ASH ISTH NHF WFH Draft Recommendations on the Management of von Willebrand Disease

Introduction

The American Society of Hematology (ASH), the International Society on Thrombosis and Haemostasis (ISTH), the World Federation of Hemophilia (WFH), and the National Hemophilia Foundation (NHF) are collaborating to develop guidelines for the diagnosis and management of VWD.

The ASH ISTH NHF WFH Guidelines on the Diagnosis and Management of von Willebrand Disease are based on systematic reviews of available evidence. Through a structured process, two guideline panels made judgements about the evidence and formed recommendations.

The public comment period occurs after recommendations are formed but before a manuscript report of the guidelines has been finalized and before organizational approval of the guidelines. Comments collected during the open comment period are provided to the guideline panel for review prior to finalizing the guidelines.

These draft recommendations are not final and therefore are not intended for use or citation.

To submit comments on the draft recommendations, please visit link to https://vwdmanagement.questionpro.com.

The public comment period for these draft recommendations is open now.

Recommendations

- **Question 1: In patients with VWD with history of severe and frequent bleeds, should we use routine prophylaxis with von Willebrand factor (VWF) or no routine prophylaxis (i.e. treatment on-demand)?**

Recommendation

In patients with VWD with history of severe and frequent bleeds, the guideline panel suggests using long term prophylaxis rather than no prophylaxis (conditional recommendation, low certainty in the evidence of effects)

- **Question 2: In patients with VWD, should we perform a DDAVP challenge/trial and choose a treatment for bleeding depending on its results, not perform the DDAVP challenge and treat with VWF concentrate and/or tranexamic acid, or not perform the DDAVP challenge and treat with DDAVP?**

Recommendation

In patients for whom desmopressin is a valid treatment option and who have a baseline VWF level < 30 IU/dL, the panel suggests performing a trial of desmopressin and treating based on the results over not performing a trial and treating with tranexamic acid or factor concentrate. (Conditional recommendations based on very low certainty). In these patients, the panel suggests against treating with desmopressin in the absence of desmopressin trial results (Conditional recommendation, based on very low certainty evidence).

Remarks:

- This recommendation does not apply to patients for whom desmopressin is not a reasonable treatment option (e.g type 3*).
- DDAVP is generally contraindicated in type 3 VWD due to lack of efficacy and in type 2B VWD due to increased platelet binding with subsequent thrombocytopenia.
- Many patients with type 2 VWD will not respond to desmopressin and require other modes of treatment.
- Patients undergoing major surgery including those sites where even small amount of bleeding may result in critical organ damage (e.g. CNS surgery) should not receive DDAVP as sole therapy.
- Adult patients with type 1 VWD and levels equal or greater than 30 IU/dL can be presumed to be desmopressin responsive and can receive desmopressin without requiring a trial but is reasonable to obtain VWF levels to confirm response when given during a therapeutic intervention.
- This recommendation does not address the choice between treating with tranexamic acid and VWF concentrate.

Good Practice Statements:

- The administration of desmopressin to patients with type 2B VWD is contraindicated, as this may cause thrombocytopenia due to increased platelet binding. Furthermore, desmopressin is generally contraindicated in patients with cardiovascular disease, patients under the age of 2, patients with type 1C VWD in the setting of surgery, and pregnant patients with preeclampsia (precautions in pregnancy).
- Patients receiving desmopressin are at risk for hyponatremia from free water retention, patients should only receive normal saline, and oral fluid intake should be restricted to prevent hyponatremia.

➢ Question 3: In patients with VWD and cardiovascular disease who require treatment with antiplatelet agents or anticoagulant therapy, should we provide such treatment or not?

Recommendation

The panel suggests in patients with VWD and cardiovascular disease who require treatment with antiplatelet agents or anticoagulant therapy to give these therapies over no treatment (conditional recommendation based on low quality evidence)

Remarks:

- The panel remarks that it Is important to reassess the bleeding risk throughout the course of treatment.

Good practice statements:

- Patients considered for treatment require individual risk and benefit of the specific therapy plan in conjunction with a multidisciplinary team that includes cardiovascular medicine specialists, hematologists, and the patient. Patient education about the risks of benefits of using antiplatelets or anticoagulants

➢ Question 4: In patients with VWD undergoing major surgery, should we keep the factor VIII level > 50 IU/dL for at least 3 days after the surgery, or the VVF activity level > 50 IU/dL for at least 3 days after the surgery?

Recommendations

The panel suggests targeting both factor VIII and VWF activity level of > 50 IU/dL for 3 days after surgery (Conditional recommendation, Very Low certainty evidence)

The panel suggests against only using factor VIII >50 IU/dL as a target level for 3 days after surgery. (Conditional recommendation, very low certainty evidence)

Remarks:

- When it is possible to keep both levels >50 IU/dL for at least 3 days after the surgery (instead of choosing only one), this should be the preferred option
- The specific target levels have to be individualized based on the situation
- The duration of the intervention can vary for specific types of surgeries

➢ Question 5: In patients with VWD undergoing minor surgery or minor invasive procedures, should we increase the VWF level to 50 IU/dL with any intervention, increase the VWF level to 50 IU/dL with any intervention and prescribe tranexamic acid, or prescribe tranexamic acid alone?

Recommendations

The panel suggests increasing VWF levels to >50 IU/dL with desmopressin or factor concentrate with the addition of tranexamic acid over raising VWF levels to >50 IU/dL with desmopressin or factor concentrate alone. (conditional recommendation, based on very low certainty evidence)

The panel suggests giving tranexamic acid alone over increasing VWF levels to >50 IU/dL with any intervention in patients with type 1 VWD with levels >30 and a mild bleeding phenotype and undergoing minor mucosal procedures. (conditional recommendation, based on very low certainty evidence)

Remarks:

- There is concern with overtreatment with option of increasing VWF to 50 IU/dL with any intervention and tranexamic acid.
- Patients with type 3 VWD will require VWF concentrate in order to achieve any significant increase in VWF levels. Use of DDAVP is contraindicated in this population due to lack of efficacy.
- Most patients with type 2 VWD (including type 2B VWD) will also require treatment with factor rather than desmopressin.
- For patients at higher risk of thrombosis, may wish to avoid combination of increased VWF level and tranexamic acid.

➢ Question 6: In women with VWD with heavy menstrual bleeding, should we prescribe tranexamic acid, hormonal therapy (i.e. levonorgestrel-releasing intrauterine system or hormonal contraceptives), or DDAVP?

Recommendations

The panel suggests using either hormonal therapy (combined hormonal contraception or levonorgestrel-releasing intrauterine system) or tranexamic acid over DDAVP to treat women with VWD with heavy menstrual bleeding who do not wish to conceive (conditional recommendation, based on very low-quality evidence).

The panel suggests using tranexamic acid over hormonal therapy and DDAVP to treat women with VWD and heavy menstrual bleeding who wish to conceive. (conditional recommendation based on very low-quality evidence).

Remarks:

- This recommendation does not imply that the interventions considered can only be prescribed as monotherapy. In some cases, multiple options can be combined especially if control of heavy menstrual bleeding is less than optimal with the initial therapy

- Desmopressin will not be effective in type 3 and many type 2 VWD patients and should not be used in type 2B VWD.
- Women may require additional treatment directed at bleeding symptoms for the first several menstrual cycles after placement of a levonorgestrel-releasing intrauterine system.

Good Practice Statements:

- The panel encourages the development of multidisciplinary clinics in which gynecology and hematology see patients jointly to facilitate the management of heavy menstrual bleeding for patients with bleeding disorders.
- Decisions regarding the use of the levonorgestrel-releasing intrauterine system should be made in a setting of shared-decision making with multidisciplinary input (e.g. gynecology, hematology, and patients)
- In some patients, there may be other benefits to use of hormonal therapy such as treatment of oligomenorrhea due to polycystic ovary syndrome or menstrual-associated migraines.
- Patients with new onset heavy menstrual bleeding should be assessed and treated for iron deficiency and anemia.
- Women with known bleeding disorders and HMB should undergo gynaecological assessment that is recommended for women with HMB in the general population to rule out common pelvic pathologies such as fibroids and polyps, especially those not responding to first line treatment.
- Special consideration is required in terms of side effects of therapy for those who are at high risk of endometrial hyperplasia/malignancies such as women over 35, those with PCO, high BMI, women with comorbidities such as diabetes and hypertension.

➢ Question 7: In women with VWD who require or desire neuraxial anesthesia during labor, should we administer VWF concentrate to achieve VWF level of 50- 150 IU/dl or >150 IU/dl?

Recommendation

In women with VWD deemed suitable for neuraxial anesthesia during labor, the panel suggests targeting VWF levels to 50-150 IU/dL over targeting a level of >150 IU/dL to allow neuraxial anesthesia. (Conditional, Very Low Certainty of Evidence)

Remarks:

- This recommendation focused on the outcomes of the anesthesia procedure itself, and not on the effects of the levels on postpartum hemorrhage (PPH) in which VWF levels of >150 IU/dL may be advised in some situations.
- Individual risk assessment should be performed, taking into account patient diagnosis and history, and for this reason the panel advocates for a third trimester visit where VWF and FVIII levels can be checked and a prospective plan formed for delivery.
- This recommendation is intended for women who desire or require neuraxial anesthesia and does not address safety.
- VWF levels should be maintained while the epidural is in place and for at least 6 hours following removal.
- Patients should also be assessed for thrombotic risk post-delivery, and treatment (such as compression stockings) provided when needed.

Good practice statement:

- Decisions regarding anesthesia and delivery should be made in the context of a multi-disciplinary discussion with input from anesthesia, hematology, and obstetrics, and these discussions should take place well in advance of the patient's due date.

- **Question 8: In women with type 1 VWD or low VWF level (may include type 2 and 3 VWD), should we prescribe tranexamic acid (or not) during the postpartum period?**

Recommendation

The Panel suggests for the use of tranexamic acid over not using it in women with type 1 VWD or low VWF level (may include type 2 and 3 VWD) during the postpartum period (conditional recommendation/ based on low certainty evidence)

Good Practice Statements:

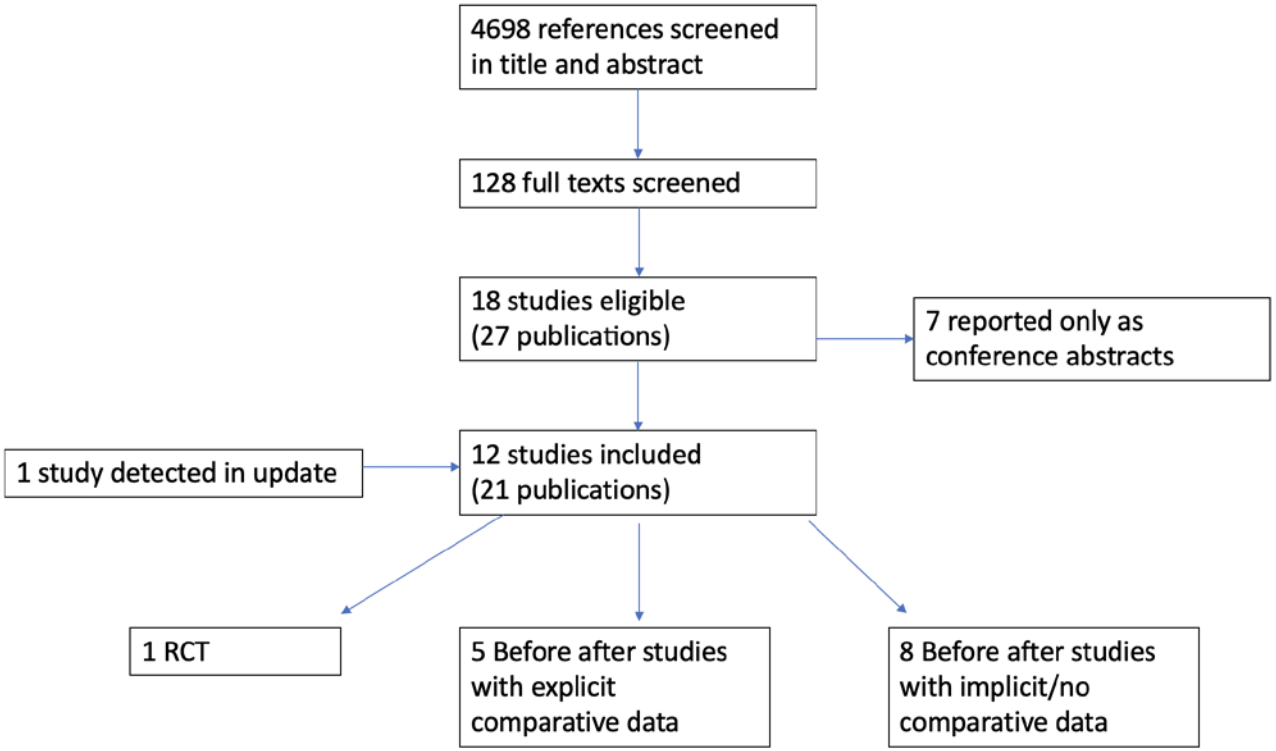
- Tranexamic acid may be given systemically via oral or intravenous routes.
- Patients who intend to breastfeed should be provided education about the safety of tranexamic acid during breastfeeding in conjunction with its benefits in reducing bleeding

There was a vote among panel members to make this recommendation a strong recommendation, based on the large body of indirect evidence showing benefits on postpartum hemorrhage, and the potentially catastrophic consequences of this outcome in women with VWD. Out of the 13 panel members who voted (those without conflicts of interest), 7 panel members voted to make this a strong recommendation. This did not meet the threshold of 80% necessary to make this a strong recommendation.

RQ1: In patients with VWD with history of severe and frequent bleeds, should we use routine prophylaxis with von Willebrand factor (VWF) or no routine prophylaxis (i.e. treatment on-demand)?

P: VWD any type, except for acquired; severe/ frequent bleeds as described by researchers (or description of potential indication of long-term prophylaxis)
I: routine long-term prophylaxis
C: no routine prophylaxis
O: Major bleeding, Serious adverse events, Joint function, Mortality, Hospitalization, Menorrhagia or HMB, Health-related QoL, Transfusions, Absence from school, work, or other required activities

After title and abstract screening of 4689 citations, we reviewed 128 full texts. This report summarizes the results from 12 studies published in 19 sources. Figure 1 illustrates the search and selection process. Please note that 2 studies provided both, comparative and non-comparative data.



We summarize 3 bodies of evidence: 1. Evidence from a randomized clinical trial in which participants were allocated to receive prophylaxis of placebo;[1] 2. Evidence from five before-after studies in which researchers provide an explicit comparison between a period in which people received prophylaxis and a period in which they did not (e.g. quantification of outcomes in both periods);[2-11] and 3. Evidence from eight before after studies in which researchers make an implicit comparison between a period in which people received prophylaxis and a period in which they did not.[3,5,11-19]

Tables 1, 2, and 3 summarize the main characteristics of the bodies of evidence. Table 4 presents the Evidence to Decision framework for this question. Tables 5, 6, and 7 present the Evidence Profiles. The appendix presents detailed assessments of risk of bias and forest plots.

Table 1: Main characteristics of RCT

Study ID	Country	Recruitment period	N	VWD type	Sex	Age	Agent prescribed for prohylaxis	Follow up
Peyvandi, 2019	Italy, Germany, Spain	2006-2016	19	Prophylaxis group, 40% type 2, 30% type 1; no prophylaxis, 55.6% type 2, 44.4% type 3	74% males	median age, 28 prophylaxis; 54 no prophylaxis	Fanhdi, Alphanate	12 months

Table 2: Main characteristics of before-after studies presenting explicit comparative data

Study	Location	N	Prophylaxis agent
Bentorp, 2005	Sweden	35	fraction I-0, Haemate P/Humate P
Bentorp, 2009	Europe	15	Willate
Borel-Derlon, 2007	Europe	4	Wilfactin
Federici, 2010	Italy	15	Fanhdi, Alphanate
Holm, 2015	NorthAmerica and Europe	80/105	NR

Table 3: Main characteristics of before-after studies presenting implicit comparative data

Study	Location	N	Prophylaxis agent
Bentorp, 2009	Europe	15	Willate
Castaman, 2013	Italy	31	Haemate
Dunkley, 2010	Australia	4	Biostate
Federici, 2007	Italy	12	Haemate
Federici, 2010	Italy	15	Fanhdi, Alphanate
Khair, 2015	England	4	Willate
Lillicrap, 2002	Canada	20	Haemate/ Humate
Nowak-Gottl, 2013	Germany	15	Willate

TABLE 4: EVIDENCE TO DECISION FRAMEWORK RECOMMENDATION QUESTION 1

Should routine prophylaxis vs. no prophylaxis be used for patients with VWD with history of severe/frequent bleeds? (RCT DATA)	
POPULATION:	Patients with VWD with history of severe/frequent bleeds RCT DATA
INTERVENTION:	Routine prophylaxis
COMPARISON:	No prophylaxis
MAIN OUTCOMES:	Spontaneous bleeds; Bleeding episodes ; Time to first bleeding; Bleeding episode lasting more than 2 days; Serious adverse events; Epistaxis episodes; GI hemorrhage episodes ; Haemarthrosis episodes ; Major bleeding; Joint function; Mortality; Heavy menstrual bleeding; Health-related QoL; Transfusions; Absence from school, work, or other required activities;
SETTING:	High income healthcare setting
PERSPECTIVE:	Clinical
CONFLICT OF INTERESTS:	The ASH conflict of interest policy for clinical practice guidelines was applied.

ASSESSMENT

Problem
Is the problem a priority?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ● **Yes** ○ Varies ○ Don't know		This question was judged to be a priority among many candidate questions to address in these guidelines

Desirable Effects
How substantial are the desirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Trivial ○ Small ○ Moderate ● **Large** ○ Varies ○ Don't know	The following is a summary of the effects of long-term prophylaxis Details are presented in Tables 5, 6, and 7	The evidence suggests the presence of benefits of long-term prophylaxis on several bleeding outcomes. These benefits were considered large and important to patients by the panel. During the meeting, the panel discussed the following with regards to the evidence - The decrease in the number of bleeds per year is considerable (decrease by 50%) - Panel noted that the available RCT does not include many women, which may raise applicability concerns. However, it was clarified that for many types of bleeding, men and women do not bleed differently therefore studies that include a majority of male subjects are still applicable to women, and therefore there

Outcomes	With no prophylaxis	With routine prophylaxis	Difference	Relative effect (95% CI)
Spontaneous bleeds assessed with: Number of events/ patient	1,000 per 1,000	**620 per 1,000** (370 to 1,000)	**380 fewer per 1,000** (630 fewer to 40 more)	**RR 0.62** (0.37 to 1.04)

follow up: mean 12 months				
Bleeding episodes assessed with: Events per patient per month follow up: mean 12 months	157 per 1,000	**38 per 1,000** (27 to 55)	**119 fewer per 1,000** (130 fewer to 102 fewer)	**Rate ratio 0.24** (0.17 to 0.35)
Time to first bleeding assessed with: Mean days follow up: mean 12 months	The mean time to first bleeding was **34.6** days	The mean time to first bleeding in the intervention group was 31.4 days higher (8.44 higher to 54.36 higher)	MD **31.4 days higher** (8.44 higher to 54.36 higher)	-
Bleeding episode lasting more than 2 days assessed with: Number of events/ bleeding episodes follow up: mean 12 months	6 per 1,000	**266 per 1,000** (64 to 1,000)	**260 more per 1,000** (59 more to 1,088 more)	**RR 45.69** (11.09 to 188.21)
Serious adverse events assessed with: number of patients follow up: mean 12 months	6 per 1,000	**15 per 1,000** (1 to 331)	**10 more per 1,000** (5 fewer to 325 more)	**RR 2.73** (0.12 to 59.57)[a]
Epistaxis episodes assessed with: events per patient per month follow up: mean 12 months	47 per 1,000	**18 per 1,000** (10 to 31)	**29 fewer per 1,000** (37 fewer to 15 fewer)	**Rate ratio 0.38** (0.21 to 0.67)
GI hemorrhage episodes assessed with: events per patient per month follow up: mean 12 months	1 per 1,000	**15 per 1,000** (2 to 116)	**14 more per 1,000** (1 more to 115 more)	**Rate ratio 13.87** (1.84 to 104.46)
Haemarthrosis episodes assessed with: events per patient per month follow up: mean 12 months	2 per 1,000	**1 per 1,000** (0 to 10)	**1 fewer per 1,000** (2 fewer to 8 more)	**Rate ratio 0.50** (0.06 to 4.50)

a. SAE reported was an intestinal perforation, which the researchers described as not associated with the study medication

is no need to rate down the certainty of the evidence for indirectness. This judgment does not apply to reproductive bleeding, but issues related to this type of bleeding are not the main focus of this question.

- It is important to consider that data from the von Willebrand Prophylaxis Network was reported in several publications. In order to not count patients twice, the study with the largest patient population and most reported outcomes was included in the analysis.

Outcomes	With no prophylaxis	With routine prophylaxis	Difference	Relative effect (95% CI)
Bleeding episodes assessed with: Number of events per patient per month follow up: median 12 months	700 per 1,000	**238 per 1,000** (175 to 322)	**462 fewer per 1,000** (525 fewer to 378 fewer)	**Rate ratio 0.34** (0.25 to 0.46)
Hospitalizations assessed with: Number of events per patient per year	714 per 1,000	**457 per 1,000** (314 to 664)	**257 fewer per 1,000** (400 fewer to 50 fewer)	**Rate ratio 0.64** (0.44 to 0.93)
Blood transfusion assessed with: Number of events/ patients	500 per 1,000	**200 per 1,000** (50 to 800)	**300 fewer per 1,000** (450 fewer to 300 more)	**RR 0.4** (0.1 to 1.6)
Heavy menstrual bleeding assessed with: Median rate per patient per year follow up: median 12 months	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.			

Outcomes	With no prophylaxis	With routine prophylaxis	Difference	Relative effect (95% CI)
Bleeding rate assessed with: episodes per patient per year follow up: median 12 months	The pooled rate of bleeding episodes per patient per year when they were receiving prophylaxis was 3.20 (95% CI, 1.96 to 5.24)			
Serious adverse events (including thrombotic events) assessed with: Number of events/ patients	There were no serious adverse events reported in any of the studies			

	follow up: median 12 months	
	Efficacy/ clinical response assessed with: Proportion of patients follow up: 12 months	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

Undesirable Effects

How substantial are the undesirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Large ○ Moderate ● **Small** ○ Trivial ○ Varies ○ Don't know	See box above.	The panel judged that the undesirable effects are very small, but still important. The panel discussed the following: - While the undesirable effects are minimal; rating the undesirable effects as “Trivial” would mislead clinicians to think that there are no potential anticipated undesirable effects and to not talk to the patient about them - Panel members, including patients, agree that side-effects are minimal for prophylaxis but never trivial; thus, a consensus for the judgement of “Small” was reached. - Other potential adverse effects for which there are no evidence, but the panel considered important to highlight: theoretical risk of thrombosis, theoretical risk of transmission of infectious agents with VWF-containing plasma products, allergic reaction, risk of inhibitor, needing an intravenous administration for prophylaxis

Certainty of evidence

What is the overall certainty of the evidence of effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Very low ● **Low** ○ Moderate ○ High ○ No included studies	The overall quality of the evidence for the outcomes critical for decision making is low	- While the evidence is very low certainty for many of the outcomes and the direction and strength of the observed effect appeared heterogeneous for specific symptoms, the overall direction of the outcomes in the included studies was consistent prompting the panel to choose "low" for overall certainty of the evidence.

Values

Is there important uncertainty about or variability in how much people value the main outcomes?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Important uncertainty or variability ● **Possibly important uncertainty or variability** ○ Probably no important uncertainty or variability ○ No important uncertainty or variability	No research evidence found	- In a survey among panel members, all of them said that patients are likely to place a high value on reducing the risk of bleeding, and some made the clarification that it is not the bleeding per se but the consequences of the bleeding on quality of life, and that the value depends on the frequency and severity of the bleeds. Several panel members suggested that the cost of infusions may outweigh the value of reducing the risk of bleeding. - Most panel members highlighted the importance of discussing the risks and benefits with the patients as part of shared decision making. As per the comments, these responses assume that the risk of thrombosis is very minimal. - Most panel members said that there is likely to be variability in values and preferences among patients. In particular, they highlighted the variability between values and preferences of caregivers making decisions versus patients themselves, as well as older adults when compared to younger adults. Based on this, the panel judged that there is possibly important uncertainty or variability in patients' values and preferences. In addition, based on this judgment, the panel highlighted the importance of the availability of educational material for providers and for patients who are candidates for prophylaxis that highlights both, the potential benefits and harms of secondary long-term prophylaxis.

