REGULAR ARTICLE

blood advances

Venous thromboembolism in patients with B-cell non-Hodgkin lymphoma treated with lenalidomide: a systematic review and meta-analysis

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Key Points

- Lenalidomide is associated with increased venous thrombosis in patients with B-cell NHL, similar to multiple myeloma.

Lenalidomide is associated with increased risk of thromboembolism (VTE) in patients with multiple myeloma. This risk has not previously been defined in B-cell non-Hodgkin lymphoma (NHL), for which lenalidomide is also an active agent. We conducted a systematic literature search in Ovid MEDLINE (1946 to February 2017), Ovid EMBASE (1974 to February 2017), The Cochrane Library (Wiley), and Web of Science Core Collection for prospective studies evaluating lenalidomide-containing regimens in B-cell NHL with adequate reporting of patient characteristics, total cycles received, and safety data including VTE rates. The primary outcome was VTE events per 100 patient-cycles by meta-analysis using random-effects models. Our literature search identified 1719 citations; 28 articles were included. For all patients with B-cell NHL receiving lenalidomide, the rate of VTE per 100 patient-cycles was 0.77 (95% confidence interval [CI], 0.48-1.12; I^2, 67%). The rate for single-agent lenalidomide was 1.09 events per 100 patient-cycles (95% CI, 0.49-1.94; I^2, 76%), the rate for lenalidomide plus biologics was 0.49 (95% CI, 0.17-0.97; I^2, 59%), and the rate for lenalidomide plus chemotherapy was 0.89 (95% CI, 0.39-1.60; I^2, 57%). Rate of VTE events in B-cell NHL patients treated with lenalidomide in clinical trials is similar to the rate in multiple myeloma. The VTE rate appears to be lowest for lenalidomide combined with a biologic compared with single-agent lenalidomide or its combination with chemotherapy. This protocol was registered at www.crd.york.ac.uk/prospero/ as #CRD42017056042.

Introduction

Lenalidomide is an immunomodulatory agent currently US Food and Drug Administration–approved for the treatment of multiple myeloma, myelodysplastic syndrome (MDS) with a 5q− deletion, and relapsed/refractory mantle cell lymphoma (MCL). Lenalidomide has antiangiogenic and immunomodulatory effects as well as direct cytotoxic activity against a variety of hematologic malignancies in both in vitro and in vivo studies.[1] Furthermore, lenalidomide has been shown to enhance the activity of rituximab. Clinically, lenalidomide has activity in relapsed aggressive[2] and indolent non-Hodgkin lymphoma (NHL)[3], both as a single agent and in combination with rituximab.[4] Emerging data have also indicated the therapeutic potential of lenalidomide plus rituximab in first-line MCL[5] and follicular lymphoma. A number of clinical trials are ongoing to evaluate the efficacy and safety of the combination of lenalidomide plus chemotherapy or targeted biologic agents in B-cell NHL.

In patients with multiple myeloma treated with lenalidomide, there is a well-documented risk of venous thromboembolism (VTE); lenalidomide carries US Food and Drug Administration black box warning for risk of VTE and pulmonary embolism for patients with multiple myeloma. This rate has been cited in

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meta-analysis by Carrier et al as 0.7 to 0.8 thrombotic events per 100 patient-cycles.[6] However, this risk has not been previously well defined in patients with B-cell NHL treated with lenalidomide and remains an important clinical question.

In a phase 2 randomized control trial comparing single-agent lenalidomide to lenalidomide plus rituximab in patients with follicular lymphoma by Leonard et al (CALGB 50401), a nonsignificant trend toward higher rate of thrombosis was seen in the group receiving lenalidomide alone vs the combination regimen.[7] Although the study was not adequately powered to detect a significant difference, it suggests a possible even greater risk for VTE in patients treated with lenalidomide as a single agent.

In the 2007 American Society of Clinical Oncology guidelines for VTE prophylaxis, outpatient prophylaxis was recommended for all patients receiving lenalidomide in combination regardless of the disease being treated.[8] However, in the 2013 update to the guidelines, these recommendations were limited only to patients with multiple myeloma being treated with lenalidomide, reflecting a lack of data regarding rates of VTE in patients with other diseases being treated with lenalidomide.[9] This underscores the need to establish rates of VTE in patients with lymphoma receiving lenalidomide to determine whether these patients may require prophylaxis as well.

We performed a systematic review of the literature to quantify the rate of VTE in patients with B-cell NHL undergoing therapy with lenalidomide, including lenalidomide in combination with chemotherapy or biologic agents. We further aimed to differentiate thrombosis rates in patients treated with different regimens that included lenalidomide.

