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REVIEW ARTICLE

Outcomes of long-term von Willebrand factor prophylaxis use in von Willebrand disease: A systematic literature review

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ABSTRACT

Background: Von Willebrand Disease (VWD) is a common inherited bleeding disorder. Patients with VWD suffering from severe bleeding may benefit from the use of secondary long-term prophylaxis.

Aim: Systematically summarize the evidence on the clinical outcomes of secondary long-term prophylaxis in patients with VWD and severe recurrent bleedings.

Methods: We searched Medline and EMBASE through October 2019 for relevant randomized clinical trials (RCTs) and comparative observational studies (OS) assessing the

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effects of secondary long-term prophylaxis in patients with VWD. We used Cochrane Risk of Bias (RoB) tool and the RoB for Non-Randomized Studies of interventions (ROBINS-I) tool to assess the quality of the included studies. We conducted random-effects meta-analyses and assessed the certainty of the evidence using the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) approach.

Results: We included 12 studies. Evidence from one placebo controlled RCT suggested that VWD prophylaxis as compared to no prophylaxis reduced the rate of bleeding episodes (Rate ratio [RR], .24; 95% confidence interval [CI], .17–.35; low certainty evidence), and of epistaxis (RR, .38; 95%CI, .21–.67; moderate certainty evidence), and may increase serious adverse events RR 2.73 (95%CI .12–59.57; low certainty). Evidence from four before-and-after studies in which researchers reported comparative data suggested that VWD prophylaxis reduced the rate of bleeding (RR .34; 95%CI, .25–.46; very low certainty evidence).

Conclusion: VWD prophylaxis treatment seems to reduce the risk of spontaneous bleeding, epistaxis, and hospitalizations. More RCTs should be conducted to increase the certainty in these benefits.

KEYWORDS
bleeding disorder, bleeding episodes, epistaxis, Hemophilia, prophylaxis, Von Willebrand Disease

1 | INTRODUCTION

Von Willebrand disease (VWD) is the most common inherited bleeding disorder and mucocutaneous bleeding is a common manifestation. While most individuals with VWD have only mild symptoms, some have more significant bleeding.[1,2] VWD is divided into three main categories, depending on the type of defect in von Willebrand factor (VWF). Type 1 represents a quantitative deficiency of VWF, type 2 represents qualitative defects in VWF, and type 3 represents the complete or almost complete absence of the VWF protein. Type 3, therefore, results in the most severe bleeding phenotype, though it is the least frequently observed type of VWD.[3,4] Because type 2 VWD represents functional defects in the VWF protein, many patients with type 2 VWD also experience severe bleeding. Type 1 VWD is the most common type, typically associated with mild to moderate bleeding symptoms. Some patients with severe type 1 VWD, however, also experience significant bleeding.

Chronic joint bleeding is mainly observed in type 3 and type 2 VWD.[3] Gastrointestinal bleeding can occur in severe VWD and appears to be particularly associated with type 2A and type 3 VWD.[3,5,6] Epistaxis, although often mild, can occur frequently, and in rare instances may even necessitate blood transfusions in some patients. Heavy menstrual bleeding is also common in female patients with VWD and can lead to significant blood loss and iron-deficiency anaemia.[7,8] When untreated, these bleeding episodes can affect patients' health and quality of life.[9–12]

Prophylaxis, or regular administration of coagulation factor concentrate to prevent bleeds, is a mainstay of haemophilia treatment. Less attention has been given to the use of prophylaxis in patients with VWD. A recent survey with the aim to prioritizing topics to cover in guidelines for the management of VWD,[13] however, showed that patients, caregivers, scientists and treaters all believed this was a key topic for guidelines to address. The aim of this article is to describe the methods and results of the evidence synthesis process used to support the development of the recommendation questions about secondary long-term prophylaxis addressed by the 2020 ASH ISTH NHF WFH 2021 guidelines on the management of VWD.[13]

2 | METHODS

2.1 | Protocol and registration

We conducted a systematic review (SR) of the literature. We did not register this SR, but followed methods pre-established and agreed on with the organizations that sponsored the development of the guidelines. We report this SR in accordance with Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) guidelines.[14]

This article addresses the question: In Patients with VWD and with history of severe and frequent bleeds what are the comparative effects of routine prophylaxis administration using VWF replacement therapy versus no routine prophylaxis?

