Incidence of venous thromboembolism and use of anticoagulation in hematological malignancies: Critical review of the literature

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A B S T R A C T

Venous Thromboembolism (VTE) frequently complicates the course of hematologic malignancies (HM) and its incidence is similar to that observed in high-risk solid tumors. Despite that, pharmacologic prophylaxis and treatment of VTE in patients with HM is challenging, mainly because a severe thrombocytopenia frequently complicates the course of treatments or may be present since diagnosis, thus increasing the risk of bleeding. Therefore, in this setting, safe and effective methods of VTE prophylaxis and treatment have not been well defined and hematologists generally refer to guidelines produced for cancer patients that give indications on anticoagulation in patients with thrombocytopenia. In this review, besides to summarize the incidence and the available data on prophylaxis and treatment of VTE in HM, we give some advices on how to use antithrombotic drugs in patients with HM according to platelets count.

1. Introduction

Venous Thromboembolism (VTE) frequently complicates the course of hematologic malignancies (HM) with a significant impact on morbidity and mortality; its incidence is similar to that observed in high-risk solid tumors (Falanga and Marchetti, 2009; Castelli et al., 2010a). Pathogenesis of VTE, also in HM, is as usual multifactorial depending on: a) type and burden of hematological malignancy, b) type of chemotherapy, c) patients related factors and d) other risk factors such as: platelet and leukocyte count, presence of infections or central venous catheter (CVC), interventional procedures (Prandoni et al., 2005). Moreover, as in solid tumor, neoplastic blood cells and/or leukemic stem cells may release procoagulant, proinflammatory and angiogenic factors including tissue factor, cancer procoagulant (Gale and Gordon, 2001) and tumor necrosis factor alpha (Grignani and Maiolo, 2000). Furthermore, the use of high-dose steroids, erythropoietic and myeloid growth factors contribute to enhance the risk of thrombosis (Wun and White, 2010; Falanga and Marchetti, 2012; Lee and Levine, 1999). In addition, chemotherapy may damage the endothelial wall and determine liver function impairment with reduction in circulating physiological anticoagulants (Falanga and Marchetti, 2012; Lee and Levine, 1999). Finally, thrombosis can also be found incidentally during the diagnostic work up or follow-up for malignancies (den Exter et al., 2012).

Despite the above evidence, prophylaxis and pharmacologic treatment of VTE in patients with HM is challenging mainly because a severe thrombocytopenia frequently complicates the course of treatments or is present since diagnosis. In this particular setting, safe and effective methods of VTE prophylaxis are challenging and mainly based on retrospective data and expert opinions. The lack of prospective studies or evidence-based guidelines in the field of VTE in HM leads hematologists to refer to guidelines produced for patients with solid cancers, not or only partially focused on anticoagulation in patients with thrombocytopenia (Carrier et al., 2013). Taking into account this premise, we performed a systematic review on incidence, prophyaxis and treatment of VTE in HM, particularly highlighting the "gray zones" in the management of frail patients, with thrombocytopenia and at high risk of bleeding

2. Methods

To identify all available studies, a detailed search related to the occurrence of thrombotic complications during hematological malignancies was performed according to PRISMA (Preferred Reporting Items for Systematic reviews and Meta-Analyses) guidelines (Moher et al., 2009). A systematic search was conducted in the electronic databases (PubMed, Web of Science, Scopus, EMBASE), using the following search terms in all possible combinations: Thrombosis, Venous

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Thromboembolism, Pulmonary Embolism, Deep Vein Thrombosis, Atypical site thrombosis, Mesenteric vein thrombosis, Cerebral sinus vein thrombosis, Acute leukemia, Acute myeloid leukemia, Acute lymphoblastic leukemia, Chronic myeloproliferative neoplasms (MPNs), Polycythemia Vera, Essential Thrombocythemia, Primary Myelofibrosis, Jak-2 (V617F) gene mutated MPN, Lymphoma, Lymphoproliferative disease, Multiple Myeloma,Chemotherapy, Radiotherapy, Anticoagulant treatment, Low Molecular Weight Heparin, Oral anticoagulants.

The search strategy was developed with the following language and publication year restrictions: abstracts written in English, with the following timeframe limit: from 1st January 1980 to 31st January 2017. Furthermore, the reference lists of all retrieved articles were manually reviewed. Two independent authors (MN and OA) analyzed each article and performed the data extraction independently. In case of disagreement, a third investigator was consulted (GA). Discrepancies were resolved by consensus. The primary endpoint was to evaluate characteristics and duration of anticoagulant treatment after VTE in patients with hematological malignancies; secondary endpoints were the occurrence and management of recurrent VTE after or during treatment for a first VTE and bleeding.

The main parameters evaluated referred to: indication to anticoagulant treatment in patients with hematological malignancies; anticoagulant treatment schedules adopted, hemorrhagic risk evaluation; efficacy measures of anticoagulant treatment; safety of anticoagulant treatment. In detail, VTE recurrence and bleeding episodes during anticoagulant treatment were evaluated, if available. The inclusion criteria required a confirmed diagnosis of hematological malignancy and VTE. Among available data, particular attention was given to frail patients at high bleeding risk due to severe thrombocytopenia (platelets count < 30.000/μL). In detail, frail subjects were considered all the patients with VTE and hematological malignancies under active chemotherapy treatment and expected or overt severe thrombocytopenia.

Major bleeding was defined as a decrease in hemoglobin of more than 2.0 g/dL, intracranial or retroperitoneal bleeding requiring surgery or blood transfusion, or any other bleeding necessitating suspension of anticoagulation and hemostatic approaches. Minor bleeds comprised all other events. All patient ages were considered.

2.1. Data extraction and quality assessment

According to the pre-specified criteria, all studies related to venous thrombosis in the course of HM were included. Single case-reports, abstract from conferences and animal studies were excluded. To be included in the analysis, a study had to provide data on venous thrombosis (clinically suspected and instrumentally diagnosed), their management, any underlying hematological malignancies and treatment. Because of the wide variability in the outcomes considered, neither formal study quality assessment nor meta-analytic evaluation were performed.