Methods

This study was performed following the PRISMA statement. In adherence to these guidelines, a protocol was registered in PROSPERO (registration #CRD42017056042). We conducted a systematic literature search to identify studies in Ovid MEDLINE (1946 to February 2017), Ovid EMBASE (1974 to February 2017), The Cochrane Library (Wiley), and Web of Science Core Collection, and reviewed the footnotes of all included studies for additional potential studies. Search terms included all subject headings and associated keywords for "non-Hodgkin lymphoma" and "lenalidomide." The full search strategy for Ovid MEDLINE is available in supplemental Table 1. To be comprehensive and limit publication bias, there were no limits placed on the search in regards to language, publication date, or study type.

We reviewed all abstracts using a structured format and reviewed candidate articles against predefined inclusion/exclusion criteria to ensure that they included prospective enrollment of patients with newly diagnosed or relapsed/refractory B-cell NHL, as well as treatment with single-agent lenalidomide or lenalidomide with additional agents, either concurrently or sequentially. Each article was screened to ensure that baseline patient characteristics, the number of cycles of lenalidomide each patient received, and safety data including rates of VTE (deep vein thrombosis or pulmonary embolism) were completely reported. Conference abstracts were initially screened but removed from eligibility as they did not include sufficient data for analysis. The authors were contacted directly if the study would otherwise have met eligibility criteria but did not report the number of patient-cycles received in the study. Two reviewers independently assessed articles for eligibility and extracted data. A quality assessment of included studies was performed using the Newcastle-Ottawa Quality Scale for Cohort Studies and the Cochrane Risk of Bias Assessment Tool for randomized controlled trials (supplemental Tables 3 and 4).

The primary outcome was defined as VTE events per patient-cycle to standardize for the vastly different number of cycles used across different studies. A VTE event was prospectively defined as grade 2 or greater venous thrombosis according to the National Cancer Institute Common Toxicity Criteria, the Common Terminology Criteria for adverse events, or the World Health Organization criteria as defined by the author of each study. Our primary outcome was subsequently converted to VTE events per 100 patient-cycles for ease of use and better comparison with the existing literature in multiple myeloma. Where the total number of patient-cycles was not reported directly, when able, this was calculated using the median number of cycles of lenalidomide received per patient multiplied by the number of patients in the trial. Where possible, we extracted patient characteristics such as median age, stage, prior therapies, and performance status.

Meta-analyses of the rates of VTE events for all included studies were conducted with the use of StatsDirect statistical software (version 3.1.12). Statistical heterogeneity was tested through the χ^2 test (ie, Cochrane Q test) and $P \leq .20$ was used to indicate the presence of heterogeneity. In the case of lack of heterogeneity, fixed-effects models were used for the meta-analyses. If heterogeneity was present ($P \leq .20$) or a small number of studies were pooled, then random-effects models were used for the meta-analyses. I^2, an index of heterogeneity, was also computed, and values above 50% indicate moderate to high heterogeneity. For the rate of VTE, the results of each study were expressed as binary proportions with exact 95% confidence intervals (CIs). For each meta-analysis of the outcome (VTE) proportion, the presence of publication bias was evaluated through a funnel plot, which is a scatter plot of the VTE outcome proportion estimated from individual studies vs a measure of study size or precision.

We subsequently performed a meta-analysis in each of 3 predefined cohorts of interest: patients treated with single-agent lenalidomide, patients treated with lenalidomide plus biologic agents, and patients treated with lenalidomide plus chemotherapy. Patients treated with both chemotherapy and biologic agents were classified in the lenalidomide plus chemotherapy cohort. Each treatment regimen meta-analysis was designed to pool the individual-study VTE proportions within each treatment regimen (ie, to improve the precision of the VTE proportion within each defined treatment regimen). No formal statistical hypothesis testing was performed to compare the meta-analytic results between the 3 treatment regimens, as this falls outside of the boundaries of meta-analysis: because each treatment regimen represents its own pooled proportion, each separate meta-analysis cannot be compared with one another to test for statistical significance.

Results

Our initial literature search identified 1719 citations. Of these, 1478 abstracts were screened and rejected as they were not clinical trials, did not include lenalidomide, or did not include patients with