2.2 | Eligibility criteria

We included randomized controlled trials (RCTs) and any type of comparative observational studies (OS) (cohort studies, case-control studies, and before-and-after studies) that reported any of the outcomes

of interest. The predefined outcomes of interest included: major bleeding, serious adverse events, joint function, mortality, and hospitalization. We included patients diagnosed with any type of VWD, who were labelled as having severe and frequent bleeds or being candidates for secondary long-term prophylaxis, according to the researchers. We excluded patients with acquired VWD. We included studies that compared the use of secondary long-term prophylaxis, defined as one factor infusion at least once a week for six months, with no secondary long-term prophylaxis. We included studies published in any language. We excluded studies published as conference abstracts.

2.3 | Information sources & search

We searched MEDLINE, EMBASE, and the Cochrane Central Register of Controlled Trials (CENTRAL) from inception until October 2019. We also manually searched the reference lists of relevant articles and existing reviews. The complete search strategy is available in Appendix 1.

2.4 | Study selection and data collection process

Independent reviewers (N.H., A.E., M.K., Y.A., H.T., A.B., H.K. S.M, S.S., J.R) conducted title and abstract and full-text screening in duplicate to identify eligible studies. We extracted data from eligible studies using piloted and standardized forms in Microsoft Excel, independently and in duplicate. Disagreements at all stages were resolved by discussion to reach consensus, and in consultation with two expert clinician scientists (RM and RB-P) when necessary. When the same study was reported in multiple publications, we included the results from the report with the largest number of patients per outcome, to avoid double counting study patients.

2.5 | Data items and study outcomes

We extracted the following information when provided; study characteristics (authors, publication year, country, study design, number of patients), long-term prophylaxis agent and regimen used, outcomes, type of outcome (i.e., dichotomous, continuous), number of events in prophylaxis group, and number of events in control group.

The authors extracted the following outcomes from each study: spontaneous bleeding, the number of bleeding episodes as events per patient per months, hemarthrosis episodes, epistaxis episodes, heavy menstrual bleeding as the median rate of event per patient per year, time to first bleeding, serious adverse events, hospitalization rate of event per patient, and mortality.

2.6 | Risk of bias assessment

We conducted the risk of bias (RoB) assessment for the RCT using the Cochrane Risk of Bias Tool for RCTs[15] and for OS using the RoB in non-randomized studies of interventions (Robins-I) tool.[16]

2.7 | Data synthesis and analysis

For dichotomous outcomes, we calculated the relative effect of therapies using risk ratios (RRs) and 95% confidence intervals (CIs), for outcomes reported as incidence rate (e.g., bleeding episodes) we calculated the relative effect of therapies using rate ratios and 95% CIs, for continuous outcomes we calculated the relative effect of therapies using the mean difference (MD) and 95% CIs. We calculated incidence ratios when there was no comparative data for an outcome. We used RevMan[17] to conduct random-effects meta-analyses for RRs and rate ratios, and R[18] to pool the results of incidence rates. When we could not perform meta-analysis, we summarized the results narratively.

2.8 | Assessment of certainty of the evidence

We used the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach to assess the certainty of the evidence of each outcome.[19] Evidence from RCTs starts as high certainty and it can be downgraded to moderate, low, or very low certainty due to RoB, inconsistency, imprecision, indirectness, and publication bias. Evidence from OS starts as low certainty and can be downgraded for the same reasons as RCTs, but can also be upgraded if large effect, and/or dose-response relationship exist. We created summary of findings tables using GradePro.[20]

2.9 | Dealing with missing data

We used the data available in the studies. Although we planned to contact the researchers if there was missing data that prevented us from pooling the results across studies, we did not have to.

2.10 | Subgroup and sensitivity analyses

We planned to conduct subgroup analyses based on VWD type. We did not plan to conduct any sensitivity analyses.

3 | RESULTS

3.1 | Study selection

We identified 4698 references for title and abstract screening, and 128 references for full text screening. We included 12 studies published in 21 sources (Figure 1). Two OS presented data as both with comparative and without comparative data which explains the difference between the reported total (12 studies) and the sum of each study type separately (14 studies).