3. Results

The search provided 556 results, of which 480 were excluded because they were single case reports or judged off the topic after scanning the title and the abstract (articles related to biological and laboratory aspects of VTE in cancer, N = 75; articles and reviews not referring to hematological malignancies, N = 297; papers reporting VTE secondary to surgical procedures or medical illness other than blood cancer, N = 108). In addition, seven studies were excluded after evaluation of the full-length paper (Fig. 1). Only three studies specifically evaluated the safety of LMWH in frail thrombocytopenic patients with hematological malignancies (Khanal et al., 2016; Lim and Enjeti, 2016; Imberti et al., 2004). However, these studies do not reach a statistical power to be considered useful.

Before the publication of the CATCH study (Lee et al., 2015a), we have identified only 5 randomized clinical studies dealing with anticoagulant treatment of VTE in cancer patients (Meyer et al., 2002; Hull et al., 2006; Lee et al., 2003; Deitcher et al., 2006; Romera et al., 2009). Only 2 of these studies (Meyer et al., 2002; Hull et al., 2006) accrued patients with HM who are generically reported as hematologic cancer, without any detail on the type and characteristics of HM. The same is reported in the CATCH study, the last of these studies, where 94/900 (10.4%) patients had an unspecified hematologic tumor (Lee et al., 2015a). Therefore, we were unable to adopt these studies for the purpose of our review.

3.1. Acute leukemia

3.1.1. Reported incidences of VTE (Table 1)

VTE incidence in AL ranges from about 2% up to 12% (Ziegler et al., 2005; Ku et al., 2009; De Stefano et al., 2005; Melillo et al., 2007; Vu et al., 2015; Rickles et al., 2007). Ku et al. (2009) have observed a 2-year VTE cumulative incidence of 5.2% in AML and 4.5% in ALL, in a cohort study on 7876 patients with acute leukemia, mainly during the first month of diagnosis: age, comorbidities and CVC were reported as the most frequent associated risk factors for VTE.

De Stefano et al. (2005) evaluated the risk of VTE in a cohort of 379 adult patients with a newly diagnosed AL; overall, VTE episodes occurred in 19 (5%) patients and in 13 cases of entire population (3.4%), it was the presenting manifestation. In particular, VTE at diagnosis was observed in 1.4% of ALL, 9.6% of APL and 3.2% of other AML. Moreover, patients treated with L-asparaginase had a 4.9 fold increased risk of thrombosis (95%CI: 1.5–16). Death rate due to thrombosis was 0.8% and, differently from AML, in ALL the occurrence of VTE increased of 40% the risk of dying within 1 year.

Estimated incidence of VTE in children with ALL, derived from prospective studies, range from 3% to 36.7% (Shapiro et al., 1993; Mitchell et al., 1994; Athale and Chan, 2003). A meta-analysis of 17 studies showed a 5.2%, rate of thrombosis in pediatric patients with ALL mainly during induction therapy with L-asparaginase (Caruso et al., 2006). A similar trend (incidence rate of 5.9%) was observed in adults with ALL from 13 published prospective studies including 323 patients (Caruso et al., 2007).

A study performed by the GIMEMA (Gruppo Italiano Malattie Ematologiche dell'Adulto) on 124 patients with acute promyelocytic leukemia (APL) treated with ATRA and Idarubicin showed an incidence rate of VTE of 8.8% (Breccia et al., 2007).

Vu et al. (2015) recently published a retrospective study on 1295 patients with AL reporting a prevalence of VTE of 10.7%. Most VTEs occurred within 3 months from diagnosis; however, most of them were upper extremity CVC related deep vein thrombosis and occurred mainly in ALL (Table 1).

3.1.2. Treatment options

Most of the reported VTE in AL are CVC-related (Oliver et al., 2015) and their anticoagulant treatment with Low Molecular Weight Heparin (LMWH) has been shown safe and effective when retrospectively compared with no treatment (Frere et al., 2014; van Doormaal et al., 2011).

Recently, in a multicenter study on 1461 patients with AL, our group has demonstrated the occurrence of non-CVC related VTE also in patients with severe thrombocytopenia (PLT < 30.000/μL). Treatment with LMWH, at a full dose for one month and adjusted regimens for the following 3 months resulted safe and effective in the reported cohort of patients with AL (Napolitano et al., 2016).