Balance of effects

Does the balance between desirable and undesirable effects favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ● **Probably favors the intervention** ○ Favors the intervention ○ Varies ○ Don't know		Based on the low-quality evidence of large benefits and small harms, in addition to the possibly important uncertainty or variability in patients' values and preferences, the panel judged that the balance of effects probably favors long-term prophylaxis.

Resources required

How large are the resource requirements (costs)?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
● **Large costs** ○ Moderate costs ○ Negligible costs and savings ○ Moderate savings ○ Large savings ○ Varies ○ Don't know	We found one study addressing costs of long-term prophylaxis, which was published in 2010.[20] Researchers estimated that the cost for a 20-day treatment with Haemate was USD 4,932, and with other plasma-derived FVIII/VWF concentrates the cost was USD 5,010. In another study,[21] a group of 13 Italian hematologists came to the consensus that cost is a key factor to consider when selecting a product for long-term prophylaxis.	- In a survey among panel members prior to the meeting, many of them were uncertain about the costs of long-term prophylaxis. Those who provided values estimated ranges from 100K to 300K United States dollars per year. During the meeting, the panel members confirmed this. Panel members also highlighted that costs depend on geographic and facility location, and cost to patient depends on insurance. - In addition, according to the responses to the survey, who pays for the intervention depends on the country. In the Netherlands the prophylaxis is fully reimbursed by the insurance. In other countries it is funded by government (Australia, NZ, UK, Canada), whereas in others (US) part of the costs may be covered by insurance but there may be deductibles or extra costs for the patients. There was mention of the treatment not being covered by insurance in some countries.

Certainty of evidence of required resources

What is the certainty of the evidence of resource requirements (costs)?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Very low ○ Low ○ Moderate ○ High ● **No included studies**	The published evidence regarding costs comes from a different setting and it may be outdated, thus there are very serious indirectness concerns and these studies did not directly inform the recommendation.	None

Cost effectiveness

Does the cost-effectiveness of the intervention favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ○ Varies ● **No included studies**	No research evidence found	Although there were no published studies addressing cost-effectiveness, the panel considered the following: - Quality of life improvement in unpublished data and the reduction of cost in hospitalization probably favors prophylaxis. - In the UK, the cost of concentrate is relatively low. The panel believes there is significant variability between countries in terms of the cost of VWF concentrates.

Equity

What would be the impact on health equity?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Reduced ○ Probably reduced ○ Probably no impact ● **Probably increased** ○ Increased ○ Varies ○ Don't know	No research evidence found	The panel believed that if long-term prophylaxis was recommended, there would be an increase in coverage leading to increased equity.

Acceptability

Is the intervention acceptable to key stakeholders?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ● **Probably yes** ○ Yes ○ Varies ○ Don't know	No research evidence found.	- In a survey among panel members prior to the meeting, acceptability of long-term prophylaxis from the patients' perspective depends on severity of symptoms, as well as benefits of prophylaxis on bleeding. Training and support from healthcare system were also mentioned as factors influencing acceptability. - The panel agrees that the intervention is probably acceptable, particularly when considering underprivileged communities who may not have access to efficient treatment of bleeding episodes. - Non-adherence to prophylaxis in VWD patients may be similar to non-adherence in hemophilia patients. - Many panel members said clinicians are willing to administer long-term prophylaxis and highlighted that the likelihood of willingness of administering it depends on the benefits outweighing the harms and the patients having a high risk of bleeding. Acceptability from clinicians can be decreased by lack of logistic support, stigma, and lack of familiarity with administering the treatment.

Feasibility

Is the intervention feasible to implement?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ● **Probably yes** ○ Yes ○ Varies ○ Don't know	In one study conducted in the Russian Federation,[22] researchers found that the possibility of using prophylaxis increased due to the increase of factor concentrate supply (increase by 1.5 fold). The evidence suggests that compliance may be an important threat to feasibility. In a consensus report of 13 experts from Italy,[21] they highlighted compliance as a key challenge when deciding which prophylaxis agent to prescribe. A study found that patients 18-25 years old are 6.2 times more likely to adhere to treatment (OR 95% CI, 1.8 to 21) than those aged 13-17 years. Patients whose mothers' had at least a Bachelor's degree were 3.8 times more likely to adhere to treatment (OR 95% CI, 1.0 to 14.3) than those whose mothers did not have such degree.[23]	Based on their evidence and their experience, the panel judged that long-term prophylaxis is probably feasible to implement.

SUMMARY OF JUDGEMENTS

	JUDGEMENT						
PROBLEM	No	Probably no	Probably yes	**Yes**		Varies	Don't know
DESIRABLE EFFECTS	Trivial	Small	Moderate	**Large**		Varies	Don't know
UNDESIRABLE EFFECTS	Large	Moderate	**Small**	Trivial		Varies	Don't know
CERTAINTY OF EVIDENCE	Very low	**Low**	Moderate	High			No included studies
VALUES	Important uncertainty or variability	**Possibly important uncertainty or variability**	Probably no important uncertainty or variability	No important uncertainty or variability			
BALANCE OF EFFECTS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	**Probably favors the intervention**	Favors the intervention	Varies	Don't know
RESOURCES REQUIRED	**Large costs**	Moderate costs	Negligible costs and savings	Moderate savings	Large savings	Varies	Don't know
CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	Very low	Low	Moderate	High			**No included studies**
COST EFFECTIVENESS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	**No included studies**
EQUITY	Reduced	Probably reduced	Probably no impact	**Probably increased**	Increased	Varies	Don't know
ACCEPTABILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know

	JUDGEMENT						
FEASIBILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know

TYPE OF RECOMMENDATION

Strong recommendation against the intervention	Conditional recommendation against the intervention	Conditional recommendation for either the intervention or the comparison	**Conditional recommendation for the intervention**	Strong recommendation for the intervention
○	○	○	●	○

CONCLUSIONS

Recommendation

In patients with VWD with history of severe and frequent bleeds, the guideline panel suggests using long term prophylaxis rather than no prophylaxis (conditional recommendation, low certainty in the evidence of effects)

Justification

The guideline panel determined that there is low certainty in the evidence for a net benefit on health outcomes from using prophylaxis over no prophylaxis in VWD patients with a history of severe and frequent bleeds. The large costs were considered to be worth this net benefit. Long term prophylaxis is likely to be acceptable and feasible to implement, and this recommendation is likely to increase equity. Thus, the desirable consequences are greater than the undesirable consequences.

Subgroup considerations

The panel highlighted that patients with a history of severe and frequent bleeds would benefit from using secondary long-term prophylaxis independent of VWD subtype.

Implementation considerations

Monitoring and evaluation

Research priorities

The panel suggested future research:

- **Large RCT study on the use prophylaxis vs on demand particularly in patients with mucosal bleeds;**
- **Studies on the use of prophylaxis for heavy menstrual bleeding;**
- **Studies on the use of prophylaxis in GI procedures;**
- **Studies on the impact of prophylaxis on quality of life; and**
- **Studies on the use Plasma vs. Recombinant VWF concentrate for prophylaxis.**
- **The role for adjuvant treatment in terms of concurrent antifibrinolytic therapy in the setting of prophylaxis when bleeding is primarily mucosal (epistaxis, HMB, GI)**
- **The role of concurrent anti-angiogenic therapies in the setting of prophylaxis when primary bleeding type is GI**

Table 5: Evidence profile from RCT data. Routine prophylaxis compared to no prophylaxis for patients with VWD with history of severe/frequent bleeds

Certainty assessment							Summary of findings				
							Study event rates (%)			Anticipated absolute effects	
Nº of participants (studies) Follow-up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty of evidence	With no prophylaxis	With routine prophylaxis	Relative effect (95% CI)	Risk with no prophylaxis	Risk difference with routine prophylaxis
Spontaneous bleeds (follow up: mean 12 months; assessed with: Number of events/ patient)											
19 (1 RCT)[1]	serious [a]	not serious	not serious	serious [b]	none	⨁⨁◯◯ LOW	9/9 (100.0%)	6/10 (60.0%)	**RR 0.62** (0.37 to 1.04)	1,000 per 1,000	**380 fewer per 1,000** (from 630 fewer to 40 more)
Bleeding episodes (follow up: mean 12 months; assessed with: Events per patient per month)											
19 (1 RCT)[1]	Very serious [a]	not serious	not serious	not serious	none	⨁⨁◯◯ LOW	1.41/9	0.34/10	**Rate ratio 0.24** (0.17 to 0.35)	157 per 1,000	**107 fewer per 1000 patient(s) per months** (from 117 fewer to 92 fewer)
Time to first bleeding (follow up: mean 12 months; assessed with: Mean days)											
19 (1 RCT)[1]	serious [a]	not serious	not serious	not serious	none	⨁⨁⨁◯ MODERATE	9	10	-	The mean time to first bleeding was **34.6** days	MD **31.4 days higher** (8.44 higher to 54.36 higher)
Bleeding episode lasting more than 2 days (follow up: mean 12 months; assessed with: Number of events/ bleeding episodes)											

Table 5: Evidence profile from RCT data. Routine prophylaxis compared to no prophylaxis for patients with VWD with history of severe/frequent bleeds

Certainty assessment							Summary of findings				
204 (1 RCT)[1]	Very serious [a]	not serious	not serious	serious [c]	none	⨁⨁◯◯ LOW	1/172 (0.6%)	17/32 (53.1%)	**RR 45.69** (11.09 to 188.21)	6 per 1,000	**260 more per 1,000** (from 59 more to 1,000 more)
Serious adverse events (follow up: mean 12 months; assessed with: number of patients) – Intestinal perforation											
19 (1 RCT)[1]	serious [a]	not serious	not serious	serious [c]	none	⨁⨁◯◯ LOW	0.05/9 (0.6%)	1/10 (10.0%)	**RR 2.73** (0.12 to 59.57) [d]	6 per 1,000	**10 more per 1,000** (from 5 fewer to 325 more)
Epistaxis episodes (follow up: mean 12 months; assessed with: events per patient per month)											
19 (1 RCT)[1]	serious [a]	not serious	not serious	not serious	none	⨁⨁⨁◯ MODERATE	0.42/9	0.16/10	**Rate ratio 0.38** (0.21 to 0.67)	47 per 1,000	**26 fewer per 1000 patient(s) per months** (from 33 fewer to 14 fewer)
GI hemorrhage episodes (follow up: mean 12 months; assessed with: events per patient per month)											
19 (1 RCT)[1]	Very serious [a]	not serious	not serious	serious [e]	none	⨁◯◯◯ VERY LOW	0.01/9	0.14/10	**Rate ratio 13.87** (1.84 to 104.46)	1 per 1,000	**13 more per 1000 patient(s) per months** (from 1 more to 103 more)
Haemarthrosis episodes (follow up: mean 12 months; assessed with: events per patient per month)											
19 (1 RCT)[1]	serious [a]	not serious	not serious	serious [b]	none	⨁⨁◯◯ LOW	0.02/9	0.01/10	**Rate ratio 0.50** (0.06 to 4.50)	2 per 1,000	**1 fewer per 1000 patient(s) per months** (from 2 fewer to 7 more)
Major bleeding - not reported											

Table 5: Evidence profile from RCT data. Routine prophylaxis compared to no prophylaxis for patients with VWD with history of severe/frequent bleeds

Certainty assessment							Summary of findings				
-	-	-	-	-	-	-	-	-	-	-	-

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

-	-	-	-	-	-	-	-	-	-	-	-

CI: Confidence interval; **RR:** Risk ratio; **MD:** Mean difference

Explanations

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. Very small number of events resulting in very wide CI
d. SAE reported was an intestinal perforation, which the researchers described as not associated with the study medication
e. OIS not met, CI may change importantly if more events are observed. Most events occurred in 1 patient

Table 6: Evidence profile from before and after studies with explicit comparative data. Routine prophylaxis compared to no prophylaxis for patients with VWD with severe/frequent bleeds

Certainty assessment							Summary of findings				
							Study event rates (%)			Anticipated absolute effects	
№ of participants (studies) Follow-up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty of evidence	With no prophylaxis	With routine prophylaxis	Relative effect (95% CI)	Risk with no prophylaxis	Risk difference with routine prophylaxis
Bleeding episodes (follow up: median 12 months; assessed with: Number of events per patient per month)											
1208 (4 observational studies) [a,3-6]	extremely serious [b]	not serious [c]	not serious	not serious	none	⨁◯◯◯ VERY LOW	700/1000 [a]	0/208	**Rate ratio 0.34** (0.25 to 0.46)	700 per 1,000 [a]	**462 fewer per 1000 patient(s) per months** (from 525 fewer to 378 fewer)
Hospitalizations (assessed with: Number of events)											
210 (1 observational study)[10]	serious [d]	not serious	not serious	not serious	none	⨁◯◯◯ VERY LOW	75/105	47/105	**Rate ratio 0.64** (0.44 to 0.93)	714 per 1,000	**235 fewer per 1000 patient(s)** (from 399 fewer to 49 fewer)
Blood transfusion (assessed with: Number of events/patients)											
20 (1 observational study)[2]	very serious [b]	not serious	not serious	serious [e]	none	⨁◯◯◯ VERY LOW	5/10 (50.0%)	2/10 (20.0%)	**RR 0.4** (0.1 to 1.6)	500 per 1,000	**300 fewer per 1,000** (from 450 fewer to 300 more)
Heavy menstrual bleeding (follow up: median 12 months; assessed with: Median rate per patient per year)											
34 (1 observational study)[6]	very serious [f]	not serious	not serious	serious [g]	none	⨁◯◯◯ VERY LOW	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.				
Serious adverse events- cannot have comparative data - not measured											

Table 6: Evidence profile from before and after studies with explicit comparative data. Routine prophylaxis compared to no prophylaxis for patients with VWD with severe/frequent bleeds

Certainty assessment							Summary of findings				
-	-	-	-	-	-	-	-	-	-	-	-
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											
-	-	-	-	-	-	-	-	-	-	-	-

CI: Confidence interval; **RR:** Risk ratio

Explanations

a. Calculated based on median rate across studies
b. Performance and detection bias likely to have happened in these studies
c. Although there is statistical inconsistency, there is no important clinical inconsistency (all studies suggest the same direction of effect)
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 7: Evidence profile from before and after studies without explicit comparative data. Routine prophylaxis compared to no prophylaxis for patients with VWD with severe/frequents bleeds

Certainty assessment							Summary of findings				
							Study event rates (%)			Anticipated absolute effects	
Nº of participants (studies) Follow-up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty of evidence	With no prophylaxis	With routine prophylaxis	Relative effect (95% CI)	Risk with no prophylaxis	Risk difference with routine prophylaxis
Bleeding rate (follow up: median 12 months; assessed with: episodes per patient per year)											
62 (4 observational studies)[11-13,16]	very serious [a]	serious [b]	not serious	serious [c]	none	⨁◯◯◯ VERY LOW	The pooled rate of bleeding episodes per patient per year when they were receiving prophylaxis was 3.20 (95% CI, 1.96 to 5.24)				
Serious adverse events (including thrombotic events) (follow up: median 12 months; assessed with: Number of events/ patients)											
145 (6 observational studies)[2,8,12,14,16]	not serious	not serious	not serious	not serious	publication bias strongly suspected [d]	⨁◯◯◯ VERY LOW	There were no serious adverse events reported in any of the studies				
Efficacy/ clinical response (follow up: 12 months; assessed with: Proportion of patients)											
51 (4 observational studies)[13,15,16,19]	very serious [e]	not serious	not serious	not serious	none	⨁◯◯◯ VERY LOW	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				
Joint function - not reported											
-	-	-	-	-	-	-	-	-	-	-	-
Mortality - not reported											
-	-	-	-	-	-	-	-	-	-	-	-
Hospitalization - not reported											
-	-	-	-	-	-	-	-	-	-	-	-

Table 7: Evidence profile from before and after studies without explicit comparative data. Routine prophylaxis compared to no prophylaxis for patients with VWD with severe/frequents bleeds

Certainty assessment							Summary of findings				
Heavy menstrual bleeding - not reported											
-	-	-	-	-	-	-	-	-	-	-	-
Health related QoL - not reported											
-	-	-	-	-	-	-	-	-	-	-	-
Transfusions - not reported											
-	-	-	-	-	-	-	-	-	-	-	-
Absence from school, work, or other required activities - not reported											
-	-	-	-	-	-	-	-	-	-	-	-

CI: Confidence interval

Explanations

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

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Appendix

Figure 1: Assessment of Risk of bias of RCT

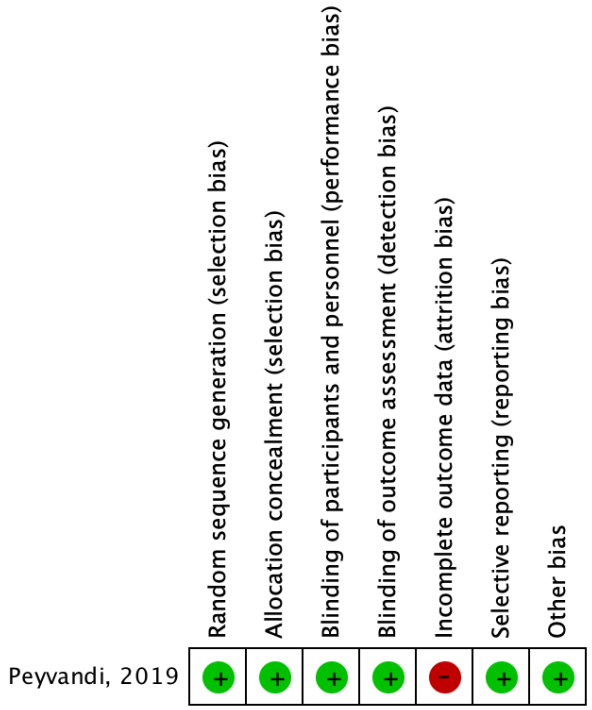
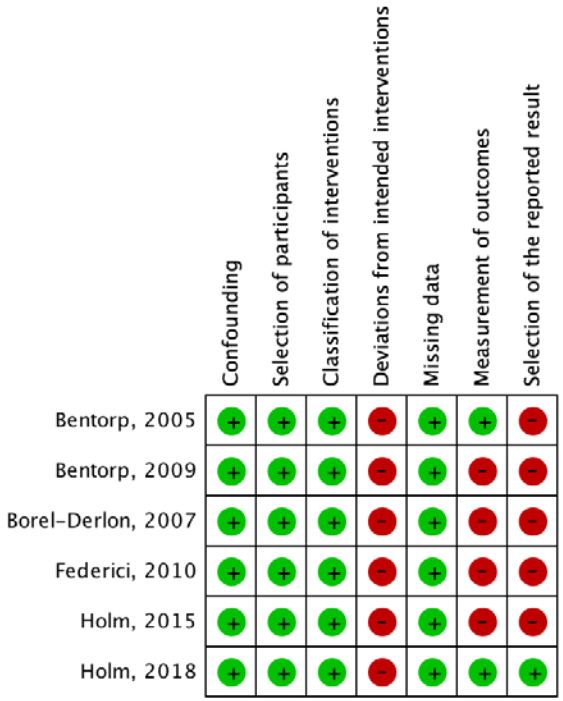


Figure 2: Assessment of risk of bias of before and after studies with explicit comparative data



*Note: Holm 2018 is same study as Holm 2015, but reports a different outcome for which there is different risk of bias

Figure 3: Forest plot outcome bleeding rate (per patient/ month)

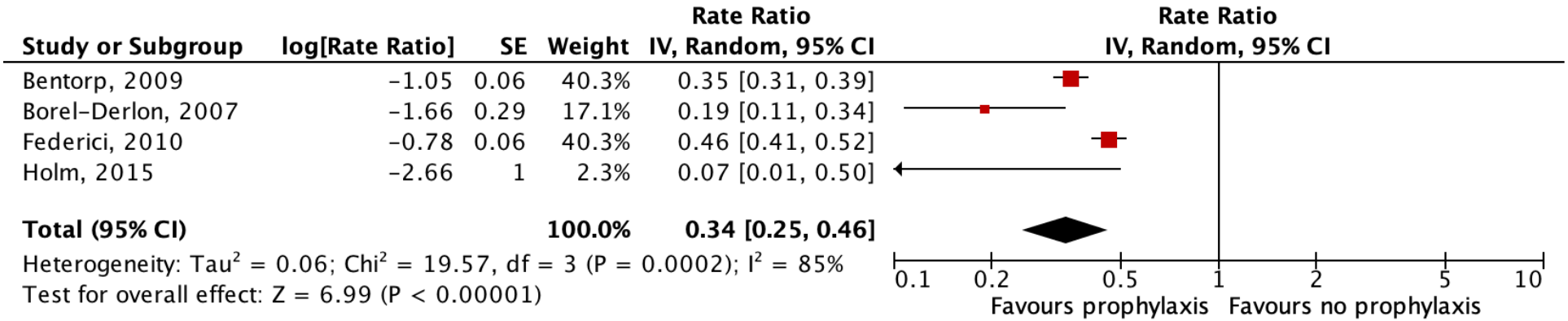


Figure 4: Assessment of risk of bias of before and after studies without explicit comparative data

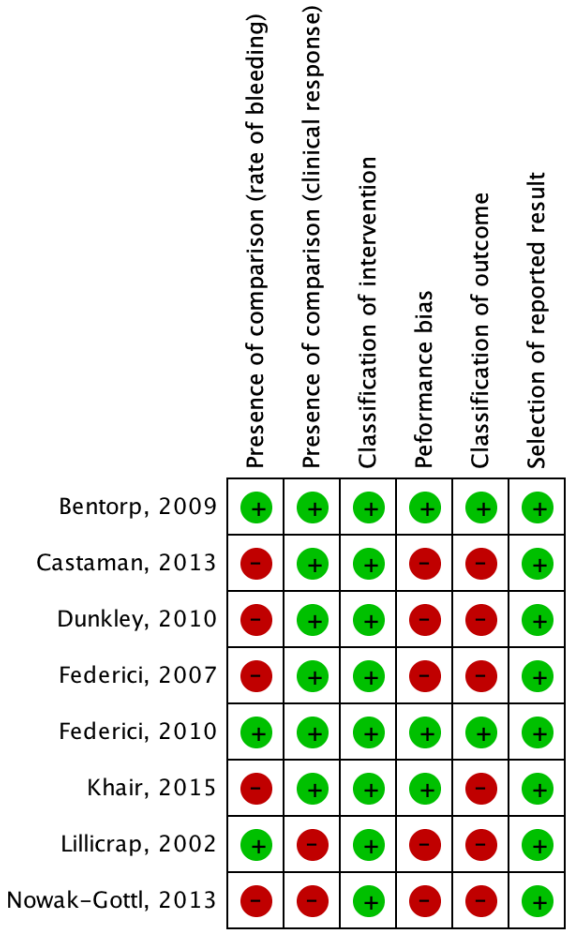
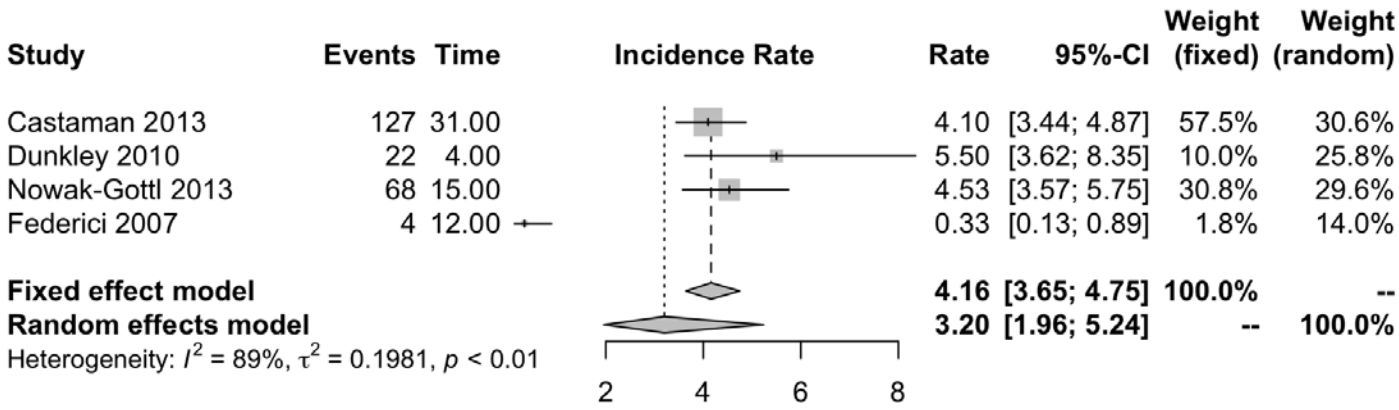


Figure 5: Analysis outcome bleeding rate (person/year)



RQ2: In patients with VWD, should we perform a DDAVP challenge/trial and choose a treatment for bleeding depending on its results, not perform the DDAVP challenge and treat with VWF concentrate and/or tranexamic acid, or not perform the DDAVP challenge and treat with DDAVP?