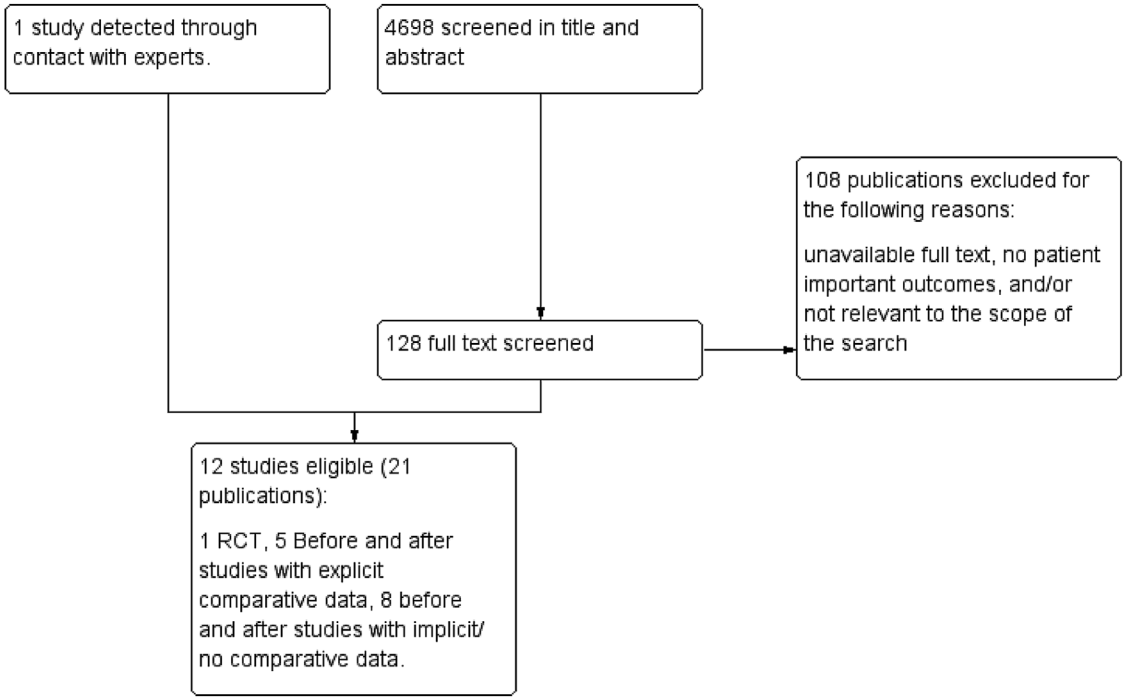

FIGURE 1 Study flow diagram for included studies

TABLE 1 List of included studies (RCTs)

Citation	Country	Recruitment period	*N*	VWD type	Sex	Age	Agent prescribed for prophylaxis	Follow-up
Peyvandi 2019	Italy, Germany, Spain	2006–2016	19	Prophylaxis Group: 30% = Type 1, 40% = Type 2, 30% = Type 3 On demand treatment: 0% = Type 1, 55.5% = Type 2, 44.5% = Type 3	74% male	On demand treatment: Median age: 54 years (Q1, Q3: 45–64) Prophylaxis treatment: Median age: 28 years (Q1, Q3: 15–48)	Fandi, Alphanate	12 months

TABLE 2 List of included studies (before and after studies with Comparative Data)

Citation	Country	N	Prophylaxis Agent
Berntorp, 2005	Sweden	35	Fraction 1-0, Haemate P/Humate P
Berntorp, 2009	Europe	15	Wilate
Borel-Derlon, 2007	Europe	4	Wilfactin
Federici, 2010	Italy	15	Fanhdi, Alphanate
Holm, 2015	North America and Europe	105	Not Reported

3.2 | Study characteristics

Tables 1–3 summarize the included studies in this review as three bodies of evidence; one randomized clinical trial (RCTs) (Table 1), before-after OS with comparative data in which researchers provided an explicit comparison between a period in which patients received prophylaxis and a period in which they did not (i.e., measurement of outcomes in both periods and comparison between the two periods) (Table 2), and before-after OS with an implicit comparison with the time period before (i.e., the outcome was measured based on perceived improvement in comparison to the time period before) (Table 3).

The included RCT is a phase III, randomized, open label trial. It compared secondary long-term prophylaxis treatment (n = 10) using VWF/FVIII concentrate [Fanhdi/Alphanate] versus on-demand treatment (n = 9) for a median study duration of 12.1 months in patients with severe/frequent bleeds.[21] Four patients from the prophylaxis group discontinued the study for the following reasons: two patients withdrew their consent, and two patients were lost to follow up.