Treatment recommendations of VTE in children with ALL are extrapolated from adults. The American College of Chest Physicians (ACCP) Evidence based Clinical Practice Guidelines for children (9th edition) defines optimal strategies for the management of thrombosis in children, with and without cancer (Monagle et al., 2012). LMWH remains the most suitable treatment option also in the setting of ALL due
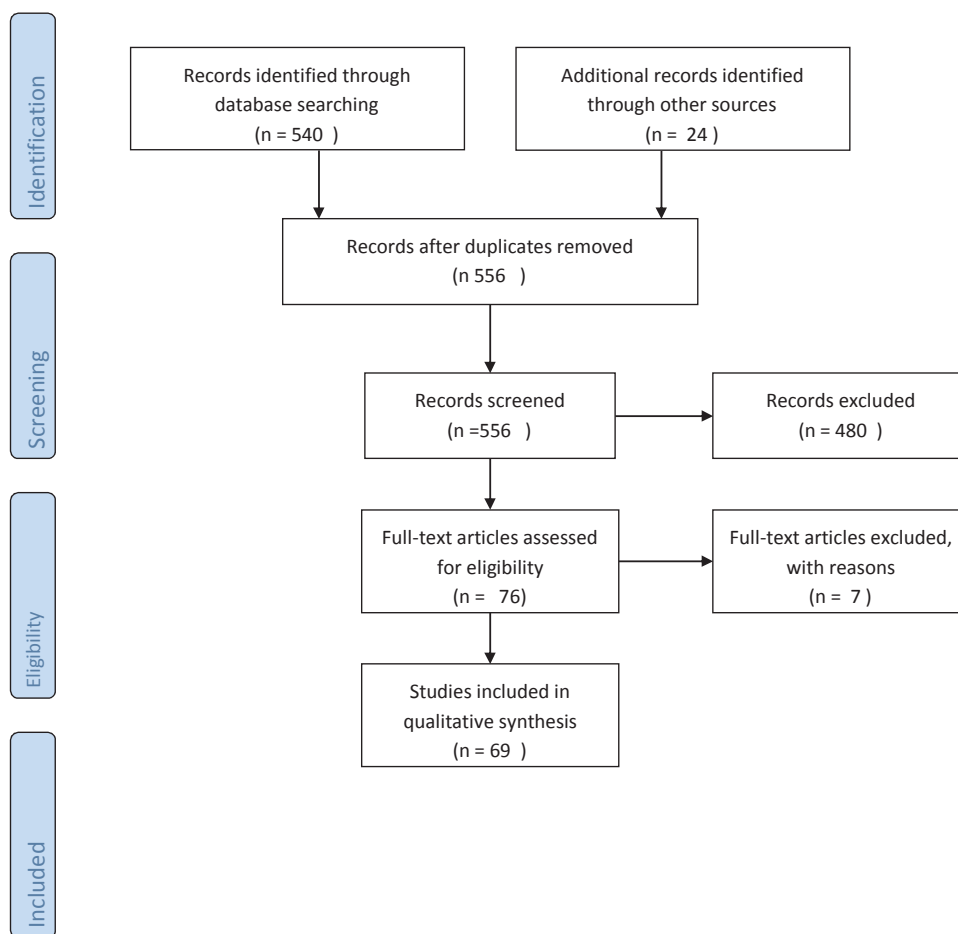
Fig. 1. PRISMA Flow Diagram.

Table 1

Incidence of vte in acute leukemias.

Reference	# pts	Type of study	# VTE	%
a) Acute Myeloid Leukemia				
21	485	Retrospective	8	1.6
22	5057	Registry	183	3.6
23	279	Observational Cohort	12	5.2
24	51	Prospective	5	8.9
25	923	Retrospective	78	8.5
b) Acute Lymphoblastic leukemia				
21	185	Retrospective	4	2.1
22	2482	Registry	113	4.5
23	69	Observational Cohort	7	10.6
24	42	Prospective	2	4.5
25	299	Retrospective	53	17.7
27	15	Prospective	1	6.6
30	1752	Meta-analisys in pediatric patients	91	5.2
31	323	Meta-analisys in adult patients	19	5.8
c) Acute Promyelocitic Leukemia				
21	49	Retrospective	3	6.1
22	337	Registry	12	3.6
23	31	Observational Cohort	5	8.4
24	10	Prospective	4	28.5
25	73	Retrospective	8	11
32	124	Prospective	13	10.5

to frequent periods of thrombocytopenia and intermittent temporary cessation for lumbar punctures. However, it is suggested that platelet count should be maintained above 50,000/μL in patients on therapeutic anticoagulation, while consideration should be given to temporary cessation or dosage reduction of anti-coagulation when there is an inability to maintain platelet count at that level (Monagle et al., 2012;

Sutor et al., 2004).

In children, to avoid late organ damages, thrombolysis is frequently taken into account as a safe treatment option; even though, a survey of pediatric hematologist and oncologists from USA, has shown no consensus on indications, dose, mode of delivery, or duration of thrombolysis therapy in young patients with ALL (Yee et al., 2009). Recently, Ross et al. (2016) have retrospectively evaluated anticoagulant treatment administered to 122 patients with malignancies, 26 of these patients (21%) were treated with direct oral anticoagulants (DOACs). This study showed VTE recurrences in 7.7% of patients receiving DOACs and 7.9% of patients treated with LMWH (P = n.s.), without significant differences in the incidence of major bleeding complications.

Therefore, from this small study DOACs seem equivalent to LMWH for safety and efficacy. However, the low number of hematological malignancies included in this study, does not allow extrapolating these results in all AL.

Antithrombin (AT) replacement is still a debated issue in the management of thrombosis after asparaginase in patients with ALL. Fresh frozen plasma transfusion resulted ineffective in raising antithrombin levels (Abbott et al., 2009), while PARKAA study (Mitchell et al., 2003) showed a trend towards efficacy and safety of AT concentrates.

So far, there are no prospective studies addressing the issue of VTE prophylaxis in patients with AL; some data can be obtained from studies on CVC-related thrombosis prophylaxis.

Lee et al. (2015b) have recently performed a survey to define prophylactic approaches of VTE in AL, they found that approximately in half cases only mechanical prophylaxis (13%) or no treatments (36%) at all were administered. When pharmacological prophylaxis was adopted, sub-cutaneous heparin, alone or in combination with mechanical prophylaxis (sequential compression device or stockings), was

the treatment of choice, either during induction or maintenance chemotherapy.

Couban et al. (2005) performed a placebo controlled study on prophylaxis with low dose warfarin to prevent CVC related thrombosis, including approximately 24% patients with AL. Prophylaxis was discontinued for platelet count < 20,000/μL or if there were many treatment interruptions. Treatment with low dose warfarin was well tolerated despite the incidence of CVC related thrombosis was not influenced by prophylaxis and treatment.

Some studies, including patients with AL and CVC-related thrombosis, have confirmed these results and the safety of prophylactic low dose warfarin (Cortelezzi et al., 2005; Del Principe et al., 2013; Niers et al., 2007).

However, a randomized prospective study conducted by Verso et al. (2005) in 385 cancer patients of whom 33(8.5%) with HM requiring CVC, did not demonstrate a utility of prophylactic therapy in reducing CVC thrombosis in the entire population. No data are available for the subgroup of patients with HM.