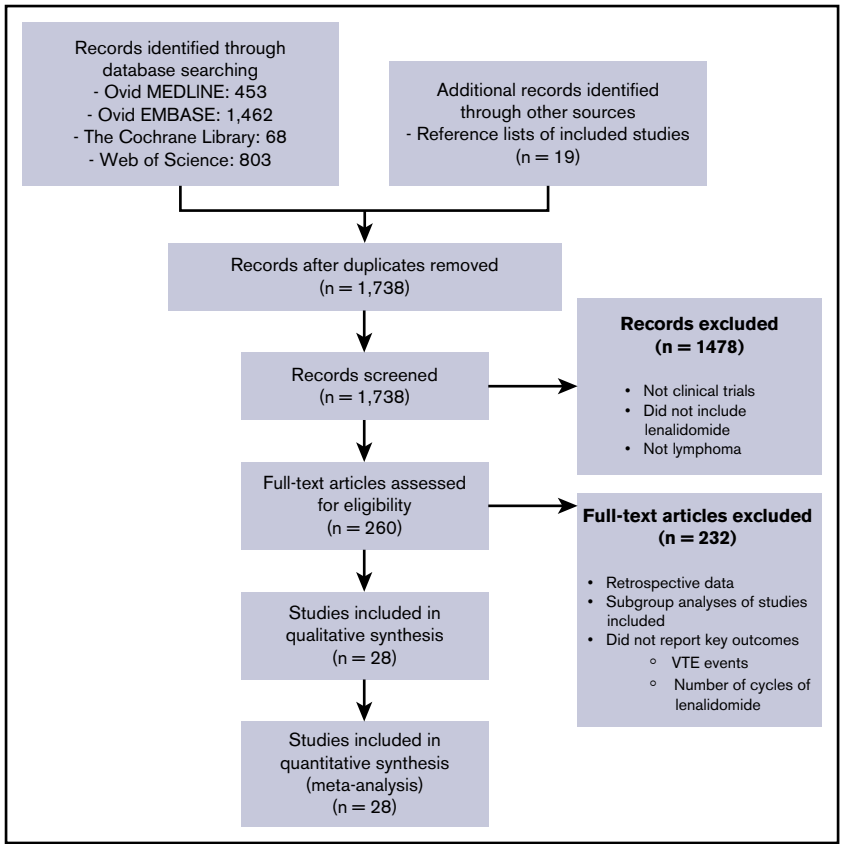

Figure 1. Study selection. PRISMA diagram showing the number of records identified in initial search, those excluded in screening, those excluded as ineligible and the final number of articles included in the study.

lymphoma. Of the 260 records remaining, 232 full-text articles were excluded as they contained only retrospective data, were subset analyses of studies already included, or did not report data including VTE events or the number of cycles patients received. Of the 260 records, 28 articles were deemed eligible for the final analysis (Figure 1; Table 1).

We further divided patients into 3 cohorts: those patients treated with lenalidomide as a single agent, lenalidomide in combination with biologic agents, and lenalidomide in combination with chemotherapy. Median age in each cohort ranged between 65 and 68 years, patients were median stage IV across all 3 cohorts, and median performance status was 0-1 across all cohorts. Of note, patients received a median of 0 prior therapies in the group being treated with lenalidomide plus chemotherapy vs a median of 3 prior therapies in the other 2 cohorts, indicating a larger population of patients receiving first-line treatment vs more patients with relapsed or refractory disease in the other cohorts (Table 2).

In total, our review identified 10 332 cycles of lenalidomide received by patients with B-cell NHL with 77 VTE events, a raw event rate of 0.75 per 100 patient-cycles. Using StatsDirect statistical software, we performed meta-analyses using random-effects models to determine pooled rates of VTE events. For all patients with lymphoma receiving lenalidomide, the pooled rate of VTE per 100 patient-cycles was 0.77 VTE events per 100 patient-cycles (95% CI, 0.48-1.12; I^2, 67%) (Table 3; Figure 2). Using random-effects models, we further calculated pooled rates of VTE events stratified by treatment type. Pooled rates for the single-agent lenalidomide cohort, as well as those treated with lenalidomide plus chemotherapy and lenalidomide plus biologics were calculated (Table 3). The pooled rate of VTE for single-agent lenalidomide was 1.09 VTE events per 100 patient-cycles (95% CI, 0.49-1.94; I^2, 76%) (Figure 3), the pooled rate for lenalidomide plus biologics was 0.49 VTE events per 100 patient-cycles (95% CI, 0.17-0.97; I^2, 59%) (Figure 4), and the pooled rate for lenalidomide plus chemotherapy was 0.89 VTE events per 100 patient-cycles (95% CI, 0.39-1.60; I^2, 57%) (Figure 5).

Using these rates, we were also able to determine the 3-month and 6-month VTE rates for all patients and for each subgroup using a binomial distribution (Table 3). For all patients with lymphoma treated with lenalidomide, 3-month and 6-month VTE risk was 2.3% and 4.5%, respectively. For patients treated with single-agent lenalidomide, 3-month risk was 3.2% and 6-month risk 6.4%, for lenalidomide plus biologics 1.5% and 2.9%, respectively, and for lenalidomide plus chemo 2.6% and 5.2%, respectively.