We identified five OS with comparative before and after data[22–26] and eight before-after studies without comparative data.[23,25,27–32] The included studies were conducted across Europe and North America including multi-center international studies, in which six prophylactic agents: Haemate P/ Humate P, Wilate, Wilfaction, Fanhdi, Alphanate, Biostate were administered to a total of 290 patients.

TABLE 3 List of included studies (before and after studies without comparative data)

Citation	Country	N	Prophylaxis Agent
Berntorp, 2009	Europe	15	Wilate
Castaman, 2013	Italy	31	Haemate
Dunkley, 2010	Australia	4	Biostate
Federici, 2007	Italy	12	Haemate
Federici, 2010	Italy	15	Fanhdi, Aphanate
Khair, 2015	England	4	Wilate
Lillicrap, 2002	Canada	20	Haemate/Humate
Nowak-Gottl, 2013	Germany	15	Wilate

3.3 | Effects of secondary long-term prophylaxis on clinical outcomes

3.3.1 | Spontaneous bleeds

Low certainty evidence from one RCT showed that secondary long-term prophylaxis may reduce spontaneous bleeds (RR, .62; 95%CI, .37–1.04) when compared to on-demand treatment[21] (Table 4).

3.3.2 | Bleeding episodes

One RCT and four OS with comparative data reported bleeding episodes as events per patient per months. Low certainty evidence from one RCT showed that secondary long-term prophylaxis may reduce bleeding episodes (rate ratio, .24; 95%CI .17–.35) when compared to on-demand treatment[21] (Table 4), and very low certainty evidence from the four OS with comparative data showed that secondary long-term prophylaxis may reduce bleeding episodes (rate ratio, .34; 95%CI, .25–.46) when compared to no prophylaxis (Table 5).[22,24–26]

3.3.3 | Hemarthrosis

One RCT reported hemarthrosis episodes. Low certainty evidence showed that prophylaxis treatment may reduce hemarthrosis episodes (rate ratio .50; 95%CI .06–4.50) when compared to no prophylaxis (Table 4).[21]

3.3.4 | Epistaxis

One RCT reported on epistaxis episodes. Moderate certainty evidence showed that prophylaxis treatment probably reduces epistaxis episodes (rate ratio of .38; 95%CI .21–.67) when compared to no prophylaxis (Table 4).[21]

3.3.5 | Heavy menstrual bleeding

One before-and-after observational study with comparative data reported on heavy menstrual bleeding as the median rate of event per patient per year. Very low certainty evidence showed that the median rate of heavy menstrual bleeding per patient per year decreased by nine episodes (median change [IQR], -9 [95%CI -9.3 to -6.0]). The median rate was 9.6 before prophylaxis and zero after prophylaxis (Table 5).[26]

3.3.6 | Time to first bleeding

One RCT reported on the time to first bleeding. Moderate certainty evidence showed that patients who received prophylaxis treatment have a MD of 31.4 days longer (95%CI 8.44 higher to 54.36 higher) when compared with no prophylaxis (Table 4).[21]

3.3.7 | Serious adverse events

One RCT and five OS without comparative reported serious adverse events. Low certainty evidence from one RCT showed that prophylaxis treatment may increase serious adverse events (relative risk 2.73; 95%CI .12–59.57) when compared to no prophylaxis (Table 4).[21] Very low certainty evidence from 5 OS without comparative data showed that there were no serious adverse events in patients treated with prophylaxis for VWD (Table 6).[22,27,30,32,33]

3.3.8 | Hospitalization

One before-after observational study with comparative data reported on hospitalization as rate of event per patient. Very low certainty evidence prophylaxis treatment may reduce hospitalization (rate ratio .64; 95%CI .44–.93) when compared to no prophylaxis (Table 5).[34]

TABLE 4 Routine prophylaxis compared to no prophylaxis for patients with VWD with history of severe/frequent bleeds (RCT DATA)