Elhasid et al. (2001) reported the safe administration of LMWH (enoxaparin, mean dose, 0.84 mg/kg once daily), in comparison with historical controls not treated with prophylactic LMWH, in preventing thrombosis in 41 patients with ALL. Enoxaparin was administered subcutaneously starting at the first dose of L-asparaginase until 1 week after the last dose. Thrombosis was not reported during 76 courses of administered treatment. In the historical control group of 50 ALL children, two had thromboembolisms during L-asparaginase treatment.

Enoxaparin prophylaxis combined to antithrombin infusion resulted effective in preventing symptomatic VTE in 41 children with ALL, when compared to antithrombin alone (n = 71), results from the reported prospective cohort study (Meister et al., 2008) however have not been yet confirmed in a randomized trial

3.2. Chronic myeloproliferative neoplasms

3.2.1. Reported incidence of VTE (Table 2)

In the largest available epidemiological study on Polycythemia Vera (PV) by the European Collaboration on Low-dose Aspirin in Polycythemia Vera (ECLAP), pulmonary embolism determined 8% of all deaths with a cumulative rate of non-fatal thrombosis of 3.8 events per 100 persons per year (Marchioli et al., 2005). Incidence of VTE prior and after trial entry are reported in Table 2, among the 1638 patients of this study, 518 were randomized to receive or not low-dose of aspirin (Landolfi et al., 2004).

The incidence of VTE in Essential Thrombocythemia (ET) has been reported in two prospective studies, as 1% patient-years (Harrison et al., 2005; Gisslinger et al., 2013). In primary myelofibrosis, non-fatal VTE was reported in 0.76% of patients per year (Barbui et al., 2010). At diagnosis, the prevalence of clinically relevant thrombosis has been reported to vary from 11 to 39% in PV and from 8 to 29% in ET (Papadakis et al., 2010; Elliot and Tefferi, 2005; Tefferi and Barbui,

2015).

Chronic myeloproliferative neoplasms (MPN) are characterized by the occurrence of VTE in atypical sites, in particular splanchnic vein thrombosis (SVT) and Budd-Chiari syndrome. Reported prevalence of SVT in MPN ranges from 1% (Gangat et al., 2006) to 23% (De Stefano et al., 2007) and higher rates of SVT are reported in female sex. Clinical risk predictors for thrombosis in MPN do not distinguish between arterial and venous events, (Carobbio et al., 2011) and include: age, a previous history of thrombosis and increased leucocyte blood count (Barbui et al., 2009). Carobbio et al. (2011) performed a multivariate analysis of 891 patients with ET for variables including age > 60 years, history of thrombosis, cardiovascular risk factors, JAK-2 mutational status, leukocyte count > 11,000/μL and platelets count > 1,000,000/μL, they observed that only male gender was significantly associated with a higher risk of VTE (HR 1.99;95% CI 1.03–3.83).

Campbell et al. (2005) studied 806 patients with ET showing a higher risk for thromboembolic events in patients with JAK-2 V617F mutated ET compared with JAK-2 V617F wild type ET.

A systematic review has shown that patients with JAK-2 (V617F) mutation have a 2-fold risk of developing thrombosis, both of venous and arterial vessels (OR 2.49 and 1.77, respectively), (Lussana et al., 2009).

In ET, the risk of thrombosis has been reported as increased by the concomitance of JAK-2 V617F mutation and inherited thrombophilia (De Stefano et al., 2009).

3.2.2. Treatment options

Current guidelines suggest managing patients with VTE in MPN like subjects with persistent risk factors (Kearon et al., 2016). In the largest available study on VTE recurrences after a first episode in MPN, long-term anticoagulation determined a 63% reduction in the risk of recurrence without a significant increase in the incidence of major bleeding, as compared with patients without antithrombotic treatment (1.2% patient-years), (De Stefano et al., 2008).

Long-term treatment with low dose aspirin determined a significant lower rate of relapses, compared to VKA (Vitamin K Antagonists) (ASA, HR 0.42; 95%CI: 0.22–0.77; VKA, HR 0.32; 95%CI: 0.15–0.64), (De Stefano et al., 2008). Moreover long-term oral anticoagulant treatment for SVT is recommended.

In a survey including 42 patients with MPN, anticoagulant therapy showed a reduction in the risk of portal vein thrombosis extension and recurrence without significantly affecting incidence and severity of bleeding complications (Condat et al., 2001).

In PV, 2 randomized clinical trials showed a significant reduction of cardiovascular events by cytoreductive treatment (for reduction of hematocrit) and low dose ASA (Landolfi et al., 2004; Marchioli et al., 2013). Prophylaxis with low doses of aspirin (ASA, 100 mg/day) has been shown to significantly reduce the risk of thrombotic events including major venous thromboembolism (RR = 0.40; 95% CI: 0.18–0.91; P = 0.0277), (Campbell et al., 2005). The clinical efficacy of

Table 2
Incidence of VTE in Myeloproliperative Neoplasms (MPN).

Ref.	MPN	# of Patients	Type of study	# VTE (%) Prior trial entry	# VTE (%) After trial entry	Risk Factors for VTE
51	PV	1638	Prospective	225 (13.7)	88 (5.4)	Age ≥65 years Prior thrombosis
53	ET	404 HU + ASA	OLRT	29 (7.1)	14 (3.5)	NR
		405 ANA + ASA		20 (4.9)	3 (0.7)	
54	ET	122 ANA	RCT	NR	2	NR
		131 HU			6	
55	PMF	707	Prospective	32 (4.5)	31 (4.4)	Age > 60 years, JAK2+, WBC ≥15.000/μL
63	ET	414 JAK2 +	Prospective	11 (2.7)	12 (2.9)	Presence of JAK2 V617F mutation
		362 JAK2 wt negative		2 (0.55)	4 (1.1)	
64	ET	1173 JAK2 +	Meta-analysis	127 (10.8)		Presence of JAK2 V617F mutation
		953 JAK2 wt		41 (4.3)		

Legend: Ref: reference number; PV: Policithemia Vera; PMF: Primary myelofibrosis; ET: Essential Thrombocitemia; HU: Hydroxiurea; ASA: Aspirin; ANA: Anagrelide; DBPCT: Double Blind Prospective Controlled trial RCT: Randomized controlled trial; OLRT = open label randomized trial; NR = not reported; wt = wild type.

prophylaxis with ASA in patients with essential Thrombocythemia is, on the contrary, not based on randomized clinical trials. Moreover, it must be taken into account the potential higher bleeding risk of patients with a platelet count > 1,500,000/μL (Barbui et al., 2011; Barbui et al., 2013).