Discussion

Data analysis from our systematic review demonstrates that patients with B-cell lymphoma treated with lenalidomide are at an increased risk of thrombosis similar to that in multiple myeloma. In a systematic review and meta-analysis by Carrier et al, a rate of 0.7 and 0.8 VTE events per 100 patient cycles was demonstrated in patients with newly diagnosed and relapsed-refractory multiple myeloma treated with lenalidomide (not including patients treated with thalidomide), respectively.[6] Our

Table 1. Trials of lenalidomide in B-cell NHL included in analysis

Treatment type/ lymphoma subtype(s)	Trial design	Disease state	Treatment	Pts	Avg. cycles per Pt	Total Pt-cycles	VTE event	Prophylaxis	Study ref. no.
Single-agent lenalidomide									
MCL	Prospective cohort	R/R	Lenalidomide	134	3	402	10	Aspirin, LMWH, or warfarin in high-risk patients	10
	RCT	R/R	Lenalidomide	167	6	1002	18	Aspirin; LMWH/warfarin if contraindicated	11
Follicular	RCT	R/R	Lenalidomide	45	10	432	7	Aspirin or LMWH in high-risk patients	7
MALT	Prospective cohort	Mixed (untreated and R/R)	Lenalidomide	18	5	86	0	Aspirin	12
DLBCL, MCL, follicular, transformed	Prospective cohort	R/R	Lenalidomide	25	6	150	0	None specified	13
DLBCL, follicular, MCL, transformed	Prospective cohort	R/R	Lenalidomide	49	5	246	2	None specified	14
DLBCL, MCL, follicular, transformed	Prospective cohort	R/R	Lenalidomide	217	8	1688	5	None specified	2
Follicular, SLL, MZL	Prospective cohort	R/R	Lenalidomide	43	6	243	3	None specified	3
Lenalidomide + biologic									
DLBCL	Prospective cohort	R/R	Lenalidomide + rituximab	17	6	107	0	Aspirin	15
	Prospective cohort	R/R	Lenalidomide + rituximab	23	4	92	0	None specified	16
MCL	Prospective cohort	R/R	Bortezomib + lenalidomide	53	6	294	3	Aspirin or LMWH in high-risk patients	17
	Prospective cohort	Untreated	Lenalidomide + rituximab	36	26	932	0	Aspirin or LMWH	5
	Prospective cohort	R/R	Lenalidomide + rituximab	44	9	379	3	Not required	18
	Prospective cohort	R/R	Lenalidomide + dexamethasone	33	7	230	0	LMWH	19
Follicular	RCT	R/R	Lenalidomide + rituximab	46	10	441	2	Aspirin or LMWH in high-risk patients	7
	Prospective cohort	Untreated	Lenalidomide + rituximab + ibrutinib	10	18	180	0	Aspirin, LMWH if contraindicated	20
Follicular, MCL, CLL, lymphoblastic, MZL	Prospective cohort	R/R	Lenalidomide + rituximab	50	16	777	2	None specified	21
DLBCL, follicular, transformed	Prospective cohort	R/R	Lenalidomide + rituximab	45	4	185	4	Not required	22
Lenalidomide + chemotherapy									
DLBCL	Prospective cohort	R/R	RICE + lenalidomide	8	7	54	0	Aspirin; LMWH if contraindicated	23
	Prospective cohort	R/R	Lenalidomide + R-ESHAP	19	3	56	2	Aspirin or LMWH in high-risk patients	24
	Prospective cohort	Untreated	Lenalidomide + R-CHOP	64	6	356	1	Aspirin	25

CLL, chronic lymphocytic leukemia; DLBCL, diffuse large B-cell lymphoma; HL, Hodgkin lymphoma; LMWH, low-molecular-weight heparin; MALT, mucosa-associated lymphoid tissue; MZL, marginal zone lymphoma; Pt(s), patient(s); R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine, prednisolone; R-CHOP21, R-CHOP repeated every 21 days; R-ESHAP, rituximab, etoposide, methylprednisolone, cytarabine, and cisplatin; R/R, relapsed/refractory; RCT, randomized controlled trial; ref. no., reference number; RICE, rituximab, ifosfamide, carboplatin, etoposide; SLL, small lymphocytic lymphoma.

Table 1. (continued)

Treatment type/ lymphoma subtype(s)	Trial design	Disease state	Treatment	Pts	Avg. cycles per Pt	Total Pt-cycles	VTE event	Prophylaxis	Study ref. no.
MCL	Prospective cohort	Untreated	Bendamustine + lenalidomide + rituximab	51	8	397	3	Aspirin or LMWH	26
	Prospective cohort		Bendamustine + lenalidomide + rituximab	42	14	577	0	None specified	27
DLBCL, follicular	Prospective cohort	Untreated	Lenalidomide + R-CHOP21	49	6	277	2	LMWH	28
DLBCL, MZL, HL, transformed, Sezary, Waldenstrom	Prospective cohort	R/R	Bendamustine + lenalidomide + rituximab	20	6	120	1	None specified	29
DLBCL, transformed, follicular	Prospective cohort	R/R	Lenalidomide + rituximab + bendamustine	41	4	155	0	None specified	30
DLBCL, follicular	Prospective cohort	Untreated	Lenalidomide + R-CHOP	24	6	133	2	Aspirin	31
Follicular, MZL, SLL, Waldenstrom	Prospective cohort	Untreated	Lenalidomide + rituximab + dexamethasone + cyclophosphamide	33	6	198	5	Aspirin; LMWH/warfarin if contraindicated	32
MCL, MZL, SLL, DLBCL, transformed	Prospective cohort	Untreated	Lenalidomide + R-CHOP	27	4	143	2	Aspirin	33