Certainty assessment							No. of patients		Effect			
№ of patients	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	routine prophylaxis	no prophylaxis	Relative (95% CI)	Absolute (95% CI)	Certainty	Importance
Spontaneous bleeds (follow up: mean 12 months; assessed with: Number of events/patient)												
1[21]	randomised trials	serious[a]	not serious	not serious	serious[b]	none	6/10 (60.0%)	9/9 (100.0%)	RR .62 (.37–1.04)	380 fewer per 1000 (from 630 fewer to 40 more)	⨁⨁◯◯ LOW	
Bleeding episodes (follow up: mean 12 months; assessed with: Events per patient per month)												
1[21]	randomised trials	very serious[a]	not serious	not serious	not serious	none	.34/10	1.41/9	Rate ratio .24 (.17–.35)	107 fewer per 1000 patient(s) per months (from 117 fewer to 92 fewer)	⨁⨁◯◯ LOW	
Time to first bleeding (follow up: mean 12 months; assessed with: Mean days)												
1[21]	randomised trials	serious[a]	not serious	not serious	not serious	none	10	9	-	MD 31.4 days higher (8.44 higher to 54.36 higher)	⨁⨁⨁◯ MODERATE	
Serious adverse events (follow up: mean 12 months; assessed with: number of patients)												
1[21]	randomised trials	serious[a]	not serious	not serious	serious[c]	none	1/10 (10.0%)	0/9[*] (.6%)	RR 2.73 (.12–59.57)[d]	10 more per 1000 (from five fewer to 325 more)	⨁⨁◯◯ LOW	
Epistaxis episodes (follow up: mean 12 months; assessed with: events per patient per month)												
1[21]	randomised trials	serious[a]	not serious	not serious	not serious	none	.16/10	.42/9	Rate ratio .38 (.21–.67)	26 fewer per 1000 patient(s) per months (from 33 fewer to 14 fewer)	⨁⨁⨁◯ MODERATE	

(Continues)

TABLE 4 (Continued)

Certainty assessment							No. of patients		Effect			
№ of patients	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	routine prophylaxis	no prophylaxis	Relative (95% CI)	Absolute (95% CI)	Certainty	Importance
Haemarthrosis episodes (follow up: mean 12 months; assessed with: events per patient per month)												
1[21]	randomised trials	serious[a]	not serious	not serious	serious[b]	none	.01/10	.02/9	Rate ratio .50 (.06–4.50)	1 fewer per 1000 patient(s) per months (from two fewer to seven more)	⨁⨁◯◯ LOW	
Major bleeding - not reported												
-	-	-	-	-	-	-	-	-	-	-	-	
Joint function - not reported												
-	-	-	-	-	-	-	-	-	-	-	-	
Mortality - not reported												
-	-	-	-	-	-	-	-	-	-	-	-	
Heavy menstrual bleeding - not reported												
-	-	-	-	-	-	-	-	-	-	-	-	
Health-related QoL - not reported												
-	-	-	-	-	-	-	-	-	-	-	-	
Transfusions - not reported												
-	-	-	-	-	-	-	-	-	-	-	-	
Absence from school, work, or other required activities - not reported												
	-	-	-	-	-	-	-	-	-	-	-	

Abbreviations: CI, confidence interval; RR, risk ratio; MD, mean difference.

[a]There is an important proportion of participants missing

[b]There is a small number of patients (OIS not met). The CI suggests appreciable benefit but also the possibility oh harm

[c]Wide CI resulting in serious imprecision.

[d]SAE reported was an intestinal perforation, which the researchers described as not associated with the study medication

*The study reports 0 events, we used .05 as baseline risk in patients not receiving prophylaxis to be able to calculate the absolute effect.

TABLE 5 Routine prophylaxis compared to no prophylaxis for patients with VWD with severe/frequent bleeds BEFORE-AFTER DATA

Certainty assessment							№ of patients		Effect			
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	routine prophylaxis	no prophylaxis	Relative (95% CI)	Absolute (95% CI)	Certainty	Importance
Bleeding episodes (follow up: median 12 months; assessed with: Number of events per patient per month)												
4[23–26]	observational studies	extremely serious[a]	not serious[b]	not serious	not serious	none	0/208	700/1000[c]	Rate ratio .34 (.25–.46)	462 fewer per 1000 patient(s) per months (from 525 fewer to 378 fewer)	⨁◯◯◯ VERY LOW	
Hospitalizations (assessed with: Number of events per patient per year)												

(Continues)

TABLE 5 (Continued)