P: VWD all types, except for acquired
I: DDAVP trial + treatment, no trial + treatment with VWF or tranexamic acid, no trial + DDAVP treatment
C: against each other. Potential comparisons

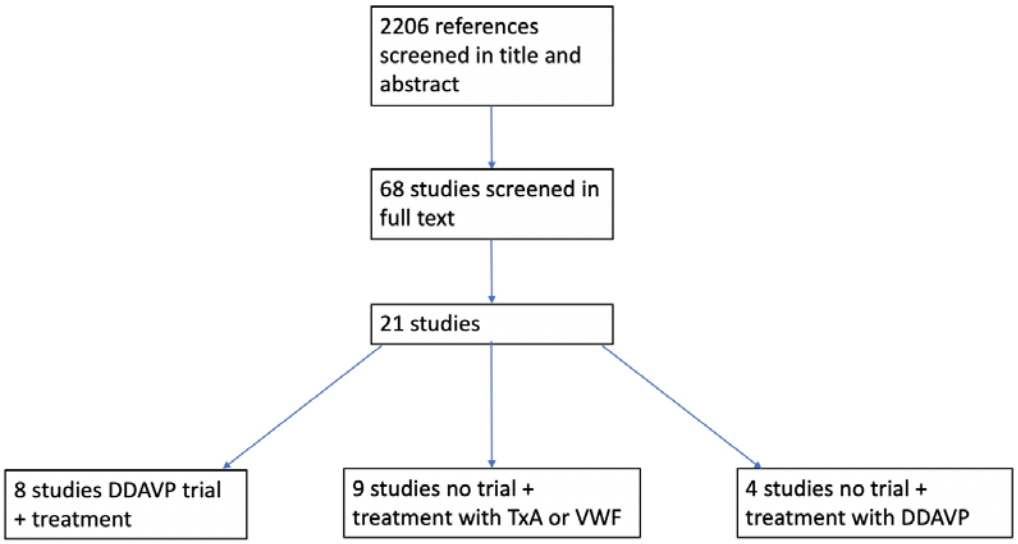
1. DDAVP trial + treatment vs. no trial + treatment with VWF or tranexamic acid
2. DDAVP trial + treatment vs. no trial + DDAVP treatment
3. No trial + treatment with VWF or tranexamic acid vs. no trial + DDAVP treatment

O: Major bleeding, SAEs, Mortality, HMB, Hospitalization, Transfusion, Thrombotic events

After title and abstract screening of 4698 references, we reviewed the full text of 86 studies. We did not find any comparative studies addressing this question.

The panel decided that case series would be helpful to inform this question. We conducted 3 systematic review of case series, one for each of the intervention arms. After title and abstract screening of 2206 references, we reviewed the full text of 68 studies. We included 21 case series: 8 in which patients received DDAVP trial + treatment,[1-8] 9 in which they received no trial + treatment with VWF or tranexamic acid,[9-17] and 4 in which they received no trial + DDAVP treatment [18-21](Figure 1)

Figure 1: Flow chart



This report contains evidence from 21 case series. The main characteristics of the included studies are presented in the appendix. In addition, the panel considered that there was another study that did not meet the eligibility criteria of including only patients with VWD, but that was helpful to inform the outcomes of adverse effects, which we also include.[22 23]

We present the Evidence to Decision Framework in Table 1. The Evidence Profiles for each of the treatment arms are presented in Tables 2, 3, and 4. The appendix contains relevant figures.

TABLE 1: EVIDENCE TO DECISION FRAMEWORK RECOMMENDATION QUESTION 2

Should DDAVP trial and treatment according to results vs. other options be used for patients with VWD?	
POPULATION:	Patients with VWD
INTERVENTION:	DDAVP trial and treatment according to results; no trial and treatment with VWF or tranexamic acid; no trial and treatment with DDAVP
COMPARISON:	Against each other
MAIN OUTCOMES:	Hemostatic efficacy; Postoperative bleeding; Hemostatic efficacy; Adverse events of treatment; Major bleeding; Mortality; Heavy menstrual bleeding; Hospitalization; Transfusion; Thrombotic events;
SETTING:	High income healthcare setting
PERSPECTIVE:	Clinical
CONFLICT OF INTERESTS:	**ASH conflict of interest declaration and management policies were applied, and the following panel members were voting panel members (determining the direction and strength of the recommendation):** • Arapshian • Connell • Couper • Flood • Grow • Kouides • Mustafa • O'Brein • Ozelo • Tosetto • Weyand **Panel members recused as a result of risk of conflicts of interest:** • Abdul Kadir • Laffan • Lavin • Leebeek

ASSESSMENT

Problem

Is the problem a priority?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ●**Yes** ○ Varies ○ Don't know		This question was prioritized by the panel among many others to be addressed in these guidelines

Desirable Effects

How do interventions compare against each other with regards to desirable effects?

JUDGEMENT

Rank the 3 interventions regarding the magnitude of desirable effects (there may be more than one intervention in each rank)

Most effective:
DDAVP trial and treatment according to results; No trial and treatment with VWF and/or tranexamic acid

Intermediate:

Last effective:
No trial and treatment with DDAVP

-

RESEARCH EVIDENCE

The following tables summarize the evidence regarding desirable and undesirable effects of the options. Tables 2, 3, and 4 present details of the evidence.

Option 1: DDAVP trial + treatment

Outcomes	Impact
Hemostatic efficacy assessed with: excellent/good/effective, when used as surgical prophylaxis	The proportion of surgical interventions in which clinicians rated the hemostatic efficacy as excellent/good/effective was 94% (95% CI, 81 to 98%). The total number of surgeries was 211
Postoperative bleeding assessed with: number of patients	The proportion of surgical events in which patients experienced postoperative bleeding was 6% (95% CI, 0.02 to 0.14). The total number of surgical events was 199
Hemostatic efficacy assessed with: good/effective, when used for treating bleeding episodes	The proportion of bleeding episodes in which clinicians rated the hemostatic efficacy as good/effective was 97% (95% CI, 79 to 100%). The total number of bleeding episodes treated were 29
Adverse events of treatment assessed with: several definitions	One study with 41 patients reported that 10/41 experienced emesis, from which 5 had to be admitted. They also reported that 1/41 patients experienced hyponatremia. Another study with 37 children reported that all of them experienced mild hyponatremia and 2/37 experienced severe hyponatremia (1 of then resulting in seizures)

Outcomes	Importance	Certainty of the evidence (GRADE)
Hemostatic efficacy assessed with: excellent/good/effective, when used as surgical prophylaxis	IMPORTANT	⨁◯◯◯ VERY LOW[a]
Postoperative bleeding assessed with: number of patients	IMPORTANT	⨁◯◯◯ VERY LOW[a]
Hemostatic efficacy assessed with: good/effective, when used for treating bleeding episodes	IMPORTANT	⨁◯◯◯ VERY LOW[a]
Adverse events of treatment assessed with: several definitions	CRITICAL	⨁◯◯◯ VERY LOW[a]

a. This is a case series, there is no explicit comparison with any other group

ADDITIONAL CONSIDERATIONS

The panel judged the desirable effects for the arms **DDAVP trial + Treatment** and **no trial + treatment with VWF concentrate or tranexamic acid** as large and ranked both interventions as the most effective. The arm **no trial and DDAVP treatment** was judged as the least effective with variable desirable effects.

During the meeting, the panel discussed the following:

-Panel noted that the different subtypes of the disease when choosing between the 3 interventions as not all patients are responsive to DDAVP, and not all patients receive trial.

Option 2: no trial + treatment with VWF or tranexamic acid

Outcomes	Impact
Bleeding episodes assessed with: Number of bleeding or excessive bleeding episodes over total number of surgeries	The pooled risk of bleeding episodes is 9% (95% CI, 2% to 34%). The total number of surgical procedures was 247.<
Hemostatic efficacy assessed with: judged as excellent or good over total number of surgeries	The proportion of surgeries in which efficacy was judged to be excellent or good was 97% (95% CI, 88% to 99%). The total number of surgical procedures was 205
Adverse events assessed with: Serious and not serious, when used as surgical prophylaxis	The proportion of participants who experienced adverse events was 2% (95% CI, 0 to 31%). The AEs reported were not serious. The total number of surgical procedures was 205
Need for transfusion assessed with: when used as surgical prophylaxis	The proportion of surgeries for which there was need for transfusion was 11% (95% CI, 5% to 22%). The total number of surgeries was 55
Hemostatic efficacy assessed with: judged as excellent or good when used to treat bleeding episodes	The proportion of bleeding episodes in which the hemostatic efficacy was judged to be excellent or good was 96% (95% CI, 91% to 98%). The total number of bleeding episodes treated was 132
Bleeding episodes assessed with: number of bleeding episodes, when used as long term prophylaxis	The number of bleeding episodes was reduced from 30 to 16 when treating patients with tranexamic acid as long-term prophylaxis instead of placebo
Adverse events assessed with: not serious, when used as long term prophylaxis	One study in which patients received tranexamic acid reported that the proportion who experienced headaches was 60%, back pain 30%, and MSK pain was 40%. The total number of patients was 17.
Excessive postpartum bleeding	Excessive bleeding occurred in 1/17 deliveries (6%)

Outcomes	Importance	Certainty of the evidence (GRADE)
Bleeding episodes assessed with: Number of bleeding or excessive bleeding episodes over total number of surgeries	IMPORTANT	⨁◯◯◯ VERY LOW[a,b]
Hemostatic efficacy assessed with: judged as excellent or good over total number of surgeries	IMPORTANT	⨁◯◯◯ VERY LOW[a]
Adverse events assessed with: Serious and not serious, when used as surgical prophylaxis	CRITICAL	⨁◯◯◯ VERY LOW[a,c]
Need for transfusion assessed with: when used as surgical prophylaxis	IMPORTANT	⨁◯◯◯ VERY LOW[a]

Hemostatic efficacy assessed with: judged as excellent or good when used to treat bleeding episodes	IMPORTANT	⨁◯◯◯ VERY LOW[a]
Bleeding episodes assessed with: number of bleeding episodes, when used as long term prophylaxis	IMPORTANT	⨁◯◯◯ VERY LOW[d]
Adverse events assessed with: not serious, when used as long term prophylaxis	IMPORTANT	⨁◯◯◯ VERY LOW[d]
Excessive postpartum bleeding	IMPORTANT	⨁◯◯◯ VERY LOW[a,d]

a. This is a case series, there is no comparison with other groups
b. Unexplained inconsistency results in imprecision. Rated down one level for both.
c. The CI shows that the risk can be minimal as well as important
d. Very small sample size

Option 3: no trial + treatment with DDAVP

Outcomes	Impact
Hemostasis during bleeding episodes assessed with: Proportion of episodes with excellent, good, or poor response	The proportion of episodes in which efficacy was excellent was 83% of 254 episodes and good in 14% of the episodes among people with mild type 1 VWD. The proportion of episodes in which efficacy was excellent was 71% of 254 episodes and good in 18% of the episodes among people with moderate type 1 VWD.
Hemostasis during surgery assessed with: Bleeding during/ surgery	A study reported that postoperative bleeding occurred in 1/14 patients who received DDAVP. Another reported that hemostasis for surgical prophylaxis was excellent in 93% of patients with mild type 1 VWD, and 73% in patients with moderate type 1 VWD
Heavy menstrual bleeding assessed with: Proportion with response	One study that enrolled 22 patients reported that 77% responded to the treatment (measured with PBAC score <100). Another that enrolled 172 patients with VWD reported that efficacy to control HMB was excellent (1 dose to control HMB) or good (2 doses) in 92% of patients
Hospitalization assessed with: Duration in days when used as surgical prophylaxis	The mean number of days of hospitalization was 6.3
Adverse events- hyponatremia and severe hyponatremia when used as surgical prophylaxis assessed with: Proportion of patients	The proportion of patients who experienced hyponatremia (<136 mMol/L) ranged from 4%-72% across 3 studies. These studies also provided evidence regarding severe hyponatremia, but they used different cut-offs for their definition. In one study with 63 patients, the proportion of patients with hyponatremia (<136 mMol/L) was 65%, and

	the proportion of patients with severe hyponatremia (<130 mMol/L) was 9.5%. In another study with 107 patients (101 of them with platelet function defects), the proportion of patients with hyponatremia (<136 mMol/L) was 72%, and the proportion of patients with [severe] hyponatremia (<131 mMol/L) was 10.3%. In a third study in which researchers recruited 108 patients, the proportion who experienced hyponatremia (<136 mmol/L was 4%, and the proportion who experienced severe hyponatremia (<126 mMol/L) was 0%.	
Adverse events- not serious assessed with: Mild to moderate headaches, facial flushing when used as bleeding treatment	The proportion of patients who reported experiencing: headaches was 9%, facial flushing was 9%, and both was 4.5%	
Adverse events- mild and moderate assessed with: Headache, flushing, nausea, dizziness, asthenia, vomiting, peripheral edema when used as surgical prophylaxis or bleeding treatment	The proportion of administrations in which AEs was reported was 43% in patient with mild type 1 VWD and 14% in those with moderate type 1 VWD	
Outcomes	**Importance**	**Certainty of the evidence (GRADE)**
Hemostasis during bleeding episodes assessed with: Proportion of episodes with excellent, good, or poor response	IMPORTANT	⨁◯◯◯ VERY LOW[a]
Hemostasis during surgery assessed with: Bleeding during/ surgery	IMPORTANT	⨁◯◯◯ VERY LOW[a]
Heavy menstrual bleeding assessed with: Proportion with response	CRITICAL	⨁◯◯◯ VERY LOW[a]
Hospitalization assessed with: Duration in days when used as surgical prophylaxis	CRITICAL	⨁◯◯◯ VERY LOW[a]
Adverse events- hyponatremia and severe hyponatremia when used as surgical prophylaxis assessed with: Proportion of patients	CRITICAL	⨁◯◯◯ VERY LOW[a]
Adverse events- not serious assessed with: Mild to moderate headaches, facial flushing when used as bleeding treatment	IMPORTANT	⨁◯◯◯ VERY LOW[a]
Adverse events- mild and moderate assessed with: Headache, flushing, nausea, dizziness, asthenia, vomiting, peripheral edema when used as surgical prophylaxis or bleeding treatment	IMPORTANT	⨁◯◯◯ VERY LOW[a]

a. This is a case series, there is no explicit comparison with other group, which is the aim of this question

Undesirable Effects

How do interventions compare against each other with regards to undesirable effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
Rank the 3 interventions regarding the magnitude of undesirable effects (there may be more than one intervention in each rank) **Least harmful:** DDAVP trial and treatment according to results; No trial and treatment with VWF and/or tranexamic acid **Intermediate:** **More harmful**: No trial and treatment with DDAVP	See box above. - Several DDAVP SE: MI, seizures, hyponatremia, which are large SEs. However, the side effects are realtively rare and are nowadays avoided when giving the treatment (fluid restriction, avoiding DDAVP in patients on SSRIs), also there is less hyponatremia in Intranasal form of the TTx.	The panel judged that the undesirable effects of **DDAVP trial + Treatment** and **no trial + Treatment with VWF or tranexamic acid** are small but still important. They also judged that the undesirable effects of **no trial + treatment with DDAVP** are moderate in comparison. The panel discussed the following potential harms of giving DDAVP without a trial: - The possibility of worsening thrombocytopenia in VWD Type 2B. - Relying on an effective response when the actual response is unknown.

Certainty of evidence

What is the overall certainty of the evidence of effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
● **Very low** ○ Low ○ Moderate ○ High ○ No included studies	The certainty of the evidence is very low. All the evidence comes from case series, in which there is no comparison between alternatives. Inferences regarding how the alternatives compare based on case series are likely to be highly biased.	The panel highlighted heterogeneity in the VWD subtype populations included in the studies in the systematic review and the 2 different bodies of case series, which raises indirectness and risk of bias. Some patients have already received a DDAVP trial or are type 3 VWD; however, the evidence is scarce, and the studies met the eligibility criteria even if the reason was the lack of reporting of important information. These issues have addressed in the assessment of certainty of the evidence.

Values

Is there important uncertainty about or variability in how much people value the main outcomes?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Important uncertainty or variability ● **Possibly important uncertainty or variability** ○ Probably no important uncertainty or variability	No research evidence found.	- The panel agrees there is important uncertainty or variability as there are patients who place a high value on the potential benefits of the DDAVP trial, and others who place a high value on the side effects of the intervention.

○ No important uncertainty or variability		

Balance of effects

Which intervention does the balance between desirable and undesirable effects favor?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
Rank the 3 interventions according to the balance of effect (there may be more than one intervention in each rank) **Best balance:** DDAVP trial and treatment according to results; No trial and treatment with VWF and/or tranexamic acid **Intermediate:** **Worst balance:** No trial and treatment with DDAVP		According to the panels' judgments, a DDAVP trial with treatment based on the results, or skipping a DDAVP challenge and treating with VWF concentrate or tranexamic acid are likely to be more effective and less harmful than skipping a DDAVP trial, but proceeding with DDAVP treatment in the setting of uncertain efficacy. Even though there is possible important uncertainty or variability, the balance of effects favors performing a DDAVP trial and treating based on the results or treating with VWF concentrate and/or tranexamic acid if an individual patient's responsiveness to DDAVP is unknown.

Resources required

How large are the resource requirements (costs)?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
Rank the 3 interventions regarding the resources required (there may be more than one intervention in each rank) **Less costs:** No trial and treatment with tranexamic acid **Intermediate costs:** No trial and treatment with DDAVP **Most costs:** DDAVP trial and treatment according to results; No trial and treatment with VWF	No research evidence found	The panel made these judgments based on their experience. In addition, they considered data collected for other recommendation questions. The panel also considered the following -There is a new generic tranexamic acid that is not expensive in the US. - In Europe/UK, tranexamic acid is approximately €1/tablet - DDAVP can be given IN or IV, and IN is much more expensive than IV. - Desmopressin trial cost: Australia $400-500, USA $100-200 (nursing time, lab costs, costs of IV tubing, and cost to have a patient in an outpatient clinic not included), Europe €300.

Certainty of evidence of required resources

What is the certainty of the evidence of resource requirements (costs)?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Very low ○ Low ○ Moderate ○ High ● **No included studies**	No research evidence found	None

Cost effectiveness

Which intervention does the cost effectiveness favor?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
Rank the 3 interventions according to the cost-effectiveness (there may be more than one intervention in each rank) Best cost-effectiveness: Intermediate cost effectiveness: Worst cost-effectiveness: ● **No included studies**	No research evidence found .	None

Equity

If recommended, which intervention would reduce health inequities the most?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
Rank the 3 interventions according to their potential to reduce inequities if recommended (there may be more than one intervention in each rank) **Most reduction:**	No research evidence found	- The panel agrees that recommending a DDAVP challenge + treating based on the results will allow patients with an established response to benefit from the treatment and would preserve costly resources, particularly for patients who need of concentrate. Thus, inequities would be reduced.

No trial and treatment with DDAVP **Intermediate reduction:** No trial and treatment with VWF and/or tranexamic acid **Less reduction:** DDAVP trial and treatment according to results		

Acceptability

Which intervention is more acceptable to key stakeholders?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
Rank the 3 interventions according to their acceptability intervention in each rank) **Best acceptability:** DDAVP trial and treatment according to results; No trial and treatment with VWF and/or tranexamic acid **Intermediate acceptability:** **Worst acceptability:** No trial and treatment with DDAVP	No research evidence found.	- In a survey to panel members before the meeting, all panels members said that most patients are willing to undergo a DDAVP challenge, but that the burden of the trial in terms of time and repeated blood draws is a factor that threatens acceptability (according to some comments, however, some patients may not accept the trial because of fear of adverse events). When asked if patients were willing to not receive the trial, some panel members said yes but many said no because this is not standard practice or because patients may feel that they are not receiving the best possible care.

Feasibility

Which intervention is more feasible to implement?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
Rank the 3 interventions according to their feasibility (there may be more than one intervention in each rank) **Most feasible:** No trial and treatment with DDAVP **Intermediate feasibility**: DDAVP trial and treatment according to results; No trial and treatment with VWF and/or tranexamic acid Least feasible:	No research evidence found	- In a survey to panel members, the threats to feasibility listed were chair space, availability, accessibility, and costs

SUMMARY OF JUDGEMENTS

	DDAVP trial + treatment	No trial + treatment with VWF or tranexamic acid	No trial + treatment with DDAVP
DESIRABLE EFFECTS	★★★	★★★	★
UNDESIRABLE EFFECTS	★★★	★★★	★
BALANCE OF EFFECTS	★★★	★★★	★
RESOURCES REQUIRED	★	★★★+ (+with tranexamic acid; treatment with VWF is ranked as: ★)	★★
COST EFFECTIVENESS			
EQUITY	★★★	★★	★
ACCEPTABILITY	★★★	★★★	★
FEASIBILITY	★★	★★	★★★

★★★ Ranked as best option in the factor considered for making the recommendation
★★ Ranked as intermediate option in the factor considered for making the recommendation
★ Ranked as worst option in the factor considered for making the recommendation

CONCLUSIONS

Recommendation

In patients for whom desmopressin is a valid treatment option and who have a baseline VWF level < 30 IU/dL, the panel suggests performing a trial of desmopressin and treating based on the results over not performing a trial and treating with tranexamic acid or factor concentrate. (Conditional recommendations based on very low certainty). **In these patients, the panel suggests against treating with desmopressin in the absence of desmopressin trial results** (Conditional recommendation, based on very low certainty evidence).

Remarks:

- This recommendation does not apply to patients for whom desmopressin is not a reasonable treatment option (e.g type 3*).
- DDAVP is generally contraindicated in type 3 VWD due to lack of efficacy and in type 2B VWD due to increased platelet binding with subsequent thrombocytopenia.
- Many patients with type 2 VWD will not respond to desmopressin and require other modes of treatment.
- Patients undergoing major surgery including those sites where even small amount of bleeding may result in critical organ damage (e.g. CNS surgery) should not receive DDAVP as sole therapy.
- Adult patients with type 1 VWD and levels equal or greater than 30 IU/dL can be presumed to be desmopressin responsive and can receive desmopressin without requiring a trial but is reasonable to obtain VWF levels to confirm response when given during a therapeutic intervention.
- This recommendation does not address the choice between treating with tranexamic acid and VWF concentrate.

GOOD PRACTICE STATEMENT: The administration of desmopressin to patients with type 2B VWD is contraindicated, as this may cause thrombocytopenia due to increased platelet binding. Furthermore, desmopressin is generally contraindicated in patients with cardiovascular disease, patients under the age of 2, patients with type 1C VWD in the setting of surgery, and pregnant patients with preeclampsia (precautions in pregnancy).

GOOD PRACTICE STATEMENT: Patients receiving desmopressin are at risk for hyponatremia from free water retention, patients should only receive normal saline, and oral fluid intake should be restricted to prevent hyponatremia.

Justification

The conditional recommendation for DDAVP trial and treatment based on the results over not performing a trial and treating with tranexamic acid or factor concentrate places a high value on the increased equity expected if this option is recommended. Both options are judged effective and unlikely to be harmful, but there is very low-quality evidence for the effects.

The conditional recommendation against treating with desmopressin in the absence of desmopressin trial results places a high value on the likely lack of benefits, potentially more side effects when, less increase in equity if recommended, and less acceptability compared with the other alternatives. Costs and cost effectiveness did not have an important bearing in this recommendation.