Alvarez-Larrán et al. (2010) performed a retrospective study on 300 patients with low-risk ET showing that thrombosis was unaffected by ASA. A subgroup analysis showed that JAK-2 mutated subjects with ET suffered more venous thrombosis than un-mutated subjects.

Low-dose ASA is currently recommended in essential thrombocythemia patients with microvascular symptoms like transient neurological attacks (Barbui, 2011).

An observational study in ET, combining ASA with chemotherapy reported a significant reduction of vascular events, including venous thrombosis, only in patients older than 60 years, when compared to chemotherapy alone (29.2 vs. 8.6 events of VTE/1000 patients year, P = 0.02) (Alvarez-Larrán et al., 2013). This significant reduction in VTE was associated to a significant increase in bleeding complications (14.4 vs. 1.4 hemorrhagic events/1000 patients-years, P = 0.006).

Combined treatment with ASA and anagrelide for ET resulted in a significant reduction of VTE when compared with ASA plus hydoxyurea (HR 0, 27; 95% CI: 0.11–0.71; P = 0.006), (Harrison et al., 2005) even though this reduction in VTE was associated with a higher bleeding risk. On the contrary, the ANAHYDRET trial (Gisslinger et al., 2013) showed no significant differences between hydroxyurea and anagrelide in the occurrence of VTE and bleeding events.

Data from the RESPONSE trial, where the new JAK-2 inhibitor ruxolitinib was administered to patients with PV unresponsive or not tolerant to hydroxyurea, showed a lower rate of VTE in the ruxolitinib group: with thromboembolic event rate per 100 patient-years of 1.8 in patients randomized to ruxolitinib vs. 8.2 in those treated with best available therapy (Verstovsek et al., 2016).

3.3. Hodgkin's and non-Hodgkin's lymphoma

3.3.1. Reported incidence of VTE (Table 3)

Two studies have prospectively evaluated VTE incidence in patients with lymphoma (Ottinger et al., 1995; Khorana et al., 2005). In the first study, conducted in 593 patients with high-grade non-Hodgkin's lymphoma, a 6.6% incidence rate of VTE was reported (Ottinger et al., 1995). The second study, performed in ambulatory patients found a VTE rate of 8.16% in Hodgkin's disease and 1.5% in non- Hodgkin's lymphoma (Khorana et al., 2005). Mohren and colleagues (Mohren et al., 2005), in a single center analysis found an overall thromboembolic event incidence of 7.7% in 1038 treated lymphoma patients with a statistically significantly higher incidence in high grade than in low-grade lymphoma. These findings, along with the fact that most patients had their thrombotic event during or after chemotherapy, suggests that histotype and chemotherapy may have a key role in triggering thrombotic events in patients with lymphoproliferative disease.

A registry-based analysis including 16,755 cases of non-Hodgkin's lymphoma, found a 4.0% 2-year cumulative incidence of acute VTE that was also a strong predictor of decreased survival (Mahajan et al., 2014). As regards to the pathogenesis of VTE in lymphomas, it has been observed that, beside the classical conditions (immobility, infections, age, CVC, chemotherapy, use of hematopoietic growth factors (Castelli et al., 2010b), a mediastinal mass in pediatric patients could be an additional risk factor (Athale et al., 2008).

A meta-analysis (Caruso et al., 2010) regarding 18,018 lymphoma patients belonging to 29 independent cohorts revealed a global IR (Incidence Risk) of thrombosis in lymphoma patients higher than 6% with most of the events occurring during the treatment of the disease. Because in the majority of the studies, patients were followed-up from diagnosis to an extent of 1–3 years (treatment period being usually of 6–12 months), this pooled IR has to be considered particularly high. However, in this meta-analysis, 95% of thrombosis occurred during

Table 3
Incidence Of VTE In Lymphomas.

Reference	# pts	Type of study	# VTE	%
a) Non Hodgkin Lymphoma				
76	593	Prospective clinical trial	34	6.6
77	267	Observational	4	1.5
78	348 High Grade	Retrospective	37	10.6
	485 Indolent		28	5.77
79	16,755	Registry	603	3.6% at 1 ys
			670	4.0% at 2 ys
81	75 Pediatric	Retrospective	9	12
82	15,410	Meta-analysis	997	6.5
b) Hodgkin Lymphoma				
77	49	Observational	4	8.16
78	193	Retrospective	14	7.25
82	2505	Meta-analysis	118	4.7
c) CNS Lymphoma				
78	12	Retrospective	1	8.33
82	54	Meta-analysis	26	48.1
86	42	Retrospective	25	59.5

treatment and therefore, it was impossible to distinguish between the thrombogenic effects of lymphoma itself or of its treatment. Nevertheless, the high rate of thrombotic events observed in lymphoma patients stands as a problem in their clinical management, irrespective of the cause, either lymphoma or the treatments. Moreover, the subgroup analyses revealed a different pooled Incidence Risks (IRs) of thrombotic events in different subtypes of lymphoma (Caruso et al., 2010). In particular, compared with all types of NHL, HL patients had a statistically lower incidence of thrombosis and high grade NHL exceeded low grade NHL in the rate of thrombotic events. An increased incidence of VTE was also observed in lymphomas with advanced stage.

Ottinger et al. (1995) investigated the risk factors for VTE in different subtypes of high grade NHL, the only independent risk factor for VTE in this population was the presence of mediastinal clear cell subtype, and the bulky mediastinal mass responsible of veins compression was the dominant cause of thrombosis. In addition, also the advanced stage was an independent risk factor for VTE. Compression of veins by local growth of lymphoma was identified as the main cause of VTE in 50% of cases, including all 12 patients who developed thrombosis before treatment and one third of patients with thrombosis during chemotherapy (Ottinger et al., 1995).

