusions.

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Founding sources: none

Does the paper focuses on malignant research? Yes.

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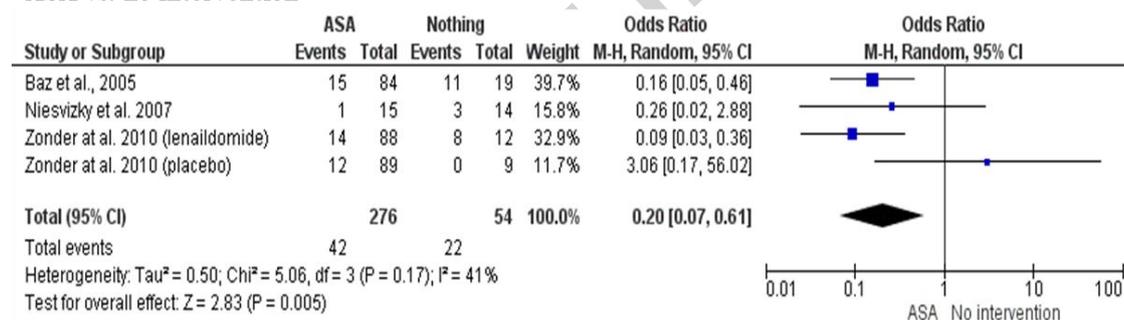
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Figure 1. Forrest plot of longitudinal studies.

ASA vs. no intervention



ASA vs. LMWH

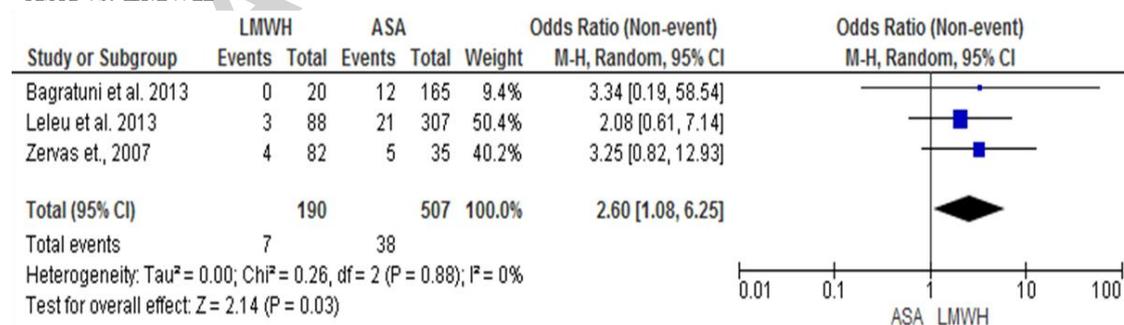


Table 1: Meta-analysis of primary and secondary outcomes in participants with multiple myeloma taking ASA vs. other interventions.

	ASA group			Comparison group		Meta-analysis			Heterogeneity	
	N of studies	N of events	N of participants	N of events	N of participants	OR	95% CI	P-value	I ² (%)	
Primary outcome: VTE										
No intervention (longitudinal)	3	42	276	22	54	0.20	0.07	0.61	0.005	41
No intervention (retrospective)	1	3	38	3	13	0.29	0.05	1.64	0.16	0
LMWH (retrospective)	1	1	40	4	65	0.53	0.08	3.55	0.52	0
LMWH (longitudinal)	3	35	507	7	190	2.60	1.08	6.25	0.03	0
LMWH (RCTs)	2	14	396	12	385	1.16	0.53	2.55	0.71	0
Secondary outcomes (only RCTs ASA vs. LMWH)										
Cardiovascular events	2	4	396	6	385	0.66	0.18	2.36	0.52	Not applicable
Any bleeding	2	9	396	4	385	1.59	0.21	12.12	0.65	40
Lost to follow-up	2	54	396	44	385	1.29	0.82	2.03	0.26	Not applicable
Deaths	2	1	396	1	385	1.00	0.66	15.81	1.00	Not applicable

In bold significant results (p value less than 0.05). Abbreviations: ASA, acetylsalicylic acid; CI, confidence intervals; VTE, venous thromboembolism; LMWH, low molecular weight heparins; N, number; OR, odds ratio, RCT, randomized controlled trial.