Subgroup considerations

Implementation considerations

Monitoring and evaluation

Research priorities

The panel suggested future research:

- **Logistics and patient impact of performing DDAVP trials;**
- **Best timepoints to obtain VWF levels following DDAVP trial.**

Table 2: Evidence profile. DDAVP trial and treatment according to results compared to other options for patients with VWD

Certainty assessment							Summary of findings
№ of participants (studies) Follow-up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty of evidence	Impact
Hemostatic efficacy (assessed with: excellent / good / effective, when used as surgical prophylaxis)							
211 (4 observational studies) [1 4 6 7]	very serious [a]	not serious	not serious	not serious	none	⨁◯◯◯ VERY LOW	The proportion of surgical interventions in which clinicians rated the hemostatic efficacy as excellent/good/effective was 94% (95% CI, 81 to 98%). The total number of surgeries was 211.
Postoperative bleeding (assessed with: number of patients)							
199 (4 observational studies) [2 3 5 8]	very serious [a]	not serious	not serious	not serious	none	⨁◯◯◯ VERY LOW	The proportion of surgical events in which patients experienced postoperative bleeding was 6% (95% CI, 0.02 to 0.14). The total number of surgical events was 199.
Hemostatic efficacy (assessed with: good / effective, when used for treating bleeding episodes)							
29 (2 observational studies) [1 7]	very serious [a]	not serious	not serious	not serious	none	⨁◯◯◯ VERY LOW	The proportion of bleeding episodes in which clinicians rated the hemostatic efficacy as good/effective was 97% (95% CI, 79 to 100%). The total number of bleeding episodes treated were 29.
Adverse events of treatment (assessed with: several definitions)							
78 (2 observational study) [3 8]	very serious [a]	not serious	not serious	not serious	none	⨁◯◯◯ VERY LOW	One study with 41 patients reported that 10/41 experienced emesis, from which 5 had to be admitted. They also reported that 2/41 patients experienced hyponatremia. Another study with 37 children reported that all of them experienced mild hyponatremia and 2/37 experienced severe hyponatremia (1 of then resulting in seizures).
Major bleeding - not reported							
-	-	-	-	-	-	-	
Mortality - not reported							
-	-	-	-	-	-	-	
Heavy menstrual bleeding - not reported							

Table 2: Evidence profile. DDAVP trial and treatment according to results compared to other options for patients with VWD

Certainty assessment							Summary of findings
-	-	-	-	-	-	-	
Hospitalization - not reported							
-	-	-	-	-	-	-	
Transfusion - not reported							
-	-	-	-	-	-	-	
Thrombotic events - not reported							
-	-	-	-	-	-	-	

CI: Confidence interval

Explanations

a. This is a case series, there is no explicit comparison with any other group

Table 3: Evidence profile. No DDAVP trial and treatment with tranexamic acid or VWF compared to other options for patients with VWD

Certainty assessment							Summary of findings
№ of participants (studies) Follow-up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty of evidence	Impact
Bleeding episodes (assessed with: Number of bleeding or excessive bleeding episodes over total number of surgeries)							
194 (4 observational studies) [13,15,17,16]	very serious [a]	not serious	not serious	serious [b]	none	⨁◯◯◯ VERY LOW	The pooled risk of bleeding episodes is 9% (95% CI, 2% to 34%). The total number of surgical procedures was 247.
Hemostatic efficacy (assessed with: judged as excellent or good over total number of surgeries)							
156 (4 observational studies)[9, 11 12,13]	very serious [a]	not serious	not serious	not serious	none	⨁◯◯◯ VERY LOW	The proportion of surgeries in which efficacy was judged to be excellent or good was 97% (95% CI, 88% to 99%). The total number of surgical procedures was 205.
Adverse events (assessed with: Serious and not serious, when used as surgical prophylaxis)							
156 (4 observational studies)[9, 11, 12, 13]	very serious [a]	not serious	not serious	serious [c]	none	⨁◯◯◯ VERY LOW	The proportion of participants who experienced adverse events was 2% (95% CI, 0 to 31%). The AEs reported were not serious. The total number of surgical procedures was 205.
Need for transfusion (assessed with: when used as surgical prophylaxis)							
58 (2 observational studies)[9, 13]	serious [a]	not serious	not serious	not serious	none	⨁◯◯◯ VERY LOW	The proportion of surgeries for which there was need for transfusion was 11% (95% CI, 5% to 22%). The total number of surgeries was 55.
Hemostatic efficacy (assessed with: judged as excellent or good when used to treat bleeding episodes)							
70 (3 observational studies) [9 11 12]	very serious [a]	not serious	not serious	not serious	none	⨁◯◯◯ VERY LOW	The proportion of bleeding episodes in which the hemostatic efficacy was judged to be excellent or good was 96% (95% CI, 91% to 98%). The total number of bleeding episodes treated was 132.

Table 3: Evidence profile. No DDAVP trial and treatment with tranexamic acid or VWF compared to other options for patients with VWD

Certainty assessment							Summary of findings
Bleeding episodes (assessed with: number of bleeding episodes, when used as long term prophylaxis)							
17 (1 observational study)[10]	not serious	not serious	not serious	serious [d]	none	⨁◯◯◯ VERY LOW	The number of bleeding episodes was reduced from 30 to 16 when treating patients with tranexamic acid as long-term prophylaxis instead of placebo
Adverse events (assessed with: not serious, when used as long term prophylaxis)							
17 (1 observational study) [10]	not serious	not serious	not serious	serious [d]	none	⨁◯◯◯ VERY LOW	One study in which patients received tranexamic acid reported that the proportion who experienced headaches was 60%, back pain 30%, and MSK pain was 40%. The total number of patients was 17.
Excessive postpartum bleeding							
15 (1 observational study) [14]	serious [a]	not serious	not serious	serious [d]	none	⨁◯◯◯ VERY LOW	Excessive bleeding occurred in 1/17 deliveries (6%)
Major bleeding - not reported							
-	-	-	-	-	-	-	
Mortality - not reported							
-	-	-	-	-	-	-	
Heavy menstrual bleeding - not reported							
-	-	-	-	-	-	-	
Hospitalization - not reported							
-	-	-	-	-	-	-	
Thrombotic events - not reported							
-	-	-	-	-	-	-	

CI: Confidence interval

Explanations

a. This is a case series, there is no comparison with other groups
b. Unexplained inconsistency results in imprecision. Rated down one level for both.

Table 4: Evidence profile. No DDAVP trial and treatment with DDAVP compared to other options for patients with VWD

Certainty assessment							Summary of findings
№ of participants (studies) Follow-up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty of evidence	Impact
Hemostasis during bleeding episodes (assessed with: Proportion of episodes with excellent, good, or poor response)							
172 (1 observational study)[21]	very serious [a]	not serious	not serious	not serious	none	⨁◯◯◯ VERY LOW	The proportion of episodes in which efficacy was excellent was 83% of 254 episodes and good in 14% of the episodes among people with mild type 1 VWD. The proportion of episodes in which efficacy was excellent was 71% of 254 episodes and good in 18% of the episodes among people with moderate type 1 VWD.
Hemostasis during surgery (assessed with: Bleeding during/ surgery)							
186 (2 observational studies)[20 21]	very serious [a]	not serious	not serious	not serious	none	⨁◯◯◯ VERY LOW	A study reported that postoperative bleeding occurred in 1/14 patients who received DDAVP. Another reported that hemostasis for surgical prophylaxis was excellent in 93% of patients with mild type 1 VWD, and 73% in patients with moderate type 1 VWD.
Heavy menstrual bleeding (assessed with: Proportion with response)							
194 (2 observational studies)[21]	very serious [a]	not serious	not serious	not serious	none	⨁◯◯◯ VERY LOW	One study that enrolled 22 patients reported that 77% responded to the treatment (measured with PBAC score <100). Another that enrolled 172 patients with VWD reported that efficacy to control HMB was excellent (1 dose to control HMB) or good (2 doses) in 92% of patients.
Hospitalization (assessed with: Duration in days when used as surgical prophylaxis)							
14 (1 observational study)[20]	very serious [a]	not serious	not serious	not serious	none	⨁◯◯◯ VERY LOW	The mean number of days of hospitalization was 6.3
Adverse events- hyponatremia and severe hyponatremia when used as surgical prophylaxis (assessed with: Proportion of patients)							

Table 4: Evidence profile. No DDAVP trial and treatment with DDAVP compared to other options for patients with VWD

Certainty assessment							Summary of findings
278 (3 observational studies) [19 22 23]	very serious [a]	not serious	not serious	not serious	none	⨁◯◯◯ VERY LOW	The proportion of patients who experienced hyponatremia (<136 mMol/L) ranged from 4%-72% across 3 studies. These studies also provided evidence regarding severe hyponatremia, but they used different cut-offs for their definition. In one study with 63 patients, the proportion of patients with hyponatremia (<136 mMol/L) was 65%, and the proportion of patients with severe hyponatremia (<130 mMol/L) was 9.5%. In another study with 107 patients (101 of them with platelet function defects), the proportion of patients with hyponatremia (<136 mMol/L) was 72%, and the proportion of patients with [severe] hyponatremia (<131 mMol/L) was 10.3%. In a third study in which researchers recruited 108 patients, the proportion who experienced hyponatremia (<136 mmol/L was 4%, and the proportion who experienced severe hyponatremia (<126 mMol/L) was 0%.

Adverse events- not serious (assessed with: Mild to moderate headaches, facial flushing when used as bleeding treatment)

22 (1 observational study)[18]	very serious [a]	not serious	not serious	not serious	none	⨁◯◯◯ VERY LOW	The proportion of patients who reported experiencing headaches was 9%, facial flushing was 9%, and both was 4.5%

Adverse events- mild and moderate (assessed with: Headache, flushing, nausea, dizziness, asthenia, vomiting, peripheral edema when used as surgical prophylaxis or bleeding treatment)

172 (1 observational study) [21]	very serious [a]	not serious	not serious	not serious	none	⨁◯◯◯ VERY LOW	The proportion of administrations in which AEs was reported was 43% in patient with mild type 1 VWD and 14% in those with moderate type 1 VWD

Major bleeding - not reported

-	-	-	-	-	-	-	

Mortality - not reported

-	-	-	-	-	-	-	

Transfusion - not reported

-	-	-	-	-	-	-	

Thrombotic events - not reported

Table 4: Evidence profile. No DDAVP trial and treatment with DDAVP compared to other options for patients with VWD

Certainty assessment							Summary of findings
-	-	-	-	-	-	-	

CI: Confidence interval

Explanations

a. This is a case series, there is no explicit comparison with other group, which is the aim of this question

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Appendix

Intervention 1: DDAVP trial + treatment

Table 1: Characteristics of included studies

Study	Setting	Country	Design	Recruitment	Use	N	% who received DDAVP
Nitu-Whalley, 2001	Hemophilia Centre and Haemostasis Unit	England	Retrospective	1988-1997	Surgical prophylaxis	>63/65	42%
Bonduel -2011	Laboratory of Thrombosis and Hemostasis	Argentina	Prospective	April 1994- July 2010	Surgical prophylaxis	92	88.90%
Sanchez-Luceros,- 2010	Hemostasis and Thrombosis department	Argentina	Retrospective	January 1999 and December 2007	Bleeding treatment and Surgical Prophylaxis (mainly surgical prophylaxis)	214	100%
Witmer - 2009	Children's Hospital	USA	Retrospective	January 1, 2000, and December 31, 2006	Bleeding treatment and surgical Prophylaxis	40	100%
Weston, H.,- 2009	Royal Brisbane and Women's Hospital	Australia	Retrospective	May 2005- 2007	Bleeding treatment and surgical Prophylaxis	47	100%
Piot - 2002	Hospital Center	France	Retrospective	1991-2000	Surgical prophylaxis	32	100%
Jimenez-Yuste, V 2002	Hospital and University	Spain	prospective	June 1999 to January 2001	Surgical prophylaxis	37	100%
Federici - 2000	Haemophilia and Thrombosis Center and Dental Center	Italy	Retrospective	March 1995 to March 1999	Surgical prophylaxis	44	93%

Figure 1: Analysis outcome Hemostatic efficacy when used as surgical prophylaxis

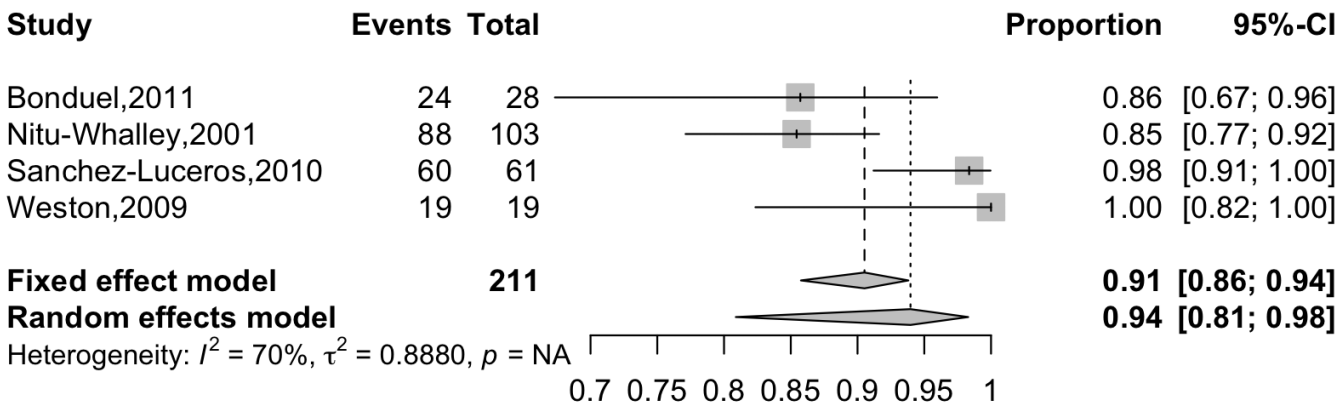


Figure 2: Analysis outcome Postoperative bleeding

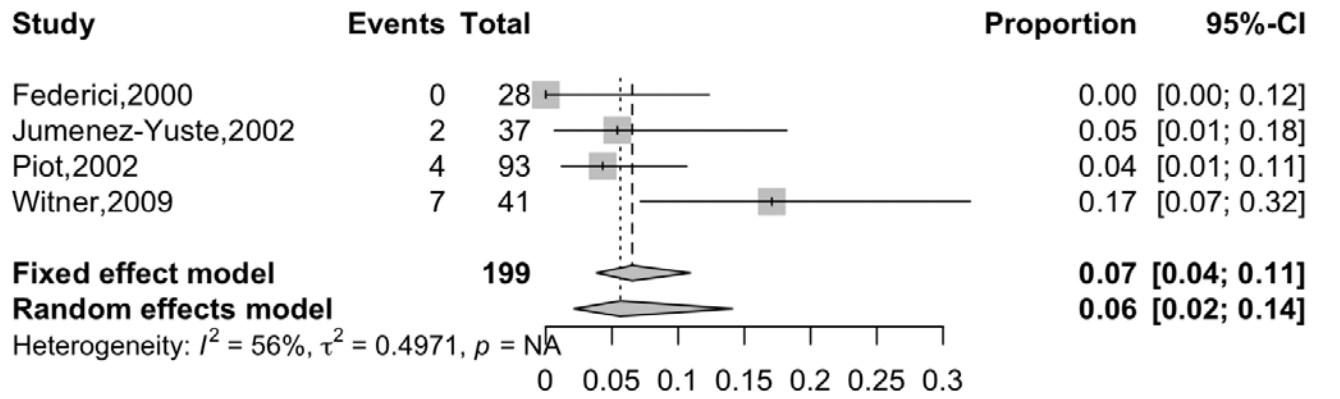
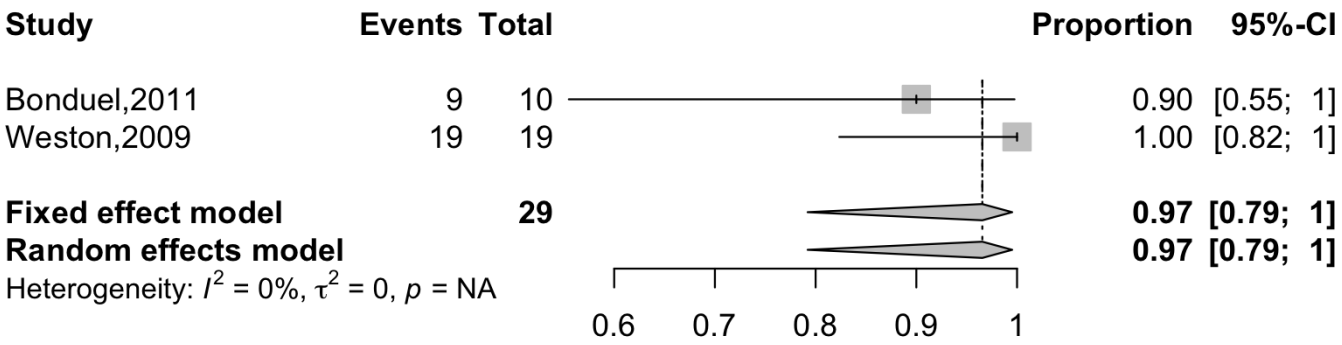


Figure 3: Analysis outcome Hemostatic efficacy when used for treating bleeding episodes



Intervention 2: No trial + treatment with tranexamic acid or VWF

Table 1: Characteristics of included studies

Study	Setting	Country	Design	Recruitment	Use	N	Agent
Eghbali, A-2016	Hospital	Iran	Prospective	March 2014 and December 2015.	Bleeding prophylaxis	17	TXA
Zulfikar- 2016	NR	Turkey	Retrospective	2003 and 2014	Surgical prophylaxis	23	vWF/factor VIII (FVIII) concentrate- Hamete P- For type 2 and Type 3, Type 1 got Hamete + DDAVP
James, 2014	5 university hospital and 1 community hospital	USA	Prospective	January 1, 2007 and December 31, 2012	Bleeding prophylaxis	32 patients with VWD and 15 were treated for 17 pregnancies	Factor concentrate 15/17, DDAVP: 2/17 prior to delivery and 16/17 received conceentrate after delivery
Gill, 2011	15 centres of USA and 2 centres of Europe	USA and Europe	Prospective	NR	Surgical prophylaxis	42	Hamete P
Dunkley- 2010	8 Hemophilia centres in Australia and Newzealand	Australia and New Zealand	Prospective	December 2004 to May 2007	Bleeding prophylaxis, treatment and surgical prophylaxis	23	Biostate
Federici- 2010	15 Hemophilia centres in Italy	Italy	Retrospective	January 2002 to December 2006	Bleeding prophylaxis, treatment and surgical prophylaxis	120	Alphanate or Fanhdi
Federici,-2002	8 Italian Centre	Italy	Retrospective	September 1999 to 2001	Bleeding prophylxis, treatement and Surgical prophylaxis (too few for the last one)	22	Fanhdi
Seaman 2019	Hemophilia Center	usa	Retrospective	January 1, 2015, and May 31, 2017	Surgical prophylaxis	37	VWF concentrate
Tagliaferri- 2015	Haemophilia Treatment Centres - 18 of them	Italy	Retrospective	January 1981 to June 2014.	Surgical prophylaxis	92 VWD patients	VWF/FVIII concentrates in 77 cases, with DDAVP alone in 24 cases and with DDAVP and VWF/FVIIIconcentrates in 7 cases.

Figure 1: Analysis outcome Bleeding episodes when used as surgical prophylaxis

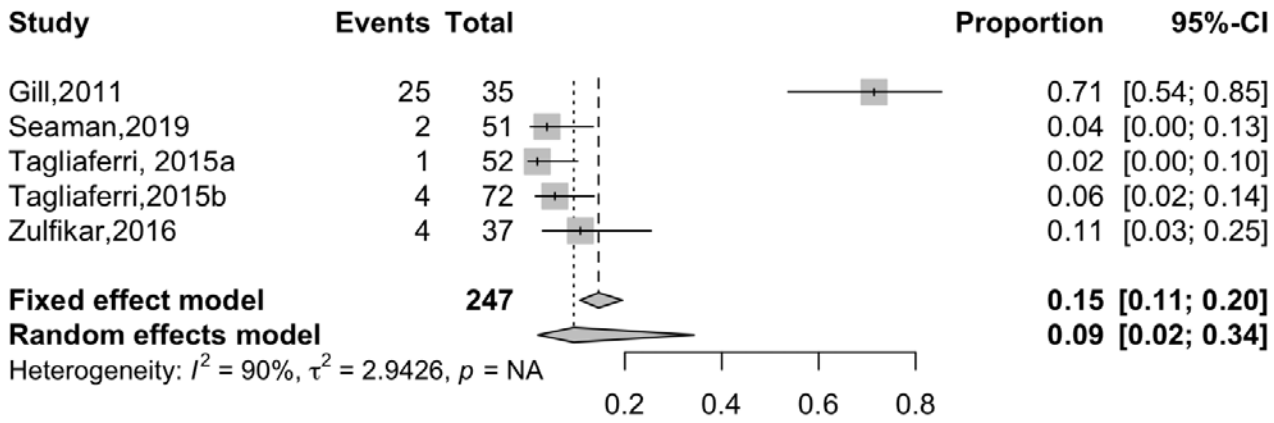


Figure 2: Analysis outcome Excellent or good hemostatic efficacy when used during surgery

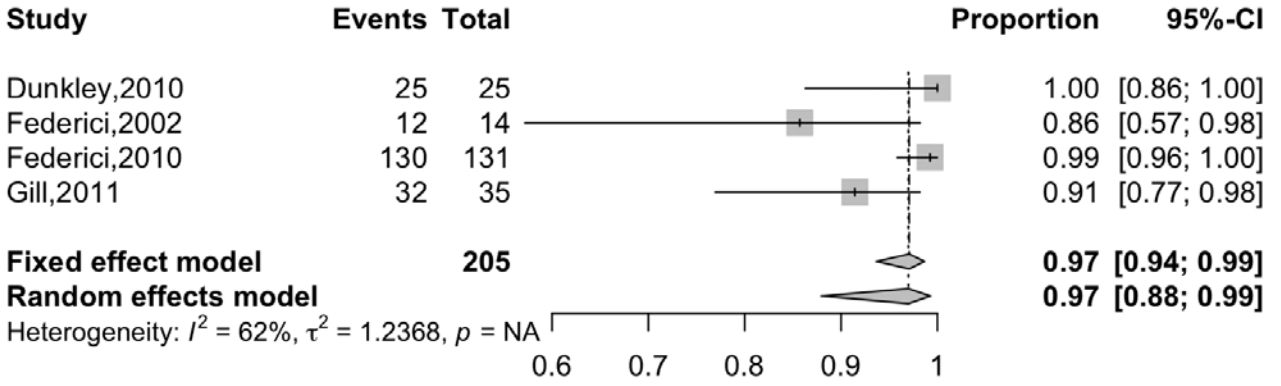


Figure 3: Analysis outcome Need for transfusion when used as surgical prophylaxis

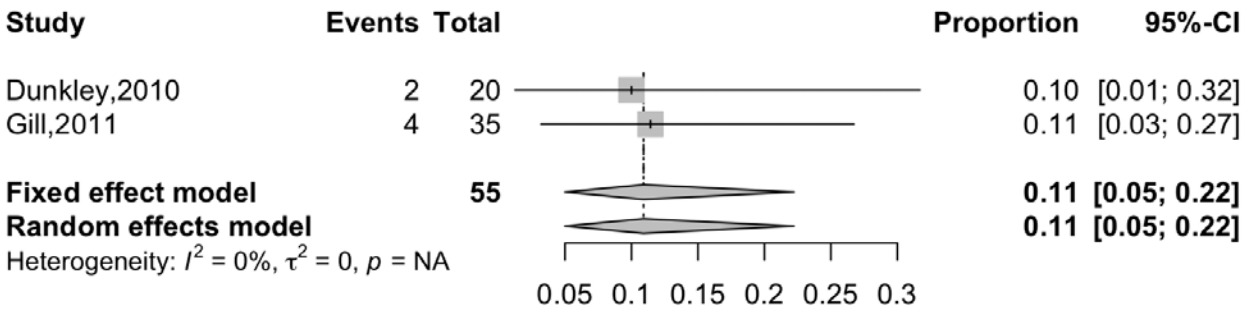


Figure 4: Analysis outcome Adverse events when used as surgical prophylaxis

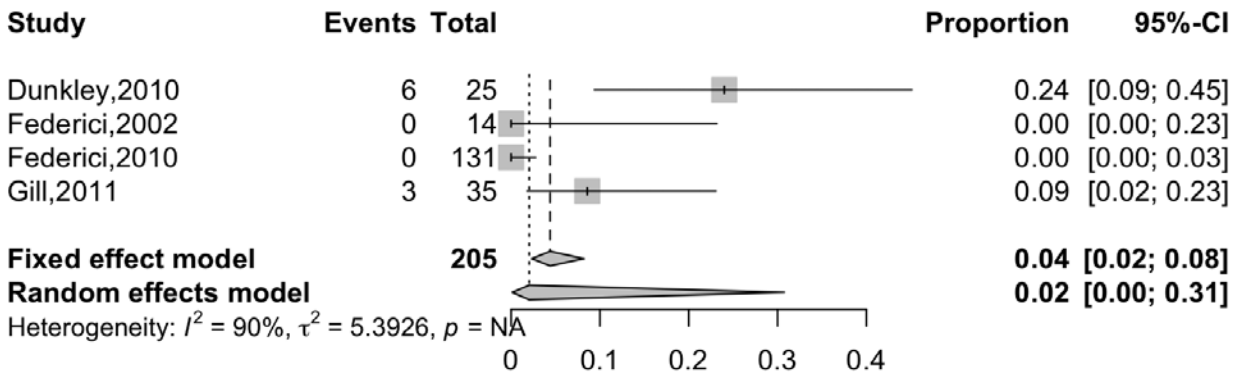
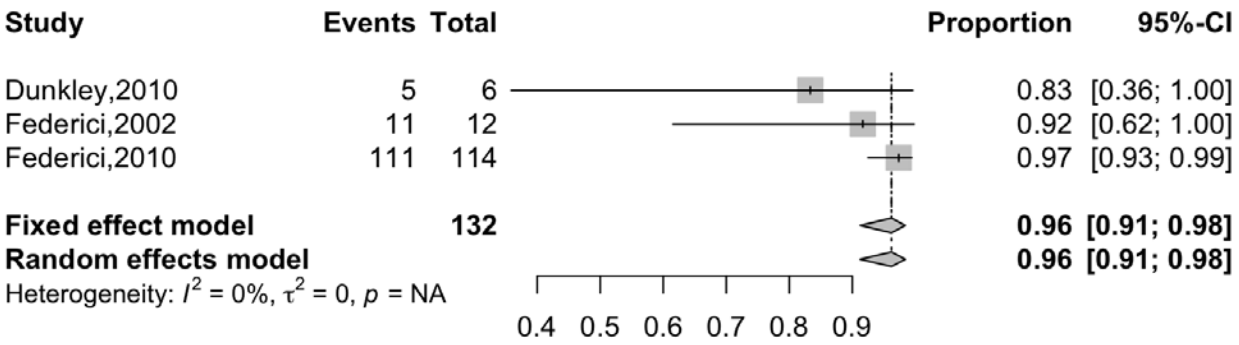


Figure 5: Analysis outcome Hemostatic efficacy when used to treat bleeding episodes



Intervention 3: No trial + treatment with DDAVP

Table 1: Characteristics of included studies

Author, year	Setting	Country	Design	Recruitment period	Type of treatment	N
Davidson-2011	Children's Hospital of Pittsburgh	USA	Retrospective	October 1, 2002, to February 1, 2009	Surgical Prevention	63
Amesse-2005	Adolescent gynecology clinic at Miami Valley Hospital or the hematology clinic at the Children's Medical Center	USA	Retrospective	July 1998 and December 2002	Bleeding treatment	36 patients and 22 received DDAVP
Gorzelnik- 2012	Pediatric Otholaryngology of Medical University of Warsaw	Poland	Retrospective	January 2008 to December 2011	Surgical prevention	16 (14 used DDAVP and 2 used Hamete)
Leissinger,- 2001	37 centres	USA	Prospective	NR	Bleeding treatment and Surgical prevention	333 total - 172 with VWD

RQ3: In patients with VWD and cardiovascular disease who require treatment with antiplatelet agents or anticoagulant therapy, should we provide such treatment or not?