A large population-based case-control study performed in cancer patients, showed that patients with lymphoma had the greatest risk of venous thrombosis (odds ratio [OR] 10.2, 95% CI, 1.4–76.9), followed by lung and gastrointestinal cancer patients (Blom et al., 2005).

Another study on more than 65,000 neutropenic cancer patients reporting more than 5000 thrombotic events revealed that patients with lymphoma and leukemia accounted for one third of venous and nearly one half of arterial events (Khorana et al., 2006). Recently, in a validated predictive model for chemotherapy associated thrombosis, lymphoma resulted in the high-risk group for developing thrombosis, along with lung, gynecologic, and genitourinary cancers with an independent OR for Thrombosis of 1.5 (0.9–2,7), (Khorana et al., 2008). These investigators indicated the following 5 variables responsible for an increased incidence of VTE: site of cancer, platelet count 350,000/μL or greater, hemoglobin less than 10 g/dL and/or use of erythropoiesis-stimulating agents, leukocyte count greater than 11,000/μL, and body mass index 35 kg/m^2 or greater.

Because data regarding the type of therapy across studies, were heterogeneous, and not all authors reported name and dosage of the drugs used, it was not possible to evaluate the role of the different treatment interventions in the risk of VTE.

As for Central Nervous System Lymphoma (CNSL), a study including different types of NHL revealed thrombotic events in 12 patients with CNSL with IR of 8.3% a rate similar to that found in other high grade NHLs (Mohren et al., 2005). In a second study, including only CNSL the

incidence rate of VTE was extremely high reaching 59% (Goldschmidt et al., 2003). This high incidence was also confirmed in the meta-analysis by Caruso et al. where among 54 CNS lymphoma, 26 (48.1%) had a VTE.

3.3.2. Treatment options

As in other hematological malignancies, the use of anticoagulant drugs may contribute to an increased risk of bleeding. Therefore, taking into account this increased bleeding risk, anticoagulation, as thromboprophylaxis, is rarely prescribed in patients with lymphoma differently from treatment of VTE. Considering that thrombosis is a frequent event in lymphoma patients and it is associated with several detrimental effects, the possibility of stratifying the risk would allow an appropriate use of anticoagulant treatment in patients at high risk according to clinical guidelines. The presence of high grade Lymphoma, advanced stage of disease, mediastinal clear cell subtype, vein compression, congenital thrombophilia and use of CVCs could represent risk factors for thrombosis occurrence and should therefore be evaluated for antithrombotic prophylaxis with LMWH.

As proposed by ASCO guidelines, in cancer patients, thromboprophylaxis may be suggested in all hospitalized lymphoma patients; whereas in outclinic patients, prophylactic anticoagulation is recommended only for those receiving thalidomide or lenalidomide, providing that in both situations a platelet count is > 50,000/μL (Lyman et al., 2007).

3.4. Monoclonal gammopathy of undetermined significance (MGUS) and multiple myeloma (MM)

3.4.1. Reported incidence of VTE (Table 4)

Compared with the general population, patients with MGUS and MM have a higher risk of deep vein thrombosis (DVT) as clearly demonstrated by Kristinsson and coworkers in a study published in 2008 (Kristinsson et al., 2008). In this study, the authors have compared the incidence of DVT in 2374 MGUS and 6192 MM to that observed in 4,187,631 patients admitted during a period of 16 years (October 1, 1980–September 30, 1996) in the US Veterans Affairs hospitals. The results of this study demonstrated that compared with the entire study population, the relative risk (RR) of DVT after a diagnosis of MGUS or MM was 3.3 (95% CI 2.3–4.7) and 9.2 (95% CI 7.9–10.8), respectively. The most prominent excess risk of DVT was found during the first year after diagnosis of MGUS (RR = 8.4; 95% CI 5.7–12.2) and MM (RR = 11.6; 95% CI, 9, 2–14.5).

The introduction of immunomodulatory (IMiDs) drugs in the

standard treatment of MM, especially when combined with dexamethasone or other glucocorticoids and/or cytotoxic chemotherapy, has further increased the risk of DVT among MM patients (Palumbo et al., 2008; Musallam et al., 2009). Two meta-analysis have confirmed these data (El Accaoui et al., 2007; Carrier et al., 2011).

In a prospective analysis of 310 individuals (Sallah et al., 2004) with MGUS the incidence of VTE was 6.1%, thus confirming the rate of 7.5% observed in a retrospective study on 174 patients (Srkalovic et al., 2004). More recently, a retrospective cohort study conducted in Italy on 1491 MGUS patients found that the VTE risk was higher when the serum monoclonal protein concentration exceeded 16 g/L (Za et al., 2013). However, in a study analyzing the Swedish Cancer Registry (Kristinsson et al., 2010) to identify all MM patients diagnosed between 1958 and 2006 and a nationwide MGUS cohort, diagnosed during the same period, the risk of thrombosis did not vary by M-protein concentration (> 10 g/L or < 10 g/L). Nevertheless, the risk of venous and arterial thrombosis was increased at 1, 5 and 10 years after diagnosis in both MGUS and MM patients (Table 4). Moreover, only IgG and IgA (but not IgM) MGUS had an increased risk for venous and arterial thrombosis. The study population of this study was represented by 18,627 MM and 5326 MGUS who were compared to 70,991 and 20,161 matched controls respectively (Kristinsson et al., 2010).

3.4.2. Treatment options for multiple myeloma

Panel consensus from the International Myeloma Work Group (IMWG) has agreed that the choice of thromboprophylaxis depends on the individual risk of VTE, as determined by patient and treatment related factors, such as obesity, prior VTE, central venous catheter or pacemaker, immobilization, recent surgery, comorbidities, blood clotting disorders, use of erythropoietin stimulating agents, and myeloma therapy (IMiDs, high dose dexamethasone or doxorubicin) (Palumbo et al., 2008).