CLL, chronic lymphocytic leukemia; DLBCL, diffuse large B-cell lymphoma; HL, Hodgkin lymphoma; LMWH, low-molecular-weight heparin; MALT, mucosa-associated lymphoid tissue; MZL, marginal zone lymphoma; Pt(s), patient(s); R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine, prednisolone; R-CHOP21, R-CHOP repeated every 21 days; R-ESHAP, rituximab, etoposide, methylprednisolone, cytarabine, and cisplatin; R/R, relapsed/refractory; RCT, randomized controlled trial; ref. no., reference number; RICE, rituximab, ifosfamide, carboplatin, etoposide; SLL, small lymphocytic lymphoma.

meta-analysis using random-effects models shows a rate of 0.77 events per 100 patient-cycles in patients with B-cell NHL treated with lenalidomide, which is similar to rates in multiple myeloma. Although the design of this study does not allow for direct statistical comparison of these values, the similarity of these rates is notable, and raises concern for the need for VTE prophylaxis in lymphoma patients receiving lenalidomide therapy. The findings of our systematic review and meta-analysis suggest that, given the similarities in rates of VTE herein described, outpatient VTE prophylaxis should be considered in B-cell NHL patients treated with lenalidomide, especially those treated with lenalidomide as a single agent.

In addition, our subgroup analyses suggest a possible differential thrombosis risk between patients treated with single-agent lenalidomide and those treated with lenalidomide in combination with other agents, especially those treated with lenalidomide in combination with biologics. The rate in our meta-analysis of patients treated with single-agent lenalidomide was 1.09 per 100 patient-cycles vs 0.49 events per 100 patient-cycles in patients treated with lenalidomide plus biologics and 0.89 in patients treated with lenalidomide plus chemotherapy. Although meta-analysis techniques do not allow for direct significance testing across the subgroups, the single-agent group appears to be associated with a higher VTE event rate. This is consistent with the findings by Leonard et al, who showed a nonsignificant trend toward increased risk for VTE in patients treated with single-agent lenalidomide vs lenalidomide plus rituximab in a phase 2 study of follicular lymphoma.[7] To put this in a clinical context, we have provided conversions of VTE risk for 3-month and 6-month time points for each treatment regimen, as provided (Table 3).

We have several hypotheses as to why single-agent lenalidomide might lead to increased risk as compared with combination therapy. A reduction in tumor burden by the addition of a second agent may account for this relatively decreased risk in those patients treated with lenalidomide and an additional agent: better control of tumor leads to less venous obstruction, and therefore a lower thrombosis risk.[7] A direct interaction between lenalidomide and tumor cells is a possibility as well, with lenalidomide having an effect on the vasculature and mediators of coagulation, as has been suggested in studies of chronic lymphocytic leukemia and multiple myeloma.[34,35] Translational studies assessing the interaction between lenalidomide and tumor are certainly indicated. Patients treated with single-agent lenalidomide may have relapsed and more aggressive NHL and may endure longer and chronic courses of therapy, increasing risk for VTE events related to their disease and comorbidities. Although the median age, stage, and performance status throughout the 3 cohorts were similar, other risk factors for thrombophilia could not be further differentiated with these study reports.

It also appears that there may be reduced risk of thrombosis seen in patients treated with lenalidomide plus biologics as compared with lenalidomide plus chemotherapy. This might be explained by the hypothesis that increased tumor burden leads to increased rates of thrombosis because more patients who received

Table 2. Characteristics of patients with B-cell NHL treated with lenalidomide

Characteristic	Single-agent Len	Len + biologics	Len + Chemo
Median age (range), y	66 (21-89)	65 (24-89)	68 (22-94)
Median stage at treatment initiation	4	4	4
Median prior therapies (range)	3 (0-13)	3 (0-7)	0 (0-7)
Median performance status (% performance status 0-1)	0-1 (88)	0-1 (67)	0-1 (87)
No. of patients	698	357	378
DLBCL, %	21	15	54
Follicular, %	13	27	10
MCL, %	54	53	26
Other lymphoma subtype, %	11	5	10
Untreated, %	2	15	57
Relapsed/Refractory, %	98	85	43
Male/Female, %	70/30	72/28	65/45
Total cycles received	4249	3387	2466
Mean cycles per patient	6	12	7

Chemo, chemotherapy; Len, lenalidomide.

lenalidomide plus chemotherapy were receiving first-line chemotherapy with potentially high disease burden as opposed to more patients who were relapsed/refractory in the lenalidomide plus biologics arm. Alternatively, tissue damage encountered during chemotherapy may exacerbate venous thrombosis in the setting of lenalidomide plus chemotherapy as compared with the lenalidomide plus biologics combination.