P: adult patients with any type of VWD, except for acquired. Any type of cardiovascular disease, event, or surgery that requires treatment with anticoagulants or antiplatelets
I: any type of antiplatelet agent or anticoagulant
C: no treatment
O: Mortality, thrombotic events, serious adverse events, major bleeding, hospitalization, transfusion, health-related quality of life, heavy menstrual bleeding

After title and abstract screening of 4698 citations, and full text screening of 18 studies, we found 1 study addressing this question, which was reported in 2 sources: a conference abstract[1] and a letter to the editor.[2] Even though this study described that there was 1 group of patients who received anticoagulants and another who did not, the researchers provided outcome data only for those who received them. Therefore, this study provided evidence from a case series. In addition, we found another case series to inform this recommendation question.[3]

This evidence report contains evidence from a total of 2 case series, and a survey that systematically collected panel members' experiences dealing with this issue.

Table 1 provides a summary of the characteristics of included studies, Table 2 presents the evidence to decision framework for this recommendation question, Table 3 is the detailed evidence profile, and Table 4 summarizes the results from the survey.

Table 1: Characteristics of included studies

Study ID	Country	Total sample size	Inclusion criteria regarding need for anticoagulant	Exclusion criteria regarding need for anticoagulant	Inclusion criteria regarding bleeding disorder	Exclusion criteria regarding bleeding disorder	Sex distribution (% females)	Age distribution	Bleeding disorder distribution	Relevant comorbidities distribution	N patients who received antiplatelets/ anticoagulants	Anticoagulant received distribution
Alessi 2012	Germany	40	Coronary artery disease, proved by coronary angiography	None reported	VWD (bleeding tendency and decreased VWF:Rco <40%) and Hemophilia A or B	Carriers, aquired inhibitors of FVIII	32.50%	Mean (SD), 70 (11.8) years	VWD 1, 80% VWD 3, 2.5% VWD acquired, 5% Hemophilia A, 12.5%	Hypertension, 100% Hyperlipoproteinemia, 52.5%	Unclear, according to text, 26. According to table, 28. Numbers in table do not add up	AAS mono, 14 patients AAS+ clopidogrel, 4 patients Clopidogrel mono, 4 patients Warfarin, 4 patients LMWH, 2 patients
Piel-Julian 2019	France	8	Coronary artery disease (Ischemic heart disease)	None reported	HA, HB, and VWD	None reported	12.50%	Mean (SD), 63 (11.3) years	HA, 62.5% HB, 12.5% VWD, 25%	Hypertension, 37.5% dyslipidaemia, 50% overweight, 62.5%	8	Long-term AAS, 62.5% short-term AAS, 12.5% Dual antiplatelet therapy for 1 month + long term AAS, 25%

TABLE 2: EVIDENCE TO DECISION FRAMEWORK RECOMMENDATION QUESTION 3

Should anti platelet agents / anticoagulant therapy vs. no treatment be used for patients with VWD?	
POPULATION:	Patients with VWD
INTERVENTION:	Anti-platelet agents/ anticoagulant therapy
COMPARISON:	No treatment
MAIN OUTCOMES:	Mortality; Thrombotic events; Major bleeding; Serious adverse events; Hospitalization; Transfusion; Health-related quality of life; Heavy menstrual bleeding;
SETTING:	High income healthcare setting
PERSPECTIVE:	Clinical
CONFLICT OF INTERESTS:	The ASH conflict of interest policy for clinical practice guidelines was applied.

ASSESSMENT

Problem
Is the problem a priority?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ● **Yes** ○ Varies ○ Don't know		This question was judged to be a priority among many candidate questions to address in these guidelines

Desirable Effects
How substantial are the desirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Trivial ○ Small ○ Moderate ● **Large** ○ Varies ○ Don't know	The following is a summary of the Evidence profile, which is presented with details in Table 3.	Based on their experience and the evidence, the panel judged the desirable anticipated effects of anticoagulants to be large. In addition, the panel discussed the large amount of indirect evidence in patients without bleeding disorders that confirms that antiplatelet and anticoagulant therapy is effective in preventing cardiovascular events in patients who require them.

Outcomes	**Impact**
Mortality assessed with: number of patients	In one study, 1 patient with hemophilia died after experiencing intracranial posttraumatic bleeding 11 years after treatment start

Thrombotic events assessed with: number of patients	In one study the researchers report that none of 6 patients who received LMWH or warfarin experienced thromboembolic events. In another study, 1 patient with hemophilia experienced critical lower limb ischemia after 2 years.	
Major bleeding assessed with: number of patients	In one study in which 26 patients with VWD received the treatment, there was 1 major bleeding observed. In another study in which 8 patients received treatment, there were 3 major bleeding events observed: 1 haemopericardium in a patient with hemophilia, 1 GI bleeding at 13 months in a patient with VWD, and 1 intracranial posttraumatic bleeding at 11 years in a patient with hemophilia.	
Outcomes	**Importance**	**Certainty of the evidence (GRADE)**
Mortality assessed with: number of patients	CRITICAL	⨁◯◯◯ VERY LOW[a,b,c]
Thrombotic events assessed with: number of patients	CRITICAL	⨁◯◯◯ VERY LOW[a,b,c]
Major bleeding assessed with: number of patients	CRITICAL	⨁◯◯◯ VERY LOW[a,c,d,e]

a. These are case series, there is no comparison with no treatment arm and therefore the risk of bias is very serious
b. The single event reported occurred in a patient with hemophilia, which was not eligible for informing this question due to applicability concerns raised at the beginning of the evidence synthesis process
c. Very small number of patients and events
d. The rate of major bleeding is much higher in one of the studies when compared to the other, this may also have to do with indirectness.
e. Half of the events occurred in patients with hemophilia, which were not eligible for informing this question due to applicability concerns raised at the beginning of the evidence synthesis process

In addition, Table 4 describes the results of the survey to systematically collect clinicians' experiences

Undesirable Effects

How substantial are the undesirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Large ● **Moderate** ○ Small ○ Trivial ○ Varies ○ Don't know	See Box above	The panel judged the undesirable effects for antiplatelet and anticoagulants as moderate. The panel discussed the following: - The events described in the studies are serious adverse events leading the panel to agree on the judgement of moderate - The likelihood of these undesirable effects would be dependent on the type of anticoagulant, the individual patient's bleeding phenotype and disease subtype. - While, according to the panel, the risk of arterial thrombotic complications in patients with cardiovascular disease and a bleeding disorders is 40-60% lower than in the general population; patients that bleed can still develop atherosclerosis. - These undesirable effects are likely to vary widely according to the severity of the individual's VWD.

Certainty of evidence

What is the overall certainty of the evidence of effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
● **Very low** ○ Low ○ Moderate ○ High ○ No included studies	The evidence comes from case series, which makes it at very high risk of bias. In addition, there are imprecision and indirectness concerns. See Table 3 for details about the assessment of the certainty of the evidence.	None

Values

Is there important uncertainty about or variability in how much people value the main outcomes?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
● **Important uncertainty or variability** ○ Possibly important uncertainty or variability ○ Probably no important uncertainty or variability ○ No important uncertainty or variability	No research evidence found	- In a survey to panel members before the meeting, panel members described that there is a need to do shared decision-making with these patients, using the evidence available regarding benefits and risks. Some panel members mentioned that the decision may be easier for patients who have

		experienced a cardiovascular event. - Most panel members perceive that there is important variability among patients regarding how they trade-off the benefits and risks.

Balance of effects

Does the balance between desirable and undesirable effects favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ● **Probably favors the intervention** ○ Favors the intervention ○ Varies ○ Don't know		Given the potentially large benefits, but moderate harms in health outcomes of anticoagulants, as well as the important uncertainty and variability on how patients trade off these outcomes, the panel judged the balance of effects probably favors the use of antiplatelet or anticoagulants. The panel also discussed the following to arrive to this judgment: - The disease course for the patients in this scenario is dynamic. The risk for complications for patients with cardiovascular disease increases over time and patients would most likely benefit from antiplatelet or anticoagulant therapies. - The panel, including the patients, highlighted the importance of protecting the heart first and to not limit patients from the benefits of antiplatelets and anticoagulants as long as a personalized treatment plan is considered and thorough patient education performed.

Resources required

How large are the resource requirements (costs)?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Large costs ○ Moderate costs ● **Negligible costs and savings** ○ Moderate savings ○ Large savings ○ Varies ○ Don't know	No research evidence found	- The panel considered that there are negligible costs and savings. The price for antiplatelet and anticoagulant is generally inexpensive. However, if bleeding prophylaxis becomes necessary because of these medications, then the cost becomes moderate or large. - The price of antiplatelet and anticoagulant is variable among countries.

Certainty of evidence of required resources

What is the certainty of the evidence of resource requirements (costs)?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Very low ○ Low ○ Moderate ○ High ● **No included studies**	No research evidence found	None

Cost effectiveness

Does the cost-effectiveness of the intervention favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ○ Varies ● **No included studies**	No research evidence found	None

Equity

What would be the impact on health equity?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Reduced ○ Probably reduced ○ Probably no impact ● **Probably increased** ○ Increased ○ Varies ○ Don't know	No research evidence found	- The panel agreed that recommending antiplatelet agents or anticoagulant therapy will probably increase equity among patients.

Acceptability

Is the intervention acceptable to key stakeholders?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ● **Probably yes** ○ Yes ○ Varies ○ Don't know	No research evidence found	Based on their experience, the panel judged that anticoagulants are likely to be acceptable to key stakeholders

Feasibility

Is the intervention feasible to implement?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ● **Yes** ○ Varies ○ Don't know	No research evidence found	Based on their experience, the panel judged that anticoagulants are feasible to administer.

SUMMARY OF JUDGEMENTS

	JUDGEMENT						
PROBLEM	No	Probably no	Probably yes	**Yes**		Varies	Don't know
DESIRABLE EFFECTS	Trivial	Small	Moderate	**Large**		Varies	Don't know
UNDESIRABLE EFFECTS	Large	**Moderate**	Small	Trivial		Varies	Don't know
CERTAINTY OF EVIDENCE	**Very low**	Low	Moderate	High			No included studies
VALUES	**Important uncertainty or variability**	Possibly important uncertainty or variability	Probably no important uncertainty or variability	No important uncertainty or variability			
BALANCE OF EFFECTS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	**Probably favors the intervention**	Favors the intervention	Varies	Don't know
RESOURCES REQUIRED	Large costs	Moderate costs	**Negligible costs and savings**	Moderate savings	Large savings	Varies	Don't know
CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	Very low	Low	Moderate	High			**No included studies**

	JUDGEMENT						
COST EFFECTIVENESS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	**No included studies**
EQUITY	Reduced	Probably reduced	Probably no impact	**Probably increased**	Increased	Varies	Don't know
ACCEPTABILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know
FEASIBILITY	No	Probably no	Probably yes	**Yes**		Varies	Don't know

TYPE OF RECOMMENDATION

Strong recommendation against the intervention	Conditional recommendation against the intervention	Conditional recommendation for either the intervention or the comparison	**Conditional recommendation for the intervention**	Strong recommendation for the intervention
○	○	○	●	○

CONCLUSIONS

Recommendation

The panel suggests in patients with VWD and cardiovascular disease who require treatment with antiplatelet agents or anticoagulant therapy to give these therapies over no treatment (conditional recommendation based on low quality evidence)

Remarks:

- **The panel remarks that it Is important to reassess the bleeding risk throughout the course of treatment.**

Good practice statements:

- **Patients considered for treatment require individual risk and benefit of the specific therapy plan in conjunction with a multidisciplinary team that includes cardiovascular medicine specialists, hematologists, and the patient.**
- **Patient education about the risks of benefits of using antiplatelets or anticoagulants**

Justification

Treatment with anticoagulant therapy or antiplatelet agents in patients with VWD who require this treatment is likely to result in large benefits and moderate harms. The quality of the evidence is very low, and there is important variability in how patients trade-off the benefits and risks. However, most patients are likely to prefer to receive treatment for the cardiovascular indication and deal with the consequences on bleeding after the acute event has passed. This recommendation places a high value on the large anticipated desirable effects of this intervention. Anticoagulant therapy and antiplatelet agents are generally inexpensive, feasible, and probably acceptable by key stakeholders. In addition, a recommendation for their use is likely to increase equity.

Subgroup considerations

Implementation considerations

Monitoring and evaluation

Research priorities

The panel suggested future research:

- **Studies on the use of prophylaxis in patients receiving antiplatelets or anticoagulation;**
- **Studies on the incidence of cardiovascular disease in patients with VWD**
- **In the setting of coronary artery stent placement, studies of the risk/benefit of bare metal stent and a shorter course of anti-platelet therapy versus a drug eluting stent and a longer course of anti-platelet therapy.**

Table 3: Evidence profile. Antiplatelet agents/ anticoagulants compared to no treatment in patients with VWD

Certainty assessment							Summary of findings
№ of participants (studies) Follow-up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty of evidence	Impact
Mortality (assessed with: number of patients)							
8 (1 observational study)[3]	very serious [a]	not serious	serious [b]	serious [c]	none	⨁◯◯◯ VERY LOW	In one study, 1 patient with hemophilia died after experiencing intracranial posttraumatic bleeding 11 years after treatment start
Thrombotic events (assessed with: number of patients)							
14 (2 observational studies)[2,3]	very serious [a]	not serious	serious [b]	serious [c]	none	⨁◯◯◯ VERY LOW	In one study the researchers report that none of 6 patients who received LMWH or warfarin experienced thromboembolic events. In another study, 1 patient with hemophilia experienced critical lower limb ischemia after 2 years.
Major bleeding (assessed with: number of patients)							
32 (2 observational studies)[2,3]	very serious [a]	serious [d]	serious [e]	serious [c]	none	⨁◯◯◯ VERY LOW	In one study in which 26 patients with VWD received the treatment, there was 1 major bleeding observed. In another study in which 8 patients received treatment, there were 3 major bleeding events observed: 1 hemopericardium in a patients with hemophilia (7 days post CABG), 1 GI bleeding at 13 months in a patient with VWD, and 1 intracranial posttraumatic bleeding at 11 years in a patient with hemophilia.
Serious adverse events - not reported							
-	-	-	-	-	-	-	
Hospitalization - not reported							
-	-	-	-	-	-	-	
Transfusion - not reported							
-	-	-	-	-	-	-	
Health-related quality of life - not reported							
-	-	-	-	-	-	-	

Table 3: Evidence profile. Antiplatelet agents/ anticoagulants compared to no treatment in patients with VWD

Certainty assessment							Summary of findings
Heavy menstrual bleeding - not reported							
-	-	-	-	-	-	-	

CI: Confidence interval

Explanations

a. These are case series, there is no comparison with no treatment arm and therefore the risk of bias is very serious
b. The single event reported occurred in a patient with hemophilia, which was not eligible for informing this question due to applicability concerns raised at the beginning of the evidence synthesis process
c. Very small number of patients and events
d. The rate of major bleeding is much higher in one of the studies when compared to the other, this may also have to do with indirectness.
e. Half of the events occurred in patients with hemophilia, which were not eligible for informing this question due to applicability concerns raised at the beginning of the evidence synthesis process

Table 4: Results from survey to systematically collect clinicians' experience

Total number of patients among those who have encountered the problem: 1755 **Number of patients who have required antiplatelets/ anticoagulants: 65**				
Outcome/ treatment	**In patients who received treatment (n=56)**		**In patients who did not receive treatment (n=9)**	
	Median (IQR)	**Mean (SD)**	**Median (IQR)**	**Mean (SD)**
Mortality	0 (0 to 0)	0 (0)	0 (0 to 0)	0 (0)
Thrombotic Events	0 (0 to 0)	2% (6%)	0 (0 to 0)	7% (2%)
Serious Adverse Events	0 (0 to 0)	6% (22%)	0 (0 to 0)	7% (2%)
Major Bleeding	0 (0 to 0)	11% (25%)	0 (0 to 0)	0 (0)
Hospitalizations	0 (0 to 3.5)%	12% (25%)	0 (0 to 0)	7% (2%)
Transfusions	0 (0 to 0)	11% (25%)	0 (0 to 0)	0 (0)
Acceptable health-related quality of life	83% (44-100)%	69% (39%)	100% (75 to 100)%	80% (50%)

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RQ4: In patients with VWD undergoing major surgery, should we keep the factor VIII level > 50 IU/dL for at least 3 days after the surgery, or the VVF activity level > 50 IU/dL for at least 3 days after the surgery?

The main eligibility criteria for selecting the evidence to inform this recommendation were:
P: VWD any type, except for acquired; hemophilia; undergoing major surgery (surgery in which a mesenchymal barrier is opened, or characterized as major by the researchers)
I: keep FVIII level >50 IU/dL for at least 3 days after surgery
C: keep VWF activity level >50 IU/dL for at least 3 days after surgery
O: Mortality, Major bleeding, Need for additional surgical procedures, Transfusion, Serious adverse events, Hospitalization, Thrombotic events
S: Randomized Clinical Trials, Comparative observational studies

After title and abstract screening of 4698 references, we screened 308 studies in full text. We did not find any comparative studies addressing this question. Conversations with the liaisons and panel members resulted in the decision of including indirect evidence. We conducted a targeted search for case series in which patients with VWD were undergoing major surgery, and researchers reported both, their FVIII levels and VWF activity levels at day 3 postoperatively or after. Researchers also had to report any of the outcomes of interest among these patients.

This evidence synthesis contains evidence from 7 case series.[1-7] Their main characteristics are presented in Table 1. We present the evidence to decision framework in Table 2, and the outcomes of the interventions, in relation to factor levels in tables 3 and 4.

Table 1: Characteristics of the included studies

Study	Design	N patients	N procedures	VWD types	% minor surgery in results	% females	Age	Surgical procedure	Agent
Rugeri, 2016	Retrospective	12	19	VWD Type 1 = 6 ; Type 2A=1; Type 2B=1; Type 2M=3; Type 3=1	0	58%	Median, 63	Total Knee Arthroplasty (TKA): 7 Total Hip (37%) Arthroplasty (THA): 12: 63%	DDAVP or VWF concentrate
Hazendonk, 2018	Retrospective	103	148	VWD Type 1= 60; Type 2=49; Type 3=1	0	67%	Median, 51	Orthopedic 36 (24%); general 26 (18%) gynaecological 24(16%)	Haemate P/ Humate P
Khair, 2017	Retrospective	19	25	VWD Type 1= 17; Type 3= 2	0	38%	Median, 7	Vascular = 6; GI=6; Uro=5; Spinal = 3; ENT =2; Neuro = 2; Cardio = 1	Wilate
Srivastava, 2017	Prospective	21	21	VWD Type 3= 17	30%	70%	36	Orthopedic =8; Obstetric/gynaecological =5; GI = 4; Dental = 2; ENT =2	Wilate
Windyga, 2011	Prospective	21	27	VWD Type 1= 4; Type 2= 8; Type 3= 15	53%	53%	Most >12	Abdominal = 10; Ortho= 7; Dental =4; Gyne= 3; Plastic= 2; Heart= 1	Wilate
Borel-Derlon, 2007	Prospective	44	108	VWD Type 1= 5, Type 2A= 14, Type 2B=9, Type 2M=1, Type 2N=1, Type 3= 14	0%	64%	37	Orthopedic = 14; Gynecological = 8; General =7; Dental = 14; GI =12; Needle liver biopsy =8; Invasive procedures = 43	Wilfactin
Dunkley, 2010	Prospective	9	10	VWD Type 1= 5, Type 2A=2; Type 2M= 6; Type 2-1(unknown subtype); Type 3=6	62%	45%	~55	One of each: Coronary artery bypass, elbow replacement, hernia, Knee replacement (2), Laminectomy, Radical prostatectomy, Synovectomy, TURP	Biostate

TABLE 2: EVIDENCE TO DECISION FRAMEWORK RECOMMENDATION QUESTION 4

Should we keep the factor VIII level > 50 IU/dL for at least 3 days after the surgery vs. keep the VVF activity level > 50 IU/dL for at least 3 days after the surgery be used for patients with VWD undergoing major surgery?	
POPULATION:	Patients with VWD undergoing major surgery
INTERVENTION:	Keep the factor VIII level > 50 IU/dL for at least 3 days after the surgery
COMPARISON:	Keep the VVF activity level > 50 IU/dL for at least 3 days after the surgery
MAIN OUTCOMES:	Mortality, major bleeding, need for additional surgical procedures, transfusions; serious adverse events; hospitalization; thrombotic events
SETTING:	High income healthcare setting
PERSPECTIVE:	Clinical
CONFLICT OF INTERESTS:	The ASH conflict of interest policy for clinical practice guidelines was applied.

ASSESSMENT

Problem

Is the problem a priority?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ● **Yes** ○ Varies ○ Don't know		This question was prioritized among several others to be addressed in these guidelines

Desirable Effects

How substantial are the desirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Trivial ○ Small ○ Moderate ○ Large ○ Varies ● **Don't know**	We summarize evidence from case series in Tables 3 and 4	Based on the limited available evidence, the panel could not make a judgment regarding the magnitude of the desirable anticipated effects of keeping factor VIII level >50 IU/dL for at least 3 days after surgery when compared to keeping VWF activity level >50 IU/dL for at least 3 days after surgery

Undesirable Effects

How substantial are the undesirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS

○ Large ○ Moderate ○ Small ○ Trivial ○ Varies ● **Don't know**	We summarize evidence from case series in Tables 3 and 4	Based on the limited available evidence, the panel could not make a judgment regarding the magnitude of the undesirable anticipated effects of keeping factor VIII level >50 IU/dL for at least 3 days after surgery when compared to keeping VWF activity level >50 IU/dL for at least 3 days after surgery Given the design of the studies, there is no evidence for patients who received only factor VIII or only VWF.