ASA is recommended for patients with one or no risk factors, and LMWH for those with more than one risk factor (Palumbo et al., 2008). However, the optimal approach to thromboprophylaxis has not yet been established and published data show conflicting results. Therefore, further randomized controlled trials are needed to address this important clinical need (Carrier et al., 2011; Al-Ani et al., 2016).

3.5. Amyloidosis AL

3.5.1. Reported incidence of VTE

Amyloidosis AL may affect hemostasis with severe thrombotic (Falk et al., 1997; Freeman et al., 2012; Halligan et al., 2006) and bleeding complications (Gamba et al., 2000; Yood et al., 1983). Nephrotic syndrome, a common presentation of AL, may contribute to the risk of VTE, in this population, because it is associated with hypercoagulability (Christiansen et al., 2014; Kerlin et al., 2012). Other potential contributors to VTE risk in AL are, as in MM, immunomodulatory agents (IMiDs) (Bennett et al., 2006). Recently Bever et al. (Bever et al., 2016) reported that 65/629 patients (7%) with AL, presenting to a single referral center, experienced at least one venous thromboembolic event and in 80% of these 65 patients, the events manifested within one year prior to or following diagnosis. In this setting, serum albumin < 3 g/dl was associated with increased risk of VTE, with a hazard ratio of 4.30 (CI 1.60–11.55; P = 0.0038). Severe bleeding complications were observed in 5 out of 57 patients with venous thromboembolism undergoing anticoagulation with LMWH. Therefore, anticoagulant treatment may be associated with significant hemorrhagic complications in amyloidosis AL. A better understanding of the causes of the patients who are at risk of VTE may help clinicians in the management of these patients and low levels (< 3 gr/dl) of serum albumin is strongly correlated with an increased risk of VTE in patients with Amyloidosis AL.

3.5.2. Treatment options for amyloidosis

Given the high rate of bleeding complications in these patients,

Table 4
Incidence Of VTE In Paraproteinemias.

Reference	# pts	Type of study	# VTE	%VTE
a) MGUS				
88	2374	Observational	31	1.3
93	310	Prospective	19	6.1
94	174	Observational	13	7.4
95	1491	Retrospective	49 before diagnosis	3.3
			33 after diagnosis	2.2
			82 Total	5.5
96	5326	Registry	85 at 1 yr	1.6
			212 at 5 yr	4.0
			317 at 10 yr	6.0
b) Multiple Myeloma				
88	6192	Observational	151	2.4
94	404	Prospective	40	9.9
96	18,627	Registry	404 at 1 yr	2.1
			722 at 5 yr	3.9
			832 at 10 yr	4.5
c) Amyloidosis AL				
100	2132	Registry	40	0.1
106	929	Retrospective	65	7

prophylactic anticoagulation cannot be recommended without prospective randomized trials determining the risk/benefit ratio of prophylactic anticoagulation.

3.6. Waldenström macroglobulinemia (MW) and lymphoplasmocitic lymphoma (LPL)

3.6.1. Reported incidence of VTE

Reports on the risk of VTE in patients with WM or LPL are limited. Hultcrantz, et al. (Hultcrantz et al., 2014) assessed the risk of venous and arterial thrombosis in WM/LPL patients in a large population-based cohort study conducted in Sweden. In this study, comparing the incidence of thromboembolism in 2190 patients with WM/LPL and 8086 matched controls, WM/LPL had a significantly increased risk of venous thrombosis and the highest risk was observed during the first year following diagnosis (HR = 4.0, 95% CI 2.5–6.4). The risk persisted significantly elevated at 5 (HR = 2.3, 95% CI 1.7–3.0) and 10 years following diagnosis (HR = 2.0, 95% CI 1.6–2.5). No increased risk of arterial thrombosis was observed at any time during follow-up time. The results are consistent with previous findings showing that patients with IgM MGUS do not have an increased risk of arterial thrombosis (Za et al., 2013). The reason for the elevated risk of venous thrombosis is as usual multifactorial and hyperviscosity associated with a high IgM paraprotein may play an important role (Stone and Bogen, 2012; Kwaan, 2013). The potential role of thromboprophylaxis in WM/LPL, especially during the first year after diagnosis and in patients treated with thrombogenic agents needs to be assessed to further improve outcome in WM/LPL patients.

3.6.2. Treatment options for WM and LPL

It has been suggested that IgM paraprotein can impair platelet aggregation and thereby prevent arterial thromboembolism (Kwaan, 2013). The findings of increased risk of VTE indicate that certain WM/LPL patients may benefit from thromboprophylaxis with LMWH.

4. Discussion

Prophylaxis and therapy of VTE remains a challenging issue in patients with HM due to the high incidence of thrombocytopenia observed in this setting. Available data on VTE in HM are often difficult to compare for several reasons: a) the different type of HM; b) the different stage of the diseases; c) the different antineoplastic chemotherapies; d) the small number of patient enrolled in the studies.

Patients with HM may have profound abnormalities of the hemostatic system, predisposing them to an increased risk of hemorrhagic complications. Therefore, because of the lack of specific guidelines for the prophylaxis and management of VTE in HM, hematologists apply the clinical experience derived from guidelines in cancer patients.

The unique contribution of this review consists in the fact that for the first time VTE diagnosis and management has been detailed for each subtype of HM.

The preferred option for prophylaxis and treatment of VTE in patients with cancer is LMWH because it is more effective than warfarin for the secondary prevention of VTE in cancer patients (Hull et al., 2006). Data related to the efficacy and safety of anticoagulation with DOACs are limited to few patients, and no reliable indications may be given. Therefore, the administration of DOACs is currently not supported by well-designed clinical trials.