Certainty assessment							№ of patients		Effect			
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	routine prophylaxis	no prophylaxis	Relative (95% CI)	Absolute (95% CI)	Certainty	Importance
1[34]	observational studies	serious[d]	not serious	not serious	not serious	none	47/105	75/105	Rate ratio .64 (.44–.93)	235 fewer per 1000 patient(s) per years (from 399 fewer to 49 fewer)	⨁◯◯◯ VERY LOW	
Blood transfusion (assessed with: Number of events/patients)												
1[22]	observational studies	very serious[a]	not serious	not serious	serious[e]	none	2/10 (20.0%)	5/10 (50.0%)	RR .4 (.1–1.6)	300 fewer per 1000 (from 450 fewer to 300 more)	⨁◯◯◯ VERY LOW	
Heavy menstrual bleeding (follow up: median 12 months; assessed with: Median rate per patient per year)												
1[26]	observational studies	very serious[f]	not serious	not serious	serious[g]	none	The median rate per patient per year decreased by 9 episodes (median change [IQR], -9 [-9.3 to -6.0]). The median rate was 9.6 before prophylaxis and 0 after prophylaxis.	⨁◯◯◯ VERY LOW				

(Continues)

TABLE 5 (Continued)

Certainty assessment							№ of patients		Effect			
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	routine prophylaxis	no prophylaxis	Relative (95% CI)	Absolute (95% CI)	Certainty	Importance
Serious adverse events- cannot have comparative data - not measured												
-	-	-	-	-	-	-	-	-	-	-	-	
Major bleeding - not reported												
-	-	-	-	-	-	-	-	-	-	-	-	
Joint function - not reported												
-	-	-	-	-	-	-	-	-	-	-	-	
Mortality - not reported												
-	-	-	-	-	-	-	-	-	-	-	-	
Health-related QoL - not reported												
-	-	-	-	-	-	-	-	-	-	-	-	
Absence from school, work, or other required activities - not reported												
-	-	-	-	-	-	-	-	-	-	-	-	

Abbreviations: CI, confidence interval; RR, risk ratio.

[a] Performance and detection bias likely to have happened in these studies.

[b] Although there is statistical inconsistency, there is no important clinical inconsistency (all studies suggest the same direction of effect).

[c] Calculated based on median rate across studies.

[d] Performance bias likely to have happened.

[e] Small number of patients and events, reflected in a very imprecise CI that suggests appreciable benefit but also the possibility of important harm.

[f] Detection bias likely to have happened.

[g] Large effect with small number of patients and events, thus the estimate is fragile.

TABLE 6 Routine prophylaxis compared to no prophylaxis for patients with VWD with severe/frequents bleeds NON COMPARATIVE DATA

Certainty assessment							№ of patients		Effect			
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	routine prophylaxis	no prophylaxis	Relative (95% CI)	Absolute (95% CI)	Certainty	Importance
Bleeding rate (follow up: median 12 months; assessed with: episodes per patient per year)												
4[27–29,32]	observational studies	very serious[a]	serious[b]	not serious	serious[c]	none	The pooled rate of bleeding episodes per patient per year when they were receiving prophylaxis was 3.20 (95% CI, 1.96–5.24)				⨁◯◯◯ VERY LOW	
Serious adverse events (including thrombotic events) (follow up: median 12 months; assessed with: Number of events/ patients)												
5[22,27,30,32,33]	observational studies	not serious	not serious	not serious	not serious	publication bias strongly suspected[d]	There were no serious adverse events reported in any of the studies				⨁⨁⨁◯ MODERATE	
Efficacy/clinical response (follow up: 12 months; assessed with: Proportion of patients)												

(Continues)

TABLE 6 (Continued)

Certainty assessment							№ of patients		Effect			
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	routine prophylaxis	no prophylaxis	Relative (95% CI)	Absolute (95% CI)	Certainty	Importance
4[28,31,32,35]	observational studies	very serious[e]	not serious	not serious	not serious	none	The hemostatic efficacy/effectiveness/clinical response was rated as excellent or good in 100% of patients in 3 of the studies, and 99.7% of the infusions in 1 of the studies				⨁⨁◯◯ LOW	
Joint function - not reported												
-	-	-	-	-	-	-	-	-	-	-	-	
Mortality - not reported												
-	-	-	-	-	-	-	-	-	-	-	-	
Hospitalization - not reported												
-	-	-	-	-	-	-	-	-	-	-	-	
Heavy menstrual bleeding - not reported												
-	-	-	-	-	-	-	-	-	-	-	-	
Health related QoL - not reported												
-	-	-	-	-	-	-	-	-	-	-	-	
Transfusions - not reported												
-	-	-	-	-	-	-	-	-	-	-	-	
Absence from school, work, or other required activities - not reported												
-	-	-	-	-	-	-	-	-	-	-	-	

Abbreviation: CI, confidence interval.