Certainty of evidence

What is the overall certainty of the evidence of effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
● **Very low** ○ Low ○ Moderate ○ High ○ No included studies	The certainty of the evidence is very low. There were no comparative studies addressing this question, and we included case series as indirect evidence.	The panel discussed that even though the studies included are the only evidence available that may be relevant to inform this recommendation, they are too indirect.

Values

Is there important uncertainty about or variability in how much people value the main outcomes?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Important uncertainty or variability ○ Possibly important uncertainty or variability ● **Probably no important uncertainty or variability** ○ No important uncertainty or variability	No research evidence found	The panel discussed that, according to their experience, most patients are likely to place a high value on preventing bleeding over any potential adverse effects of the interventions considered in this recommendation.

Balance of effects

Does the balance between desirable and undesirable effects favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS

○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ○ Varies ● **Don't know**	No research evidence found	Because there is limited evidence that does not allow to make judgments regarding how the effects of keeping factor VIII level >50 IU/dL for at least 3 days after surgery compare to those of keeping VWF activity level >50 IU/dL for at least 3 days after surgery, the panel could not make a judgment regarding the balance of effects.

Resources required

How large are the resource requirements (costs)?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Large costs ○ Moderate costs ● **Negligible costs and savings** ○ Moderate savings ○ Large savings ○ Varies ○ Don't know	No research evidence found.	In a survey to panel members before the meeting, they estimated that the costs of keeping FVIII levels > 50 IU/dL for 3 days was 5-12K US dollars depending on the weight of the patient. The cost may vary across settings. Many panel members were uncertain about the costs, but there was mention than cost may not be a limiting factor. During the meeting, the panel also discussed the following: - The costs should not only consider the cost of the intervention, but also the cost of monitoring the levels for 72 hours. - In some settings like Italy, the price of VWF concentrate is much higher than Factor VIII concentrate. Based on these considerations, the panel judged that there is no important difference in the costs between the 2 interventions, and thus that there are negligible costs or savings when using one over another.

Certainty of evidence of required resources

What is the certainty of the evidence of resource requirements (costs)?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS

○ Very low ○ Low ○ Moderate ○ High ● **No included studies**	No research evidence found	None

Cost effectiveness

Does the cost-effectiveness of the intervention favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ○ Varies ● **No included studies**	No research evidence found	None

Equity

What would be the impact on health equity?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Reduced ○ Probably reduced ○ Probably no impact ● **Probably increased** ○ Increased ○ Varies ○ Don't know	No research evidence found	Given that FVIII levels are more feasible to obtain on a routine basis, a recommendation for keeping FVIII levels >50 IU/dL for at least 3 days over keeping VWF activity levels >50 IU/dL for at least 3 days is more likely to increase equity.

Acceptability

Is the intervention acceptable to key stakeholders?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS

○ No ● **Probably no** ○ Probably yes ○ Yes ○ Varies ○ Don't know	No research evidence found	In a survey to panel members before the meeting, many said that they are uncertain about whether **patients** feel that keeping only one of the levels >50 IU/dL for 3 days is **safe**. Some said that patients may feel safe if it is recommended and justified by their treating doctor. One patient expressed concerns about the cut-off and said >50 IU/dL seems too low. One panel member mentioned that some patients are more concerned with outcomes than precise levels being followed. Some panel members said that clinicians would not feel that keeping only one of the levels > 50 IU/dL for 3 days is safe. Some panel members said that they are uncertain about how clinicians would feel. A few said that clinicians may feel safe if there is good-quality evidence supporting this recommendation. Responses varied across panel members when asked if clinicians **would be willing** to keep only one of the levels >50 IU/dL, reflecting an important variability in acceptability. Some panel members said yes and others said no, some reflected the variability and others mentioned that the decision may depend on specific factors, such as feasibility. One panel member commented that due to the poor turnaround of one of the options, it is likely that many clinicians use only 1 anyway. Also, the issue of current guidelines recommending both could be a threat to acceptability. During the meeting the panel discussed that: - historically, patients were monitored using FVIII levels, this may make this option more acceptable Therefore, the panel discussed that it is unlikely that one option is more acceptable than the other.

Feasibility

Is the intervention feasible to implement?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ● **Probably yes** ○ Yes ○ Varies ○ Don't know	No research evidence found.	In a survey to panel members before the meeting, there was mention of 2 considerations regarding feasibility - There must be a method to have levels checked in all settings, if only one of the levels is recommended -Higher purity VWF concentrate is becoming more available, which may influence this recommendation as it makes it more feasible to increase only VWF activity level. During the meeting the panel discussed: -There is a great variability across settings in terms of ability to run tests to monitor VWF activity level (e.g. VWF;RCo, VWF:GP1bM). Therefore, the panel judged that keeping the FVIII levels >50 IU/dL for at least 3 days after surgery is more likely to

		be acceptable than keeping VWF activity levels >50 IU/dL for at least 3 days after surgery

SUMMARY OF JUDGEMENTS

	JUDGEMENT						
PROBLEM	No	Probably no	Probably yes	**Yes**		Varies	Don't know
DESIRABLE EFFECTS	Trivial	Small	Moderate	Large		Varies	**Don't know**
UNDESIRABLE EFFECTS	Large	Moderate	Small	Trivial		Varies	**Don't know**
CERTAINTY OF EVIDENCE	**Very low**	Low	Moderate	High			No included studies
VALUES	Important uncertainty or variability	Possibly important uncertainty or variability	Probably no important uncertainty or variability	**No important uncertainty or variability**			
BALANCE OF EFFECTS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	**Don't know**
RESOURCES REQUIRED	Large costs	Moderate costs	**Negligible costs and savings**	Moderate savings	Large savings	Varies	Don't know
CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	Very low	Low	Moderate	High			**No included studies**
COST EFFECTIVENESS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	**No included studies**
EQUITY	Reduced	Probably reduced	Probably no impact	**Probably increased**	Increased	Varies	Don't know
ACCEPTABILITY	No	**Probably no**	Probably yes	Yes		Varies	Don't know
FEASIBILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know

TYPE OF RECOMMENDATION

Strong recommendation against the intervention	**Conditional recommendation against the intervention**	Conditional recommendation for either the intervention or the comparison	Conditional recommendation for the intervention	Strong recommendation for the intervention
○	•	○	○	○

CONCLUSIONS

Recommendation

The panel suggests targeting both factor VIII and VWF activity level of > 50 IU/dL for 3 days after surgery (Conditional recommendation, Very Low certainty evidence)
The panel suggests against only using factor VIII >50 IU/dL as a target level for 3 days after surgery. (Conditional recommendation, very low certainty evidence)

Remarks:
- When it is possible to keep both levels >50 IU/dL for at least 3 days after the surgery (instead of choosing only one), this should be the preferred option
- The specific target levels have to be individualized based on the situation
- The duration of the intervention can vary for specific types of surgeries

Justification

There is no evidence regarding how the two options compare with regards to their effects on health outcomes. Even though one of the options is more likely to be feasible to implement, there are several threats to feasibility and acceptability that make it unlikely that clinicians would choose only one of the options. Therefore, the panel suggests keeping both VWF activity level >50 IU/dL and FVIII level >50 IU/dL for at least 3 days in patients undergoing major surgery.

While keeping the Factor VIII level above 50 IU/dL for 3 days after surgery may be logistically easier, especially in centers with long turnaround times for VWF activity levels or limited access to VWF concentrate as compared to Factor VIII preparations, only administering Factor VIII may not adequately address the underlying hemostatic defect present in patients with VWD. Keeping VWF levels > 50 IU/dL allows VWF to perform multiple physiologic roles in hemostasis and in most cases will simultaneously maintain FVIII levels >50 IU/dL as well during the critical time in the perioperative setting.

Subgroup considerations

Patients with specific subtypes of VWD, such as Type 2 and 3, may not achieve adequate hemostasis if only Factor VIII levels are maintained after surgery.

Implementation considerations

Monitoring and evaluation

Research priorities

- Randomized clinical trial to determine whether maintaining Factor VIII activity of VWF levels >50 IU/dL for at least 3 days after surgery leads to different outcomes, with particular attention and stratification by types of procedure and their associated bleeding risk.

Table 3: Factor levels (at day 3) and outcome data among studies presenting them at the patient level

Study	FVIII levels	VWF levels	Hemostatic efficacy
Khair 2015	Mean Max, 134.4	Mean max, 92.4	Excellent, 92% Good, 4% Poor, 4%
Study	**FVIII levels**	**VWF levels**	**Postoperative bleeding complications**
Khair 2015	Mean Max, 134.4	Mean max, 92.4	0
Study	**FVIII levels**	**VWF levels**	**Adverse events**
Khair 2015	Mean Max, 134.4	Mean max, 92.4	0
Study	**FVIII levels**	**VWF levels**	**Thrombotic events**
Khair 2015	Mean Max, 134.4	Mean max, 92.4	0
Dunkley, 2010	Median (IQR), 115 (97-134)	Median (IQR), 85 (67-103)	**0**

Table 4: Factor levels (at day 3) and outcome data among studies presenting them at the procedure level

Study	FVIII levels	VWF levels	Hemostatic efficacy
Rugeri, 2016	Median (IQR), 174 (153-220)	Median (IQR), 210 (87-210)	Excellent, 74% Good, 11% Fair, 5% Poor, 11%
Borel-Derlon, 2007	Median (IQR), 240 (100-314)	Median (IQR), 94 (48-136)	Excellent, 84% Good, 16%
Dunkley, 2010	Median (IQR), 115 (97-134)	Median (IQR), 85 (67-103)	100%
Study	**FVIII levels**	**VWF levels**	**Major Bleeding**
Rugeri, 2016	Median (IQR), 174 (153-220)	Median (IQR), 210 (87-210)	5%
Borel-Derlon, 2007	Median (IQR), 240 (100-314)	Median (IQR), 94 (48-136)	0
Study	**FVIII levels**	**VWF levels**	**Hemoglobin drop or RBC transfusion**
Srivastava 2017	Mean (range), 92 (82-102)	Mean (range), 41 (32-50)	6.70%
Borel-Derlon, 2007	Median (IQR), 240 (100-314)	Median (IQR), 94 (48-136)	3%
Dunkley, 2010	Median (IQR), 115 (97-134)	Median (IQR), 85 (67-103)	20%
Study	**FVIII levels**	**VWF levels**	**Symptomatic VTE**
Rugeri, 2016	Median (IQR), 174 (153-220)	Median (IQR), 210 (87-210)	0.00%
Srivastava 2017	Mean (range), 92 (82-102)	Mean (range), 41 (32-50)	0%
Study	**FVIII levels**	**VWF levels**	**Wound infection**
Rugeri, 2016	Median (IQR), 174 (153-220)	Median (IQR), 210 (87-210)	0.00%
Study	**FVIII levels**	**VWF levels**	**Receiving =/>2 units**
Rugeri, 2016	Median (IQR), 174 (153-220)	Median (IQR), 210 (87-210)	58.00%
Study	**FVIII levels**	**VWF levels**	**Estimated blood loss**
Rugeri, 2016	Median (IQR), 174 (153-220)	Median (IQR), 210 (87-210)	427 (70-1500) ml
Study	**FVIII levels**	**VWF levels**	**Duration of hospitalization**
Rugeri, 2016	Median (IQR), 174 (153-220)	Median (IQR), 210 (87-210)	5 (3-13) days

References

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RQ5: In patients with VWD undergoing minor surgery or minor invasive procedures, should we increase the VWF level to 50 IU/dL with any intervention, increase the VWF level to 50 IU/dL with any intervention and prescribe tranexamic acid, or prescribe tranexamic acid alone?

The main eligibility criteria for selecting the evidence to inform this recommendation were:
P: VWD any type, except for acquired, (and hemophilia), undergoing minor surgery (any invasive operative procedure in which only skin or mucosal membranes and connective tissue are resected; for example, any dental treatment, teeth extraction, dental cleaning, biopsies, joint aspiration, circumcision, cataract extraction/ surgery, intraocular lens implantation, intrauterine devices placement, colposcopy, endoscopy, colonoscopy. Also, anything described as minor by the researchers)
I: Increase VWF level to 50 IU/dL with any intervention, Increase VWF level to 50 with any intervention + TxA, TxA alone
C: Against each other. Potential comparisons

1. Increase VWF level to 50 IU/dL with any intervention vs Increase VWF level to 50 IU/dL with any intervention + TxA
2. Increase VWF level to 50 IU/dL with any intervention vs TxA
3. Increase VWF level to 50 IU/dL with any intervention + TxA vs TxA alone

O: Major bleeding, Need for additional hemostatic agents, Need for additional surgical procedures, SAEs, Mortality, Hospitalization, Transfusion, Inability to perform the surgery
S: Randomized Clinical Trials, Comparative observational studies

After title and abstract screening of 4698 references, we screened 308 studies in full text. We found 2 randomized clinical trials comparing the use of factor + TxA versus factor alone (comparison 1).[1 2] In addition, the panel decided that indirect evidence from case series of patients whose levels were increased to 50 IU/dL with factor alone, and case series of patients who received TxA alone could be helpful to inform this recommendation question.

This evidence report contains evidence from 2 randomized clinical trials that inform comparison 1,[1 2] 8 case series in which patients received factor replacement therapy alone,[3-11] and 4 case series in which patients received TxA alone.[12-15] The appendix presents the main characteristics of the included studies.

Table 1 presents the evidence to decision framework for this question. Tables 2, 3, and 4 present the Evidence Profiles. The appendix contains relevant figures.

TABLE 1: EVIDENCE TO DECISION FRAMEWORK RECOMMENDATION QUESTION 5

Should increasing VWF level to 50 IU/dL vs. increasing VWF to 50 IU/dL + TxA be used for patients with VWD undergoing minor surgery?	
POPULATION:	Patients with VWD undergoing minor surgery
INTERVENTION:	Increasing VWF level to 50 IU/dL with any intervention and tranexamic acid; increasing the VWF level to 50 IU/dL with any intervention; Tranexamic acid
COMPARISON:	Against each other
MAIN OUTCOMES:	Postoperative bleeding; Side effects; Major bleeding; Blood loss; Serious adverse events; Mortality; Need for additional hemostatic agents; Need for additional surgical procedures; Inability to perform the surgery.
SETTING:	High Income Healthcare Setting
PERSPECTIVE:	Clinical
CONFLICT OF INTERESTS:	The ASH conflict of interest policy for clinical practice guidelines was applied.

ASSESSMENT

Problem

Is the problem a priority?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ● **Yes** ○ Varies ○ Don't know		This question was prioritized by the panel among several others to be addressed in these guidelines

Desirable Effects

How do interventions compare against each other with regards to desirable effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
Rank the 3 interventions regarding the magnitude of desirable effects (there may be more than one intervention in each rank) **Most effective:** Increasing VWF level to 50 IU/dL with any intervention and tranexamic acid **Intermediate**: increasing the VWF level to 50 IU/dL with any intervention **Least effective:** Tranexamic acid	The tables below summarize the evidence. Details can be found in Tables 2, 3, and 4	The evidence suggests that increasing VWF level to 50 IU/dL with any intervention and prescribing tranexamic acid would provide the **most desirable effects** with regards to hemostasis. When making the judgement of most effective the panel particularly considered patients with severe bleeding phenotypes. However, the panel noted that not all patients will require an increase in VWF level to 50 IU/dL in conjunction with tranexamic acid to have good outcomes.

Outcomes	**Importance**	**Certainty of the evidence (GRADE)**
Postoperative bleeding assessed with: Number of people	IMPORTANT	⨁◯◯◯ VERY LOW[a,b,c]
Side effects assessed with: requiring withdrawal	IMPORTANT	⨁⨁◯◯ LOW[a,c]

Major bleeding assessed with: requiring transfusion	CRITICAL	⨁⨁◯◯ LOW[a,b]
Blood loss assessed with: postoperative, mL	IMPORTANT	⨁◯◯◯ VERY LOW[a,b,d]

a. Randomization and allocation concealment were at unclear or high risk of bias in both trials
b. The panel judged that there are serious applicability concerns owing to all the patients having hemophilia
c. Small number of patients and events overall, very wide CI
d. Small number of patients

Outcomes	With increasing VWF to 50 + TxA	With increasing VWF level to 50	Difference	Relative effect (95% CI)
Postoperative bleeding assessed with: Number of people	103 per 1,000	**651 per 1,000** (219 to 1,000)	**547 more per 1,000** (116 more to 1,826 more)	**RR 6.29** (2.12 to 18.65)
Side effects assessed with: requiring withdrawal	34 per 1,000	**0 per 1,000** (0 to 0)	**34 fewer per 1,000** (34 fewer to 34 fewer)	not estimable
Major bleeding assessed with: requiring transfusion	0 per 1,000	**0 per 1,000** (0 to 0)	**0 fewer per 1,000** (0 fewer to 0 fewer)	not estimable
Blood loss assessed with: postoperative, mL	The mean blood loss per participant was 84.1 mL (range four to 323) in the increasing FVIII level to 50 (n = 14) and 61.2 mL (range one to 749) in the increase level+ TXA group (n = 14, P = 0.02)			

Outcomes	Importance	Certainty of the evidence (GRADE)
Bleeding complications assessed with: hemorrhagic complications/ bleeding complications/ postoperative bleeding	IMPORTANT	⨁◯◯◯ VERY LOW[a,b]

Hemostasis during surgery assessed with: excellent/good; adequate- as judged by clinician	IMPORTANT	⨁◯◯◯ VERY LOW[a]
Need for additional hemostatic agents assessed with: Number with requirement of factor replacement postoperatively	CRITICAL	⨁◯◯◯ VERY LOW[a,c]
Hospitalization assessed with: needed for performing the procedure	CRITICAL	⨁◯◯◯ VERY LOW[a]
Transfusion assessed with: number of patients who needed them	CRITICAL	⨁◯◯◯ VERY LOW[a,d]
Serious adverse events assessed with: Thrombotic events	CRITICAL	⨁◯◯◯ VERY LOW[a]
Adverse events assessed with: Number who developed inhibitors	IMPORTANT	⨁◯◯◯ VERY LOW[a,b]
Adverse events assessed with: Several definitions	IMPORTANT	⨁◯◯◯ VERY LOW[a]

a. These are case series, there is no comparisons with other groups
b. The CI shows that the proportion can be very small or not so small
c. Very small number of patients
d. The CI is very wide and suggests that the proportion can be very small to very large

Outcomes	**Impact**
Bleeding complications assessed with: hemorrhagic complications/ bleeding complications/ postoperative bleeding	The proportion of surgeries in which there were bleeding complications was 11% (95% CI, 6 to 19%). The total number of surgeries was 281
Hemostasis during surgery assessed with: excellent/good; adequate- as judged by clinician	The proportion of procedures in which hemostasis was judged as appropriate was 98% (95% CI, 91 to 99%).
Need for additional hemostatic agents assessed with: Number with requirement of factor replacement postoperatively	The proportion of participants who required factor replacement postoperatively was 54% (7/13). Among these patients, 5 required continuous replacement.

Hospitalization assessed with: needed for performing the procedure	In 1 study in which researchers report outcomes of 13 liver or percutaneous biopsies, all 13 patients had to be hospitalized for performing the procedure
Transfusion assessed with: number of patients who needed them	The proportion of participants who needed transfusions was 2% (95% CI, 0 to 50%). The total number of surgeries was 54.
Serious adverse events assessed with: Thrombotic events	There were 3 studies that reported this outcome, and all 3 showed that no thrombotic events occurred. The total number of surgeries was 94.
Adverse events assessed with: Number who developed inhibitors	The proportion of patients who developed inhibitors was 2% (95% CI 0 to 21%).
Adverse events assessed with: Several definitions	Four studies reported AEs. Three of them reported observing no allergic reactions (0/28 surgeries), no wound infections (0/11 surgeries), and no "adverse events" (0/29). One study reported that in 1/65 patients there was a vasovagal episode that required hospitalization for observation.

Outcomes	Importance	Certainty of the evidence (GRADE)
Bleeding assessed with: Several definitions- number of events/ total of patients or surgeries	CRITICAL	⨁◯◯◯ VERY LOW[a]
Hospitalization assessed with: days per surgery	CRITICAL	⨁◯◯◯ VERY LOW[a]

a. The evidence comes from case series, in which there is no comparison with other options

Outcomes	Impact
Bleeding assessed with: Several definitions- number of events/ total of patients or surgeries	The pooled analysis showed that the proportion of patients or surgeries in which there is bleeding is 14% (95% CI 9% to 20%).

	Hospitalization assessed with: days per surgery	The mean number of days in hospital per surgery performed was 4 (no CI provided)

Undesirable Effects

How do interventions compare against each other with regards to desirable effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
Rank the 3 interventions regarding the magnitude of undesirable effects (there may be more than one intervention in each rank) **Least harmful:** Tranexamic acid **Intermediate:** Increasing the VWF level to 50 IU/dL with any intervention **More harmful:** Increasing VWF level to 50 IU/dL with any intervention and tranexamic acid	See box above	The panel agrees that tranexamic acid has the **least harmful** undesirable effects in comparison to therapies used to increase VWF levels, which have the potential of causing development of antibodies or allergic side effects. The panel also discussed that when two interventions are prescribed, there may be an additive effect with regards to side effects. This led the panel to judge increasing the VWF level to 50 IU/dL with any intervention in conjunction with tranexamic acid as most harmful. However, the panel noted that none of the three treatment options are likely to result in frequent and important harms.

Certainty of evidence

What is the overall certainty of the evidence of effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
● **Very low** ○ Low ○ Moderate ○ High ○ No included studies	The certainty of the evidence varies across comparisons. The highest certainty of evidence for critical outcomes is low, and the lowest is very low	The panel discussed that the only available studies to inform this recommendation are indirect.

Values

Is there important uncertainty about or variability in how much people value the main outcomes?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Important uncertainty or variability ● **Possibly important uncertainty or variability** ○ Probably no important uncertainty or variability ○ No important uncertainty or variability	No research evidence found	The panel discussion reflected the variability on how patients trade-off potential benefits and side effects. Patients in the panel meeting placed a high value on avoiding the side-effects, while clinicians placed a high value on avoiding bleeding.

		The panel also highlighted the value that is placed on the specific outcomes may vary according to the type of minor surgery and its associated bleeding risk. Thus, the panel judged that there is possibly important uncertainty or variability in patients' values and preferences.

Balance of effects

Which intervention does the balance between desirable and undesirable effects favor?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
Rank the 3 interventions according to the balance of effect (there may be more than one intervention in each rank) **Best balance:** Increasing VWF level to 50 IU/dL with any intervention and tranexamic acid, Increasing the VWF level to 50 IU/dL with any intervention **Worst balance:** Tranexamic acid		Based on the likelihood of desirable effects on hemostasis and the potential for side effects the panel ranked two interventions (Increasing VWF level to 50 IU/dL with any intervention and tranexamic acid, Increasing the VWF level to 50 IU/dL with any intervention) as having the best balance of effects. - Increasing VWF level to 50 IU/dL with any intervention in conjunction with tranexamic acid was judged to have the most benefits, but also potentially the most side effects - Increasing the VWF level to 50 IU/dL with any intervention has intermediate efficacy and also intermediate side effects

Resources required

How large are the resource requirements (costs)?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
Rank the 3 interventions regarding the resources required (there may be more than one intervention in each rank) **Less costs**: Tranexamic acid **Intermediate costs:** Increasing the VWF level to 50 IU/dL with any intervention **Most costs: :** Increasing VWF level to 50 IU/dL with any intervention and tranexamic acid	No research evidence found	In a survey to panel members before the meeting, they described that cost varies across settings and country. They said factor concentrate was expensive and costs more than desmopressin. The estimated cost for one unit of factor ranged from 0.6 - 1 US dollar. Panel members also said that tranexamic acid is considerably more inexpensive option when compared to factor replacement therapy or DDAVP. According to the responses, however, in many settings the treatment cost is fully covered by government. In others it is covered by insurance, but some patients may have co-payments. Due to this, some panel members considered that cost is not as important in this scenario as in others.