From our results it is evident that randomized controlled trials (RCT) dedicated to the incidence, prophylaxis and treatment of VTE in HM are lacking with the exception of studies conducted in PV and ET (Table 2). These RCT specifically designed for PV and ET have clearly indicated that the introduction, since the diagnosis, of aspirin in the treatment of these patients clearly prevent cardiovascular events. Moreover, from these studies it was evident the role of JAK2 mutation and leukocytosis as risk factors for VTE. As for acute leukemias, the

presence of severe thrombocytopenia during induction and consolidation therapies has greatly limited the use of antithrombotic prophylaxis and treatments in these patients. Therefore, we urgently need RCT to identify safe and efficient antithrombotic drugs that may be utilized in patients with acute leukemias during induction and consolidation therapies. These studies should also contribute to verify which is the lower platelet level for safe and efficient administration of these drugs. Unfortunately, the RCT conducted in cancer patients do not provide useful clinical information about the HM enrolled in these studies. Therefore, their results did not contribute to the solution of this problem and the few studies available in acute leukemias did not have sufficient statistical power to answer these important questions.

Several studies with low statistical power, suggest that antithrombotic drugs are needed to prevent VTE in MM patients treated with IMiDs even though none of these studies has clearly indicated which should be the preferred drug. Therefore, investigators use aspirin of LMWH as prophylaxis based on what has been suggested by a panel consensus from the IMWG (Palumbo et al., 2008). However, also in this setting we need well-designed randomized clinical trials to have useful guidelines based on objective results rather than on expert opinions. Awaiting these studies, we continue to use what has been proposed by the panel consensus of the IMWG (Palumbo et al., 2008). Because of their similarity with solid tumors, prophylaxis and treatment of VTE in Hodgkin and non-Hodgkin lymphomas may follow the guidelines proposed for cancer patients (Lyman et al., 2007).

Table 5 summarize our personal suggestions for the prophylaxis and treatment of VTE in HM. We suggest discontinuation of antithrombotic drugs for platelets count ≤ 50.000/μL in case of aspirin and with platelets count ≤ 20,000/μL in case of LMWH. Full dose of aspirin and LMWH should be given with platelets count > 50,000/μL. In case of platelets count between 20,000 and 50,000/μL, we suggest a 50% dose reduction of LMWH.

5. Conclusion

VTE is a frequent complication in patients with HM. Observational studies and the few randomized controlled trials, mainly conducted in cancer patients, over the last two decades have contributed to our better understanding of the pathogenesis of VTE and its management. Future studies in this setting should provide a solution to the following questions:

1) Which is the best antithrombotic prophylaxis and treatment for VTE in hospitalized and ambulatory patients with HM?
2) Which is the best antithrombotic prophylaxis and treatments for VTE in patients at standard or elevated bleeding risk?
3) Which may be the role of DOACs in the prophylaxis and treatment of VTE in HM?

To answer these questions, randomized controlled trials are urgently needed in order to compare the efficacy and safety of the various antithrombotic agents in the different HM. These studies will provide guidelines on how to approach VTE complications in the different HM. So far, these studies have been well conducted only in PV and ET where the routine use of ASA prophylaxis has deeply contributed to the prevention of major and minor cardiovascular events.

Conflict of interest statement

None.

Author's contributions

GA and SS conceived the study, AO and MN performed literature search, data analysis and wrote the article. GA and SS critically revised the paper; all authors gave their final approval to the submitted version.

Table 5
Suggested Strategies for Prophylaxis and Treatment of VTE in Hematological Malignancies by Platelets count.

	Platelets ≥50,000/µL Prophylaxis Therapy		> 20,000/µL e < 50,000/µL Prophylaxis Therapy		≤ 20,000/µL Prophylaxis Therapy	
A. Myeloproliferative Disorders						
Acute Myeloid Leukemia and Myelodysplastic Syndrome	*LMWH*[a]	*LMWH*[b]	*LMWH*[a]	*LMWH*[b]	*Stop LMWH*	*Stop LMWH*
Polycythemia Vera and Essential Thrombocythemia	*ASA*	*LMWH*[b]	*LMWH*[a]	*LMWH*[b]	*Stop LMWH*	*Stop LMWH*
Myelofibrosis	Usually not recommended with the exception of selected high risk conditions	*LMWH*[b]	Usually not recommended with the exception of selected high risk conditions	*LMWH*[b]	*Not recommended*	IVC filter
B. Lymphoproliferative Disorders						
Acute Lymphoid Leukemia	*LMWH*[a]	*LMWH*[b]	*LMWH*a	*LMWH*[b]	*Stop LMWH*	*Stop LMWH*
Hodgkin Lymphoma	*ASA*[c]	*LMWH*[b]	*LMWH*[a]	*LMWH*[b]	*Stop LMWH*	*Stop LMWH*
Non Hodgkin Lymphoma • Diffuse large B cell Lymphoma • Follicular Lymphomas • Lymphoplasmacytic Lymphoma and Waldenström Disease • CNS Lymphoma • Other Lymphomas	*LMWH as indicated in ASCO guidelines* [87]	*LMWH as indicated in ASCO guidelines* [87]	*Reduce by 50% the Prophylactic dosage of LMWH indicated in ASCO guidelines* [85]	*Reduce by 50% the Therapeutic dosage of LMWH indicated in ASCO guidelines* [85]	*Stop LMWH*	*Stop LMWH*
Multiple Myeloma	*ASA*[c]	*LMWH*[b]	*LMWH*[a]	*LMWH*[b]	*Discontinue LMWH*	*Discontinue LMWH*
Amyloidosis AL	Only in selected high risk conditions	IVC filter?	Not recommended	IVC filter	Not recommended	IVC filter

Legend: **LMWH** (Low Molecular Weight Heparin); **ASA** (Aspirin); **IVC** (Intra venous Caval).

[a] *Tnzaparin:* 4500 IU daily; *Dalteparin:* 5000 IU daily; *Enoxaparin:* 4000 IU daily).
[b] *Tinzaparin:* 175 IU/Kg daily up to 6 months; *Dalteparin:* 200 IU daily for the 1st month, 150 IU daily for the following 5 months; *Enoxaparin:* 100 IU twice daily).
[c] *ASA* (Aspirin: 80–100 mg daily).

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