There were limitations of our analysis, both in statistical methodology and data collection. From a statistical standpoint, this analysis treats each cycle of lenalidomide as an independent observation, whereas in reality multiple cycles can come from the same patient. In addition, given that we could not directly compare the risk in different treatment subgroups, we felt that calculating separate meta-analyses for each cohort separately improved the precision of estimates within each treatment group, allowing us to comment on differences in thrombosis risk across different subgroups.

We also intended to perform pooled rates of VTE events stratified by lymphoma subtype. However, due to the method through which data are extracted, this proved difficult. Many of the papers included in our meta-analysis were studies that enrolled multiple lymphoma subtypes to the same trial. Although the included papers reported the total number of VTE events and cycles received, they did not detail which specific patient had the VTE event. For example, if a trial treated patients with diffuse large B-cell lymphoma, MCL, and follicular lymphoma and had 2 VTE events, we could not determine which lymphoma subtypes had the VTE event, as this was typically not specifically reported. Although it is technically possible to use random-effects models to create Forest plots using only the single-subtype trials because a significant number of patients included in the analysis were enrolled in trials that contained multiple lymphoma subtypes, we felt that to present Forest plots excluding them would be disingenuous and not clinically useful. We have included the raw event rates per patient cycle and per 100 patient cycles in supplemental Table 2 for reference.

In terms of limitations in collecting data, many of the studies included did not report the total number of cycles received by patients; in these cases this figure was estimated by multiplying the median number of cycles per patient by the number of patients in the study. In other cases, the number of cycles could not be estimated, leading to the inability to include several important articles in our analysis.[36-40] In addition, none of the studies from which we extracted our data were designed to study VTE as an outcome but rather reported them as adverse events. The patients in these studies were also, by definition, enrolled in clinical trials and therefore may reflect highly selected, healthier patients than patients being treated in real-world routine practice who may experience higher rates of VTE due to comorbidities.

Table 3. Pooled VTE events per 100 patient cycles by treatment modality using random-effects models

Treatment cohort	Pooled VTE events/patient-cycle	Pooled VTE events/100 patient-cycles	95% CI	3-mo VTE risk, %	6-mo VTE risk, %
All patients treated with lenalidomide	0.007685	0.77	0.48-1.12	2.3	4.5
Single-agent lenalidomide	0.0109	1.09	0.49-1.94	3.2	6.4
Lenalidomide + biologics	0.00486	0.49	0.17-0.97	1.5	2.9
Lenalidomide + chemotherapy	0.00891	0.89	0.39-1.60	2.6	5.2