Certainty of evidence of required resources

What is the certainty of the evidence of resource requirements (costs)?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Very low ○ Low ○ Moderate ○ High ● **No included studies**	No research evidence found	None

Cost effectiveness

Which intervention does the cost effectiveness favor?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
Rank the 3 interventions according to the cost-effectiveness (there may be more than one intervention in each rank) ○ Best cost-effectiveness: ○ Intermediate cost effectiveness: ○ Worst cost-effectiveness: ●**Don't know**	No research evidence found	None

Equity

If recommended, which intervention would reduce health inequities the most?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
Rank the 3 interventions according to their potential to reduce inequities if recommended (there may be more than one intervention in each rank) ○ Most reduction: ○ Intermediate reduction: ○ Less reduction:	No research evidence found	The panel discussed that recommending tranexamic acid alone would probably increase equity because it is the easiest and cheapest option and may open up the option of minor surgeries for patients. However, in high resource settings both factor concentrate, and tranexamic acid are available leading the panel to the judgement of **Don't Know.**

●**Don't know**		

Acceptability

Which intervention is more acceptable to key stakeholders?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
Rank the 3 interventions according to their acceptability by key stakeholders (there may be more than one intervention in each rank) ○ Best acceptability: ○ Intermediate acceptability: ○ Worst acceptability: ●**All acceptable**	No research evidence found	In a survey to panel members before the meeting, the fear of gastrointestinal adverse events of tranexamic acid was described as an issue that may decrease the acceptability of this therapy. During the meeting, the panel discussed that the acceptability of all treatment options depends on the feasibility and balance of effects, which is likely to vary according to patients' values and preferences. Based on this, and their experience, panel members judged that all options are acceptable**.** However, in patients with type 1 VWD with factor levels >30 IU/dL the burden and costs of factor might make this option not acceptable given the low likelihood of bleeding.

Feasibility

Which intervention is more feasible to implement?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
Rank the 3 interventions according to their feasibility (there may be more than one intervention in each rank) **Most feasible**: Tranexamic acid **Intermediate feasibility**: Increasing VWF level to 50 IU/dL with any intervention and tranexamic acid, Increasing the VWF level to 50 IU/dL with any intervention Least feasible:	No research evidence found	The panel discussed that tranexamic acid is the most feasible intervention because of its low costs and wide availability. In addition, because tranexamic acid is so feasible to implement, the panel judged that there is no important difference in feasibility between the other two options.

SUMMARY OF JUDGEMENTS

	Increase VWF to 50 IU/dL with any intervention	Increase VWF to 50 IU/dL with any intervention + TxA	Tranexamic acid alone
DESIRABLE EFFECTS	★★	★★★	★
UNDESIRABLE EFFECTS	★★	★	★★★
BALANCE OF EFFECTS	★	★★★	★★★

RESOURCES REQUIRED	★★	★	★★★
COST EFFECTIVENESS	**No Included Studies**		
EQUITY	**Don't Know**		
ACCEPTABILITY	**They are all acceptable**		
FEASIBILITY	★★	★★	★★★

★★★ Ranked as best option in the factor considered for making the recommendation
★★ Ranked as intermediate option in the factor considered for making the recommendation
★ Ranked as worst option in the factor considered for making the recommendation

CONCLUSIONS

Recommendation

The panel suggests increasing VWF levels to >50 IU/dL with desmopressin or factor concentrate with the addition of tranexamic acid over raising VWF levels to >50 IU/dL with desmopressin or factor concentrate alone. (conditional recommendation, based on very low certainty evidence)

The panel suggests giving tranexamic acid alone over increasing VWF levels to >50 IU/dL with any intervention in patients with type 1 VWD with levels >30 and a mild bleeding phenotype and undergoing minor mucosal procedures. (conditional recommendation, based on very low certainty evidence)

Remarks:
- There is concern with overtreatment with option of increasing VWF to 50 IU/dL with any intervention and tranexamic acid.
- Patients with type 3 VWD will require VWF concentrate in order to achieve any significant increase in VWF levels. Use of DDAVP is contraindicated in this population due to lack of efficacy.
- Most patients with type 2 VWD (including type 2B VWD) will also require treatment with factor rather than desmopressin.
- For patients at higher risk of thrombosis, may wish to avoid combination of increased VWF level and tranexamic acid.

Justification

Given that they both have similar balance of effects, the recommendation for increasing VWF levels to >50 IU/dL with desmopressin or factor concentrate with the addition of tranexamic acid over raising VWF levels to >50 IU/dL with desmopressin or factor concentrate alone places a high value on the synergistic effects of both VWF tranexamic acid given their different mechanisms of action as well as the minimal side effect profile of tranexamic acid.

The recommendation for giving tranexamic acid alone over increasing VWF levels to >50 IU/dL with any intervention in patients with type 1 VWD with levels >30 and a mild bleeding phenotype undergoing minor mucosal procedures places a high value on the small amount of resources required, the feasibility of prescribing tranexamic acid in a scenario in which the likelihood of bleeding episodes is low, and avoiding the burden and cost of associated with administering factor concentrate in these patients.

Subgroup considerations

Implementation considerations

Monitoring and evaluation

Research priorities

The panel suggested future research:

- **Studies on the use of tranexamic acid vs. no tranexamic acid in specific procedures and whether there are differences by procedure, anatomical site, or VWD subtype;**

Table 2: Evidence profile. Increasing VWF level to 50 IU/dL compared to increasing VWF to 50 IU/dL + TxA for patients with VWD undergoing minor surgery

Certainty assessment							Summary of findings				
							Study event rates (%)			Anticipated absolute effects	
№ of participants (studies) Follow-up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty of evidence	With increasing VWF to 50 + TxA	With increasing VWF level to 50	Relative effect (95% CI)	Risk with increasing VWF to 50 + TxA	Risk difference with increasing VWF level to 50
Postoperative bleeding (assessed with: Number of people)											
59 (2 RCTs)[1 2]	serious [a]	not serious	serious [b]	serious [c]	none	⨁◯◯◯ VERY LOW	3/29 (10.3%)	20/30 (66.7%)	**RR 6.29** (2.12 to 18.65)	103 per 1,000	**547 more per 1,000** (from 116 more to 1,000 more)
Side effects (assessed with: requiring withdrawal)											
59 (2 RCTs)[1 2]	serious [a]	not serious	not serious	serious [c]	none	⨁⨁◯◯ LOW	1/29 (3.4%)	0/30 (0.0%)	not estimable	34 per 1,000	**30 fewer per 1,000** (from 130 fewer to 80 more) [d]
Major bleeding (assessed with: requiring transfusion)											
31 (1 RCT)[2]	serious [a]	not serious	serious [b]	serious [c]	none	⨁◯◯◯ VERY LOW	0/15 (0.0%)	0/16 (0.0%)	not estimable	0 per 1,000	**0 fewer per 1,000** (from 120 fewer to 120 more) [d]
Blood loss (assessed with: postoperative, mL)											
28 (1 RCT)[1]	serious [a]	not serious	serious [b]	serious [e]	none	⨁◯◯◯ VERY LOW	The mean blood loss per participant was 84.1 mL (range four to 323) in the increasing FVIII level to 50 (n = 14) and 61.2 mL (range one to 749) in the increase level+ TXA group (n = 14, P = 0.02)				
Serious adverse events - not reported											
-	-	-	-	-	-	-	-	-	-	-	-

Table 2: Evidence profile. Increasing VWF level to 50 IU/dL compared to increasing VWF to 50 IU/dL + TxA for patients with VWD undergoing minor surgery

Certainty assessment							Summary of findings				
Mortality - not reported											
-	-	-	-	-	-	-	-	-	-	-	-
Need for additional hemostatic agents - not reported											
-	-	-	-	-	-	-	-	-	-	-	-
Need for additional surgical procedures - not reported											
-	-	-	-	-	-	-					
Inability to perform the surgery - not reported											
-	-	-	-	-	-	-	-	-	-	-	-

CI: Confidence interval; **RR:** Risk ratio

Explanations

a. Randomization and allocation concealment were at unclear or high risk of bias in both trials
b. The panel judged that there are serious applicability concerns owing to all the patients having hemophilia
c. Small number of patients and events overall, very wide CI
d. Meta-analysis performed in RD because there were 0 events in both arms in 1 trial
e. Small number of patients

Table 3: Evidence profile. Increasing VWF level to 50 IU/dL with any intervention compared to other options for patients with VWD undergoing minor surgery

Certainty assessment							Summary of findings		
№ of participants (studies) Follow-up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty of evidence	Study event rates (%)		Impact
							With other options	With increasing VWF level to 50 with any intervention	
Bleeding complications (assessed with: hemorrhagic complications/ bleeding complications/ postoperative bleeding)									
278 (6 observational studies)[4 5 7 9-11]	very serious [a]	not serious	not serious	serious [b]	none	⨁◯◯◯ VERY LOW			The proportion of surgeries in which there were bleeding complications was 11% (95% CI, 6 to 19%). The total number of surgeries was 281
Hemostasis during surgery (assessed with: excellent/good; adequate- as judged by clinician)									
88 (3 observational studies)[6 8 11]	very serious [a]	not serious	not serious	not serious	none	⨁◯◯◯ VERY LOW			The proportion of procedures in which hemostasis was judged as appropriate was 98% (95% CI, 91 to 99%).
Need for additional hemostatic agents (assessed with: Number with requirement of factor replacement postoperatively)									
13 (1 observational study)[10]	very serious [a]	not serious	not serious	serious [c]	none	⨁◯◯◯ VERY LOW			The proportion of participants who required factor replacement postoperatively was 54% (7/13). The proportion who required continuous replacement was 38% (5/13).
Hospitalization (assessed with: needed for performing the procedure)									
13 (1 observational study)[9]	very serious [a]	not serious	not serious	not serious	none	⨁◯◯◯ VERY LOW			In 1 study in which researchers report outcomes of 13 liver or percutaneous biopsies, all 13 patients had to be hospitalized for performing the procedure
Transfusion (assessed with: number of patients who needed them)									
51 (3 observational studies)[4 7 10]	very serious [a]	not serious	not serious	serious [d]	none	⨁◯◯◯ VERY LOW			The proportion of participants who needed transfusions was 2% (95% CI, 0 to 50%). The total number of surgeries was 54.
Serious adverse events (assessed with: Thrombotic events)									

Table 3: Evidence profile. Increasing VWF level to 50 IU/dL with any intervention compared to other options for patients with VWD undergoing minor surgery

Certainty assessment							Summary of findings
76 (3 observational studies)[4 6 11]	very serious [a]	not serious	not serious	not serious	none	⨁◯◯◯ VERY LOW	There were 3 studies that reported this outcome, and all 3 showed that no thrombotic events occurred. The total number of surgeries was 94.

Adverse events (assessed with: Number who developed inhibitors)

39 (2 observational studies)[7 8]	very serious [a]	not serious	not serious	serious [b]	none	⨁◯◯◯ VERY LOW	The proportion of patients who developed inhibitors was 2% (95% CI 0 to 21%).

Adverse events (assessed with: Several definitions)

133 (4 observational studies)[4 8 9 11]	very serious [a]	not serious	not serious	not serious	none	⨁◯◯◯ VERY LOW	4 studies reported AEs. Three of them reported observing no allergic reactions (0/28 surgeries), no wound infections (0/11 surgeries), and no "adverse events" (0/29). One study reported that in 1/65 patients there was a vasovagal episode that required hospitalization for observation.

Need for additional surgical procedures - not reported

-	-	-	-	-	-	-	

Mortality - not reported

-	-	-	-	-	-	-	

Inability to perform the surgery - not reported

-	-	-	-	-	-	-	

CI: Confidence interval

Explanations

a. These are case series, there is no comparisons with other groups
b. The CI shows that the proportion can be very small or not so small
c. Very small number of patients
d. The CI is very wide and suggests that the proportion can be very small to very large

Table 4: Evidence profile. Tranexamic acid compared to other options for patients with VWD undergoing minor surgery

Certainty assessment							Summary of findings
№ of participants (studies) Follow-up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty of evidence	Impact
Bleeding (assessed with: Several definitions- number of events/ total of patients or surgeries)							
119 (4 observational studies)[12-15]	very serious [a]	not serious	not serious	not serious	none	⨁◯◯◯ VERY LOW	The pooled analysis showed that the proportion of patients or surgeries in which there is bleeding is 14% (95% CI 9% to 20%).
Hospitalization (assessed with: days per surgery)							
22 (1 observational study)[15]	very serious [a]	not serious	not serious	not serious	none	⨁◯◯◯ VERY LOW	The mean number of days in hospital per surgery performed was 4 (no CI provided)
Need for additional hemostatic agents - not reported							
-	-	-	-	-	-	-	
Need for additional surgical procedures - not reported							
-	-	-	-	-	-	-	
Serious adverse events - not reported							
-	-	-	-	-	-	-	
Mortality - not reported							
-	-	-	-	-	-	-	
Transfusion - not reported							
-	-	-	-	-	-	-	
Inability to perform the surgery - not reported							
-	-	-	-	-	-	-	

CI: Confidence interval

Explanations

a. The evidence comes from case series, in which there is no comparison with other options

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Appendix 1: Comparative studies

Table 1: Characteristics of the included studies

	Forbes, 1972	**Walsh, 1971**
N	28 patients	31 patients
Age	13 to 65	Mean, 34 years
Type of surgery	Dental extraction (n= 32)	Dental extraction
Bleeding disorder	Hemophilia A (71%) and B (29%)	Hemophilia A (94%) and B (6%)
Regimen	1 g TxA 3x per day, started 2 hours before extraction and continued for 5 days in half	6 gr of EACA 4x per day, 2 hours before extraction and continued for 10 days in half
Other interventions	FVIII or FIX IV 1 hour before extraction Tetracycline in all	FVIII concentrate to raise to 50% in all
Design	Randomized controlled trial	Randomized controlled trial

Figure 1: Risk of bias of the included studies

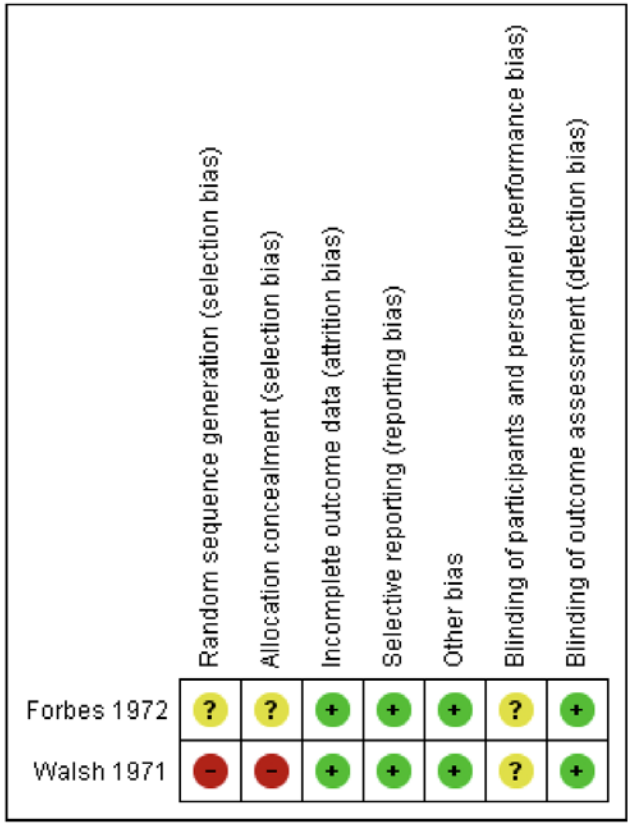


Figure 2: Analysis outcome bleeding (number of people)

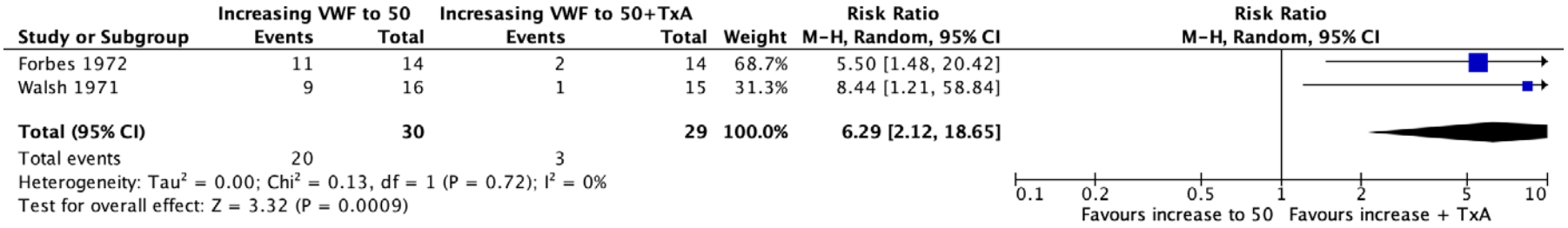
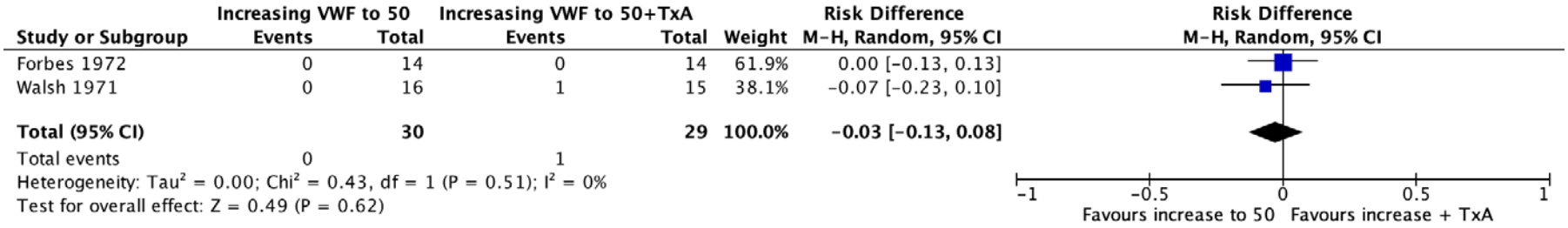


Figure 3: Analysis outcome side effect requiring withdrawal



Appendix 2: Case series of VWF alone

Table 1: Characteristics of included studies

Author	Setting	Country	Design	Recruitment period	N participants	Bleeding disorder distribution	Surgeries	Intervention
Shin	Inpatient, Multiicenter	Canada	Retrospective	1992-2003	65	Hemophilia A= 45 (69%); Hemophilia B=9 (14%) ;VWD type 1= 9 (14%); Dysfibrinogenemia = 1 (1.5%); VWD + Hemophilia A = 1 (1.5%)	100% Liver Biopsy, Transvenous	Regimen was variable
Venkataramani	Inpatient	USA	Prospective	1993-1997	15	Hemophilia A= 9; Hemophilia B= 3; VWD= 1	100% Liver Biopsy, Percutanous	factor replacement with a goal of achieving 100% activity before biopsy.
Scharrer	Outpatient and inpatient	Germany	Retrospective	Since 1974	468	"Mild" VWD= 328	Dental surgerical procedures = 28; Cesarian section = 9; tonsillectomy = 5; Orthopedic = 17; Miscellaneous = 11 Total = 70	Haemate P
Mansouritogrghabeh	3 hospitals	Iran	Retrospective	2009-2011	136	Hemophilia A, 74%; hemophilia B, 26%	100 % circumcision	factor concentrates
Rodriguez	Hemophilia center database- Mayo Clinic	USA	Retrospective	2000-2007	12	Hemophilia A: 24 (Mild = 8, Moderate = 2, Severe = 14); Hemophilia B: 5(Mild = 3, Moderate = 1, Severe = 1); VWD: 15 Type 1= 11, Type 2 = 3, Type 3= 1; Bernard-Soulier syndrome = 1; mild XI deficiency = 1; mild VII deficency = 1	100% circumcision	factor replacement
Rivard	Inpatient	USA and UK (multi-center)	Retrospective	1997-2005	39	VWD: 39 (Type 1= 18, Type 2= 12, Type 3= 9)	28 minor, 21 invasive procedures, 12 major surgeries in 39 subjects - results minor surgery combined with invasive procedures.	Alphanate (VIII/ von Willebrand factor concentrate)
Viswabandya	Inpatient and outpatient	India	Retrospective	Unclear	11	VWD (Type 1 = 3, Type 2= 6, Type 3= 2)	16 minor surgeries: upper and lower GI scopy = 6, dental extraction: 5, dental scaling: 2, cystoscopy and IVU= 2, renal angiogram = 1	Koate DVI
Franchini	Inpatient and outpatient	Italy	Retrospective	1996-2002	26	VWD (Type 1, 19; Type 2B, 7)	Minor surgery = 11, dental extractions = 11, major surgery = 14, invasive = 7, total = 43	Haemate

Figure 1: Analysis outcome postoperative bleeding

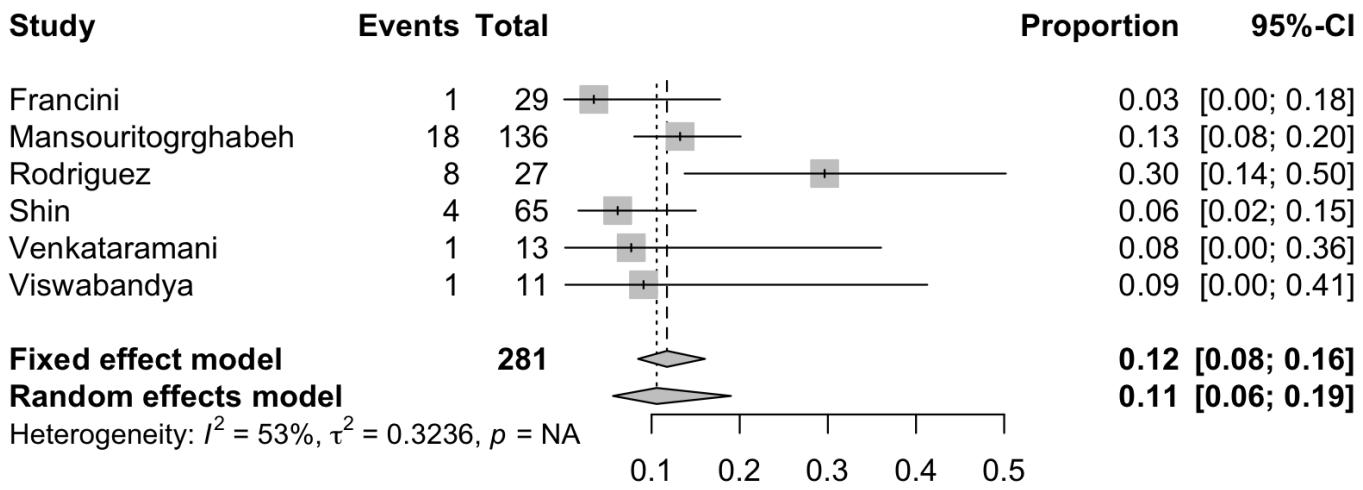


Figure 2: Analysis outcome hemostasis during surgery excellent or good

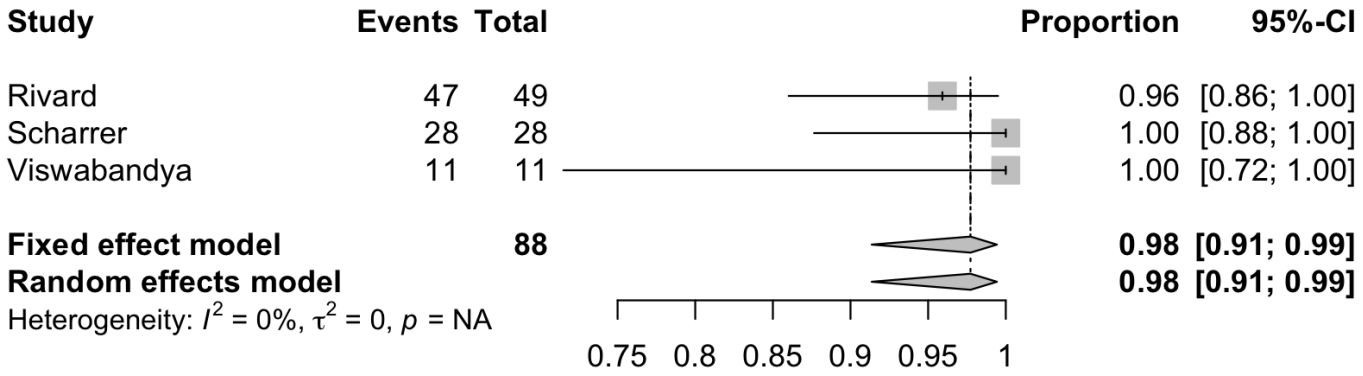


Figure 3: Analysis outcome transfusion

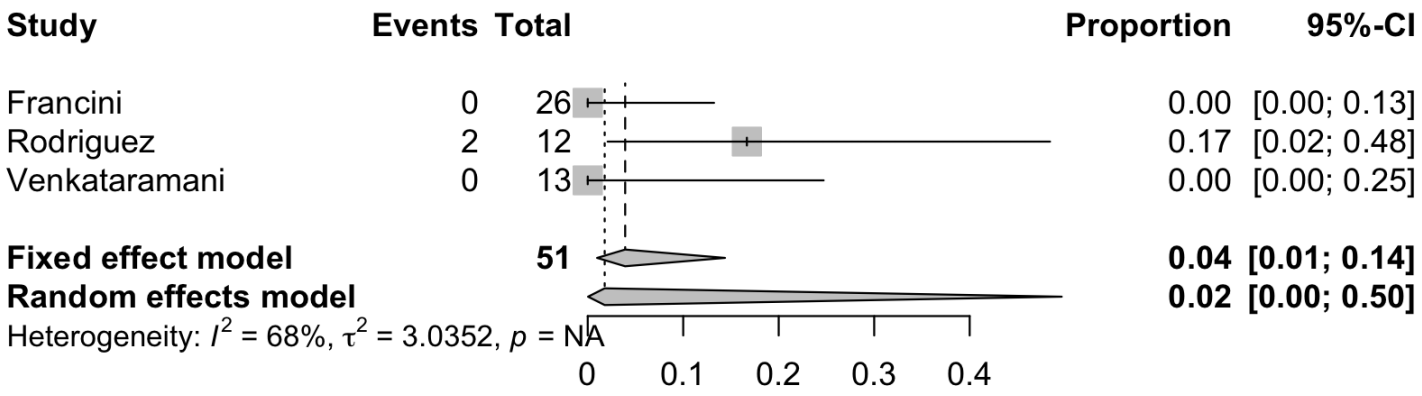
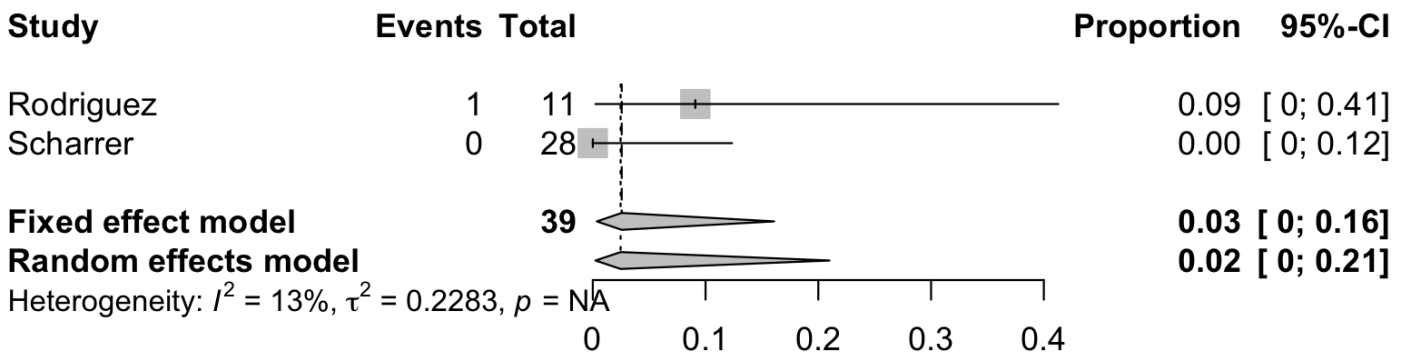