[a]No comparison provided.

[b]There is one study that shows a much smaller estimate than the others.

[c]The limits of the confidence interval of the pooled estimate suggests very different magnitudes of effect.

[d]Several studies do not provide any information about this outcome.

[e]No comparison provided and detection bias likely to have happened.

4 | DISCUSSION

In this SR, we summarize the outcomes of secondary long-term prophylaxis in patients with VWD and severe and frequent bleeds. Moderate to very low certainty evidence from RCTs and OS suggests that prophylaxis treatment reduces the risk of bleeding episodes, hospitalization, heavy menstrual bleeding, and epistaxis; and improved the time to first bleeding event. Prophylaxis may also reduce the number of spontaneous bleeds and hemarthrosis. Prophylaxis seemed to result in higher number of serious adverse events in RCT and no increase in serious adverse events in OS. Additional outcomes were reported, including gastrointestinal bleeding and bleeding lasting more than two days. In this manuscript, however, we only included the outcomes prioritized by the guideline panel. This review has several strengths. To include all the potentially relevant evidence in a context in which there are not many studies, we used broad eligibility criteria. We provide a comprehensive overview from three different bodies of evidence.

The low certainty of evidence in many studies highlight the need for future research with a focus on any of the aspects addressed in this SR to inform decision-making confidently. While there were several OS reporting on prophylaxis in patients with VWD, the patient burden of receiving prophylaxis weighted with the benefits of prophylaxis is poorly reported in literature making implications for clinical practise restricted.

Moreover, although VWD is a relatively common bleeding disorder, the population that has a disease severity enough to require prophylaxis is low, which may have attributed to the low enrollment numbers, and RCTs need a larger number of patients to make a valid assessment on the use of prophylactic treatment in patients with VWD. Further research on the use of prophylaxis compared to on demand treatment is needed. Research on the impact of prophylaxis use for the management of mucosal bleeding, menstrual bleeding, GI bleeding and on quality of life will aid clinicians in determining the best management plan for patients with severe bleeding. There was little accounting for possible confounders in the studies included in our review. Further RCTs and well-designed comparative OS in which researcher account for confounding factors are needed to address the use of prophylaxis in patients with VWD and the patient enrolment issues and may be informative than the literature available to date. Possible confounding factors can help future researchers to plan their studies include gender, age, VWF levels, VWD classification, and comorbidities.

This review has a few limitations. The findings of the review are limited by the articles and the study design of the included studies. Quality of life (QoL) and Cost effectiveness data was not reported in the studies eligible to be included in our review, which may warrant future research that assesses QoL and cost effectiveness as important outcome sin patients with VWD.

It can be concluded that based on in general low certainty evidence VWD prophylaxis treatment seems to reduce the risk of spontaneous bleeding, epistaxis, and hospitalizations. More RCTs should be conducted to increase the certainty in these benefits with focus on the relative efficacy for the more common specific bleeding of hemarthroses and epistaxis.

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CONFLICT-OF-INTEREST

FWGL serves as data safety monitoring board at Roche which markets a prophylactic treatment of bleeding episodes in patients with hemophilia A with factor VIII inhibitors.

AUTHORS CONTRIBUTIONS

Reem A. Mustafa, Romina Brignardello-Petersen, Nedaa M. Husainat, and Mohamad A. Kalot contributed to study design, study selection, data extraction, statistical analysis, and interpretation of results. Abdallah El Alayli, Shaneela Shahid, Yazan Aljabiri, Alec Britt, Hani Turkmani, Hussein El-Khechen, Shahrzad Motaghi, John Roller contributed to study selection and data extraction. Nedaa M. Husainat, Abdallah El Alayli, Romina Brignardello-Petersen, Razan Mansour and Reem A. Mustafa contributed to drafting the report; Alberto Tosetto, Rezan Abdul-Kadir, Michael Laffan, Angela Weyand, Frank W.G. Leebeek, Alice Arapshian, Peter Kouides, Paula James, Nathan T. Connell, and Veronica H. Flood contributed to the interpretation of results, and critical revision of the report.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author.

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

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