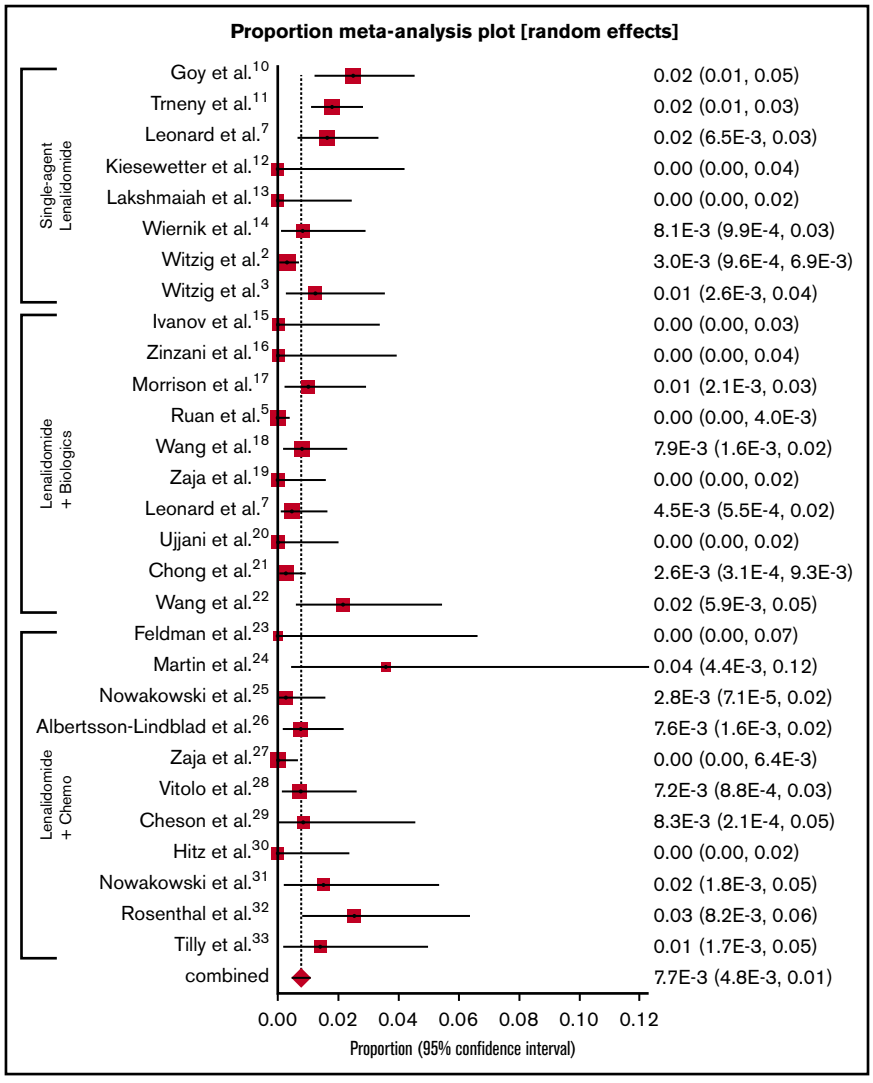

Figure 2. Forest plot: VTE events per patient cycle for all B-cell NHL patients treated with lenalidomide. A forest plot representing the proportion of VTE events per patient-cycle for all included articles. X-axis, VTE events per patient cycle; y-axis, the name of each included study. Squares represent proportions for individual studies; diamond represents pooled proportion.

As previously described by Carrier et al in the study of VTE in myeloma, we were also limited by the limitations of the toxicity definitions used in the different studies: National Cancer Institute Common Toxicity Criteria, the Common Terminology Criteria for adverse events, or the World Health Organization criteria. These classifications do not differentiate between distal and proximal

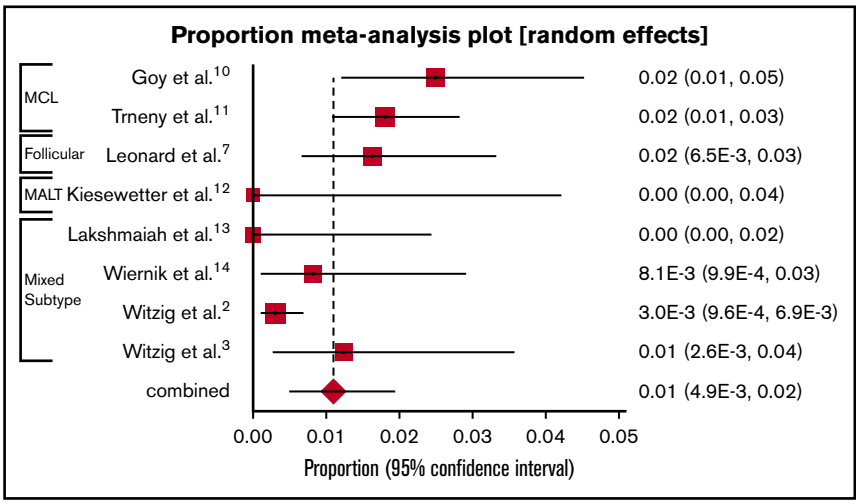

Figure 3. Forest plot: VTE events per patient cycle for all B-cell NHL patients treated with single-agent lenalidomide. A forest plot representing the proportion of VTE events per patient-cycle for patients receiving single-agent lenalidomide. X-axis, VTE events per patient-cycle. Squares represent proportions for individual studies; diamond represents pooled proportion. MALT, mucosa-associated lymphoid tissue lymphoma.

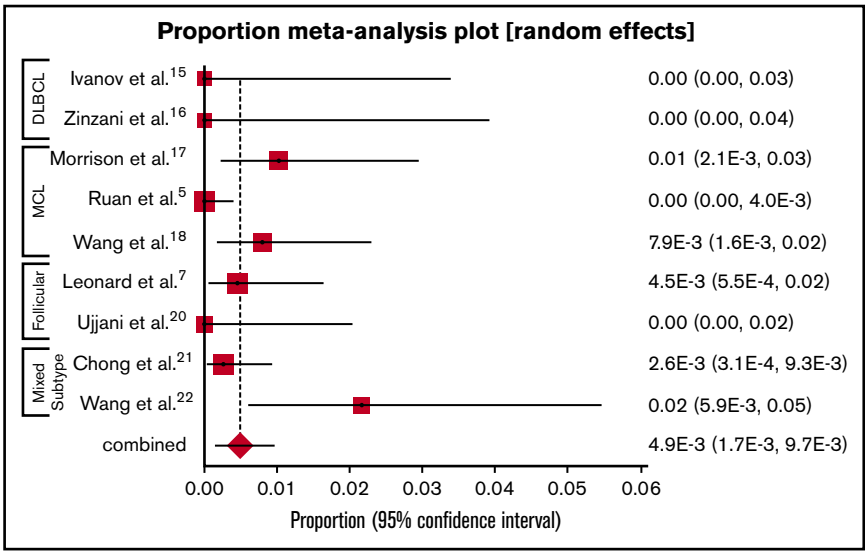

Figure 4. Forest plot: VTE events per patient cycle for all B-cell NHL patients treated with lenalidomide plus biologics. A forest plot representing the proportion of VTE events per patient-cycle for patients receiving lenalidomide plus biologics. X-axis, VTE events per patient-cycle. Squares represent proportions for individual studies; diamond represents pooled proportion.

DVT or upper vs lower extremity DVT, which could change clinical management.[6] Screening and monitoring for VTE was also not standardized.

We were also limited in our ability to analyze the effects of VTE prophylaxis or differential risk across different disease sub-types. Some studies did not report prophylaxis methodology, left the choice to the discretion of individual investigators, or did not report which patients with VTE events were receiving VTE prophylaxis and which had not received prophylaxis. In addition, as described herein, many studies that included multiple disease subtypes of lymphoma did not report adverse events with disease subtype included, minimizing our ability to differentiate by disease subtype. Given that we were only able to extract the data from study data as a whole rather than from each individual patient, we were also unable to adjust these findings by age, gender, or ethnicity. The differential risk of thrombosis across different lymphoma subtypes, and the implementation and efficacy of prophylaxis remain of great clinical importance and warrant future study, especially given that we do not have prophylaxis safety data for certain regimens.

In conclusion, patients with B-cell NHL treated with lenalidomide, whether alone or in combination with other therapeutic agents, appear to be at substantial risk of VTE events. These rates appear to be similar to those in multiple myeloma on lenalidomide therapy. In addition, there appears to be a trend toward increased risk of thrombosis associated with lenalidomide therapy when used as a single agent. Additional assessment of the risk of VTE in this patient population with regards to lymphoma subtypes and treatment specifics is needed, as none of the trials with lenalidomide in our analysis were designed to assess for VTE; future studies of VTE in this patient population should clearly define VTE as an outcome. Further studies assessing the benefit of VTE prophylaxis, as well as the thrombosis risk in

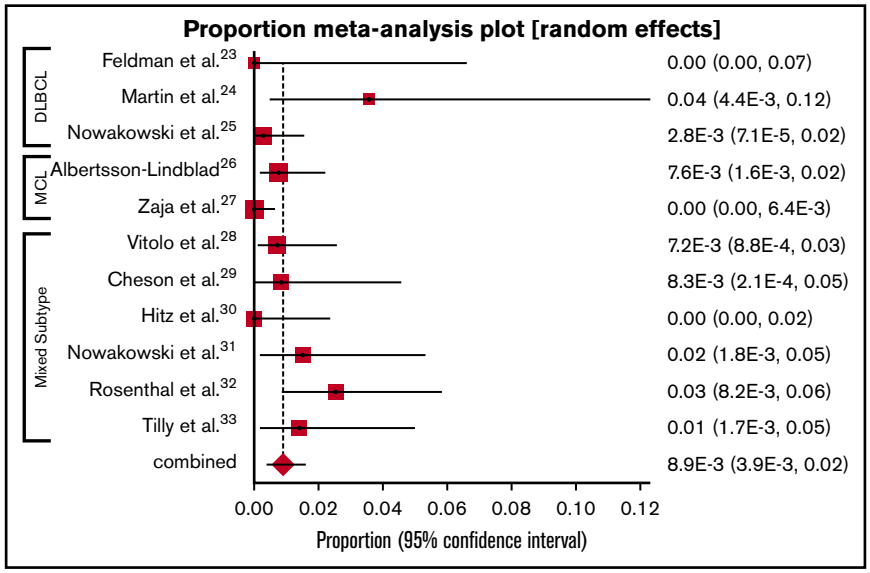

Figure 5. Forest plot: VTE events per patient cycle for all B-cell NHL patients treated with lenalidomide plus chemotherapy. A forest plot representing the proportion of VTE events per patient-cycle for patients receiving lenalidomide plus chemotherapy. X-axis, VTE events per patient-cycle. Squares represent proportions for individual studies; diamond represents pooled proportion.

different subtypes of B-cell NHL, are warranted to further define lenalidomide-associated VTE risk and appropriate supportive strategy for thromboprophylaxis.

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Authorship

Contribution: S.Y. contributed to study design, background research, data extraction, statistical analysis, and writing of the report with input from J.P.L. and J.R.; M.D. contributed to study design, search strategy, and writing of the Methods section; H.H. and P.J.C. contributed to statistical analysis; J.P.L. contributed to study design and editing of the report; and J.R. contributed to study design, data extraction, and editing of the report.

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