Figure 4: Analysis outcome development of inhibitors

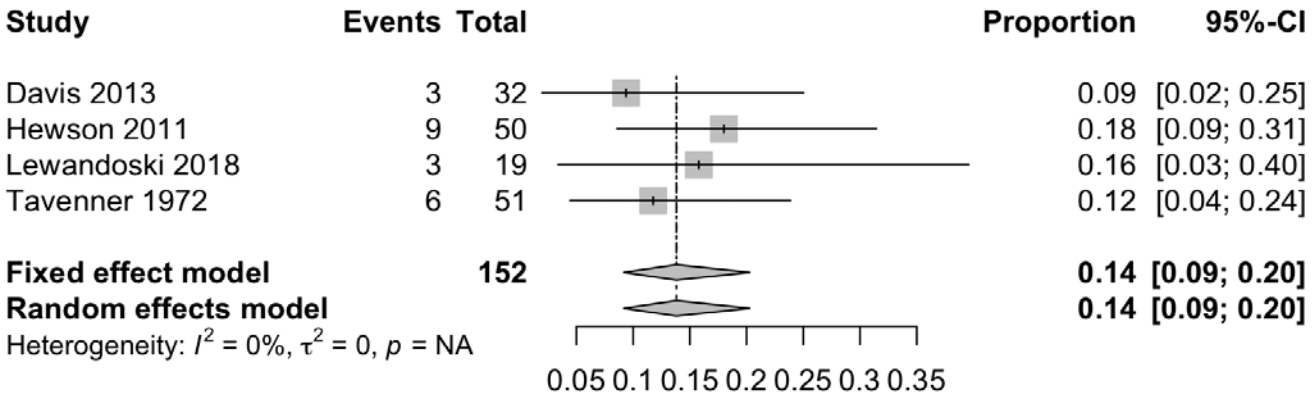


Appendix 3: Case series of TxA alone

Table 1: Characteristics of included studies

Author	Setting	Country	Design	Recruitment period	Number of patients	Distribution of bleeding disorders	Distribution of surgeries performed	Agent and TxA regimen provided before the surgery for bleeding
Davis 2013	Haemophilia Centre	Australia	Prospective	Sept 2010 to June 2012	28 patients and 32 surgeries	Hemophilia, 71.5% VWD, 18%	11 gastroscopies, 12 colonoscopies, 8 gastroscopies and colonoscopies during the same procedure, 1 flexible sigmoidoscopy	Tranexamic acid 1 g oral 8 hourly to commence the night before the procedure
Hewson 2011	Dental Unit	Australia	Prospective	NR	50 patients and 113 surgeries	Hemophilia, 74% VWD, 26%	113 dental extractions carried out for the 50 patients, 31 were surgical and 82 simple extractions	Local administratiton of 5% tranexamic acid in dental sockets
Lewandowski- 2018	Clinical Provincial Hospital	Poland	Retrospective	2005-2015	19	Hemophilia, 88% VWD, 12%	Dental extractions	Tranexamic acid transfusion approximately 30 minutes before the surgery in a single intravenous infusion (25 mg/kg of body weight) and continued oral administration of the substance after tooth extraction until the wound healed
Tavenner- 1972	General Hospital	Birmingham-UK	Retrospective	1960-1971	22 patients and 51 surgeries	Hemphilia, 86% Christmas disease, 14%	Dental extractions	Half hour before the time of extraction tranexamic acid given was as Cyklokapron in tablet form in dosage of 1-5 g every 6 hourly and continued the time that the patient discharged

Figure 1: Analysis outcome bleeding



RQ 6: In women with VWD with heavy menstrual bleeding, should we prescribe tranexamic acid, hormonal therapy (i.e. levonorgestrel-releasing intrauterine system or hormonal contraceptives), or DDAVP?

P: VWD, all types except for acquired; hemophilia, or inherited bleeding disorders; HMB, seeking for first line therapy
I: Tranexamic acid, hormonal therapy, DDAVP
C: against each other. Potential comparisons

1. tranexamic acid vs hormonal therapy
2. tranexamic acid vs DDAVP
3. hormonal therapy vs DDAVP

O: Control of HMB, Major bleeding, SAEs, Need for surgery, Need for multiple treatments, Absence from school, work, or other required activities, HRQoL, Transfusions, Anemia/ Iron deficiency

After title and abstract screening of 4698 references, we reviewed 76 studies in full text. We found 2 comparative studies. The panel members let us know about another study, which we were not able to find due to how it was indexed in the electronic databases.

In addition, the panel considered that case series regarding IUD could be informative, given that this option had not been assessed in the comparative studies.

Furthermore, we systematically collected the panel members' experience facing this scenario through a survey.

This evidence report contains evidence from 2 comparative studies: one randomized clinical trial (comparison 2)[1] and one observational study.[2] The third eligible study (comparison 3)[3] did not report outcome data clearly, and we were not able to get more information from the researchers to include it in this evidence synthesis. In addition, we include evidence from 5 case series (levonorgestrel-releasing intrauterine system).[4-8] The appendix provides a description of the main characteristics of the included studies.

Table 1 presents the Evidence to Decision Framework for this question. Tables 2, 3, and 4 present the Evidence Profiles. Table 5 presents the results of the collection of panel members' experience. The appendix presents relevant tables and figures.

TABLE 1: EVIDENCE TO DECISION FRAMEWORK RECOMMENDATION QUESTION 1

Should DDAVP vs. tranexamic acid be used for women with VWD with HMB?	
POPULATION:	Women with VWD with HMB
INTERVENTIONS:	DDAVP, hormonal therapy, tranexamic acid
COMPARISON:	All against each other
MAIN OUTCOMES:	Change in menstrual blood loss; Quality of life; Side effects; Severe side effects; Major bleeding; Need for surgery; Need for additional treatment; Menstruation duration; Absence from school, work, and other required activities;
SETTING:	High Income Healthcare Setting
PERSPECTIVE:	Clinical
CONFLICT OF INTERESTS:	The ASH conflict of interest policy for clinical practice guidelines was applied.

ASSESSMENT

Problem
Is the problem a priority?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ● **Yes** ○ Varies ○ Don't know	A study in which researchers surveyed 423 women with VWD aged 16 or above estimated that 79% of them experience heavy menstrual bleeding.[9] Women with severe heavy menstrual bleeding reported low QoL scores than those without heavy menstrual bleeding. In a qualitative study[10] women agreed that their well being during school or work was negatively affected by HMB, and in a survey all women with HMB (n=15) perceived limitations in the overall life activities[11] In a survey to 81 patients with Type 1 VWD,[12] researchers reported that the proportion that report that their clothes are stained by menses is 69% and the proportion that reports a history of anemia is 64%. In the same study the researchers reported a negative impact of HMB on family activities and ability to enjoy daily life[13] A narrative review[14] reported a very similar number of patients affected by HMB, and provided references from studies that provide data similar to the above.	This question was prioritized among several others to be addressed in these guidelines

Desirable Effects
How do interventions compare against each other with regards to desirable effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
Please rank the options with regards to the desirable effects **Most effective:** Hormonal Therapy **Intermediate effectiveness**: Tranexamic Acid **Least effective:** DDAVP	The following tables provide a summary of the evidence. Details can be found in Tables 2, 3, and 4 We did not find evidence for the comparison between tranexamic acid and hormonal therapy. **Comparison: tranexamic acid vs DDAVP**	Because hormonal therapy is not an option when women wish to conceive, the panel considered women who do not wish to conceive to make the judgment for this factor as well as others. The evidence suggests that hormonal therapy with combined oral contraceptives or a levonorgestrel-releasing intrauterine system would provide the most desirable effects with regards to controlling heavy menstrual bleeding. Even though the evidence focused only on the two types of therapy specified,

Outcomes	with tranexamic acid	With DDAVP	Difference	Relative effect (95% CI)
Change in menstrual blood loss assessed with: Change from baseline on PBAC follow up: 2 months	The mean change in menstrual blood loss was **0**	The mean change in menstrual blood loss in the intervention group was 41.6 higher (19.6 higher to 63.6 higher)	MD **41.6 higher** (19.6 higher to 63.6 higher)	-
Quality of life assessed with: Several scales (HRQoL, SF-36, CES-D, RUTA) follow up: 2 months	The researchers do not provide an explicit comparison between the groups. Scores across instruments and domains suggested improvement for both interventions, but this was statistically significant only for domains/ instruments			
Side effects assessed with: Most common: headaches follow up: 2 months	52 per 1,000	**0 per 1,000** (0 to 0)	**52 fewer per 1,000** (52 fewer to 52 fewer)	not estimable
Severe side effects follow up: 2 months	0 per 1,000	**0 per 1,000** (0 to 0)	**0 fewer per 1,000** (0 fewer to 0 fewer)	not estimable

Outcomes	Importance	Certainty of the evidence (GRADE)
Change in menstrual blood loss assessed with: Change from baseline on PBAC follow up: 2 months	CRITICAL	⨁⨁⨁◯ MODERATE[a,b]
Quality of life assessed with: Several scales (HRQoL, SF-36, CES-D, RUTA) follow up: 2 months	CRITICAL	⨁⨁◯◯ LOW[b,c]
Side effects assessed with: Most common: headaches follow up: 2 months	IMPORTANT	⨁⨁◯◯ LOW[a,b,d]
Severe side effects follow up: 2 months	CRITICAL	⨁⨁◯◯ LOW[a,b,d]

a. Allocation sequence generation and concealment unclear in the publication. However, we clarified with the researchers the procedures they used
b. Patients analyzed had not responded to treatment with oral contraceptives. Patients seeking for first line treatment may be importantly different from those seeking second line treatment
c. Lack of blinding could have affected the reporting of this subjective outcome
d. Few events, results are likely to be fragile

the panel judged that this desirable effects are likely to be similar with other types of combined hormonal contraception.

Comparison: Hormonal therapy vs DDAVP

Outcomes	With hormonal therapy	With DDAVP	Difference	Relative effect (95% CI)
Effectiveness assessed with: Alleviation of symptoms follow up: median 30 months	857 per 1,000	**771 per 1,000** (566 to 1,000)	**86 fewer per 1,000** (291 fewer to 197 more)	**RR 0.90** (0.66 to 1.23)
Menstrual flow assessed with: mean PBAC score over follow up follow up: median 30 months	The mean menstrual flow was **105.1** points	The mean menstrual flow in the intervention group was 0.9 points higher (9.89 lower to 11.69 higher)	MD **0.9 points higher** (9.89 lower to 11.69 higher)	-
Adverse events (not serious) assessed with: reported by patients follow up: median 30 months	0 per 1,000	**0 per 1,000** (0 to 0)	**0 fewer per 1,000** (0 fewer to 0 fewer)	**RR 5.87** (0.34 to 101.31)

Outcomes	Importance	Certainty of the evidence (GRADE)
Effectiveness assessed with: Alleviation of symptoms follow up: median 30 months	CRITICAL	⨁◯◯◯ VERY LOW[a,b]
Menstrual flow assessed with: mean PBAC score over follow up follow up: median 30 months	CRITICAL	⨁◯◯◯ VERY LOW[a]
Adverse events (not serious) assessed with: reported by patients follow up: median 30 months	IMPORTANT	⨁◯◯◯ VERY LOW[a,b]

a. Assignment to treatment was done by clinician and patient preference. No matching or control of confounding
b. The CI suggests the possibility of appreciable benefit and appreciable harm. Small sample size.

Non comparative evidence: Hormonal therapy with levonorgestrel-releasing intrauterine system

Outcomes	Impact
Control of heavy menstrual bleeding assessed with: PBAC score	In one study with 16 women, the PBAC score changed from a range of 98 to 386 before the intervention, to 0 to 75 after the intervention. A second study with 26 women reported that the median (range) PBAC changed from 255 (134 to 683) before the intervention to 35 (0 to 89) after the intervention.
Health-related quality of life assessed with: Kadir questionnaire	In one study with 26 women, the median (range) QOL scores increased from 26 (13 to 48) to 52 (39 to 59)
Anemia assessed with: number of women	in 1 study with 7 women, the proportion with anemia before or after the intervention was 0
Hemoglobin assessed with: g/dL	There were 4 studies that reported this outcome, but the results were presented in a way that did not allow pooling. Overall levonorgestrel-releasing intrauterine system resulted in an improvement of hemoglobin. - In 1 study with 16 patients, 12.5% had hemoglobin <11g/dL before the intervention, and 0 after - In 1 study with 26 patients, Hb median (range) was 11.2 g/dL (9.7 to 13) before the intervention and 13.2g/dL (11.2- 14.3) after the intervention - In 1 study with 6 women, mean Hb was 12.2 g/dL before the intervention and 13 g/dL after the intervention - In 1 study with 13 women, mean (range) Hb level was 11.1 g/dL (3 to 15.9) before the intervention and 13.4 g/dL (12 to 14.8) after the intervention
Menstruation duration assessed with: several definitions	Duration of menstrual bleeding reduced from 9 to 3 days (1 study, 7 patients) - Proportion of women in whom duration decreased, 71% (1 study, 7 women) - Reporting of periods "much better", 100% (1 study, 16 patients)
Complications assessed with: Expulsions and malpositions	The proportion of women with expulsions was 15 % (3/20), and the proportion of women with malposition was 10% (2/10)
Absence from school, work, or other required activities assessed with: periods affecting life	In one study with 16 women, the proportion whose life was affected by the periods was 0. There was no data about the proportion before the intervention was administered
Adverse effects assessed with: not defined	In 1 study with 16 women, the proportion who experienced side effects was 0

Outcomes	Importance	Certainty of the evidence (GRADE)
Control of heavy menstrual bleeding assessed with: PBAC score	CRITICAL	⨁◯◯◯ VERY LOW[a,b]
Health-related quality of life assessed with: Kadir questionnaire	CRITICAL	⨁◯◯◯ VERY LOW[a]
Anemia assessed with: number of women	IMPORTANT	⨁◯◯◯ VERY LOW[a,b]
Hemoglobin assessed with: g/dL	IMPORTANT	⨁◯◯◯ VERY LOW[a]
Menstruation duration assessed with: several definitions	CRITICAL	⨁◯◯◯ VERY LOW[a,b]
Complications assessed with: Expulsions and malpositions	IMPORTANT	⨁◯◯◯ VERY LOW[a,b]
Absence from school, work, or other required activities assessed with: periods affecting life	CRITICAL	⨁◯◯◯ VERY LOW[a,b,c]
Adverse effects assessed with: not defined	CRITICAL	⨁◯◯◯ VERY LOW[a,b]

a. These are case series, there is no comparison with the other options
b. Overall sample size is small
c. There is no comparison with a period without the intervention

Undesirable Effects

How do interventions compare against each other with regards to desirable effects?

JUDGEMENT

Please rank the options with regards to the undesirable effects

Least harmful: Tranexamic Acid

Intermediate harms: IUD is better than OCP

More harmful: DDAVP

RESEARCH EVIDENCE

See box above. Details can be found in Tables 2, 3, and 4

ADDITIONAL CONSIDERATIONS

The panel judged that Tranexamic acid has the **least harmful** undesirable effects in comparison to Hormonal Therapy and DDAVP.

Based on the evidence and their experience, the panel agrees that the **harms of hormonal IUD (Intrauterine Device (IUD) and Combined Oral Contraceptive (COCP)** are similar. IUDs are less likely to result in side effects when compared to COCPs. However, IUDs require surgical insertion, which might result in complications. When compared to tranexamic acid and DDAVP, the potential harms of IUD and COCP were judged as intermediate.

		The panel also discussed the following: - Even when properly positioned, expulsion of the levonorgestrel-releasing intrauterine system occurs more frequently in women with bleeding disorders, possibly due to increased menstrual bleeding during the first few periods after insertion. The evidence, however, suggests that the rate of expulsion is low. - A potential side effect of unopposed progesterone is an increase in the risk of ovarian cysts, which are generally asymptomatic and self-limited, although some patients may require modification of therapy.

Certainty of evidence

What is the overall certainty of the evidence of effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
●**Very low** ○ Low ○ Moderate ○ High ○ No included studies	The quality of the evidence varies across comparisons from low to very low	The panel discussed that even though the studies included are the only evidence available that may be relevant to inform this recommendation, they are indirect.

Values

Is there important uncertainty about or variability in how much people value the main outcomes?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Important uncertainty or variability ● **Possibly important uncertainty or variability** ○ Probably no important uncertainty or variability ○ No important uncertainty or variability	No research evidence found	The panel discussion reflected the variability on how patients trade-off the potential benefits and side-effects. Patients from the panel placed a high value on the side effects, including concerns for breakthrough bleeding, while clinicians placed a high value on reducing bleeding.

Balance of effects

Which intervention does the balance between desirable and undesirable effects favor?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
Rank the interventions according to the balance of effect (there may be more than one intervention in each rank) **Best balance**: Hormonal Therapy **Intermediate:** Tranexamic Acid **Worst balance:** DDAVP		Based on the likelihood of desirable effects on controlling heavy menstrual bleeding the panel ranked hormonal therapy as having the best balance of effects. The panel also discussed that the specific hormonal therapy with the best balance of effects will depend on the patient's preference after providing the proper counselling and educational material.

Resources required

How large are the resource requirements (costs)?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
Rank the interventions regarding the resources required (there may be more than one intervention in each rank) **Less costs:** Tranexamic Acid **Intermediate costs:** Hormonal Therapy **Most costs:** DDAVP	No research evidence found	In a survey to panel members before the meeting, some panel members highlighted that costs of hormonal therapy, Tranexamic acid and DDAVP may vary importantly across settings. During the meeting, the panel discussed and agreed that tranexamic acid would be the **least costly** and DDAVP as the **most costly**, particularly intranasal DDAVP.

Certainty of evidence of required resources

What is the certainty of the evidence of resource requirements (costs)?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Very low ○ Low ○ Moderate ○ High ● **No included studies**	No research evidence found	None

Cost effectiveness

Which intervention does the cost effectiveness favor?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
Rank the interventions according to the cost-effectiveness (there may be more than one intervention in each rank) ○ Best cost-effectiveness: ○ Intermediate cost effectiveness: ○ Worst cost-effectiveness: ● **No included studies**	No research evidence found	None

Equity

If recommended, which intervention would reduce health inequities the most?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
Rank the interventions according to their potential to reduce inequities if recommended (there may be more than one intervention in each rank) **Most reduction:** Combined Hormonal Contraception and IUD **Intermediate reduction:** Tranexamic Acid **Less reduction:** DDAVP	No research evidence found	In a survey to panel members before the meeting, several panel members mentioned that hormonal therapy with the levonorgestrel-releasing intrauterine system is the option with the most accessibility issues and thus recommending it may reduce equity However, during the meeting the panel discussed and agreed that recommending combined hormonal contraception or hormonal IUD would probably increase equity despite accessibility issues. This can particularly impact economically marginalized communities and populations that view oral contraceptives as controversial. Recommending oral contraceptives may prompt a discussion on their use as first line treatment for women from these communities with VWD who do not wish to get pregnant.

Acceptability

Which intervention is more acceptable to key stakeholders?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
Rank the interventions according to their acceptability intervention in each rank) **Best acceptability:** Tranexamic Acid **Intermediate acceptability:** Hormonal (depending on time-frame of wanting to get	In a survey to 75 women, 40% had used oral contraceptives, 69% had used DDAVP, and 26% had used antifibrinolytics. The proportion of women who reported being satisfied with their care was 95%.[15]	In a survey to panel members before the meeting, several considerations were brought up. Responses varied across panel members when asked if women with HMB were willing to receive all the interventions. Some said yes and others said no. There were arguments regarding increased and decreased acceptability of the options.

pregnant) **Worst acceptability:** DDAVP		The personal desire for contraception may make hormonal therapy the preferred option to some women and the less preferred option in others. Among panel members who said not all women are willing to receive all the interventions, some mention that DDAVP may be the less preferred option. During the meeting, the panel discussed that the acceptability of Tranexamic Acid would be the best because it has the least side effects among the treatment options. The panel also discussed the following: - Negative first experience of hormonal therapy in terms of side effects affects acceptability. - More physicians are familiar with the use of tranexamic acid or oral contraceptive pills - In transgender or intersex patients, hormonal therapy may be less acceptable/contraindicated than other options.

Feasibility

Is the intervention feasible to implement?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
Rank the 3 interventions according to their feasibility by key stakeholders (there may be more than one intervention in each rank) **Most feasible**: Tranexamic Acid **Intermediate feasibility:** OCP **Least feasible:** DDAVP	No research evidence found.	In a survey to panel members before the meeting, the majority said that administering hormonal therapy with oral contraceptives is a feasible option. Some highlighted that it is more feasible than the alternatives. Some concerns and threats to feasibility, however, were described: • patient adherence is usually good but some patients may not remember to take the pill every day • there may be religious preference and concerns about the intervention promoting sexual activity in younger patients, in particular adolescents • side effects of the pill may be an important concern to some patients and decrease feasibility due to decreased acceptability. According to panel members, the issues that threaten feasibility (particularly for homronal therapy) are: • history of side effects • parental acceptance in younger patients • religious and cultural perception • invasiveness of some of the options, and • desire to get pregnant. During the meeting the panel discussed that tranexamic acid is the **most feasible** intervention because of the low costs and wide availability.

		The panel also discussed that comparative feasibility will vary across settings depending on the infrastructure.

SUMMARY OF JUDGEMENTS

	Tranexamic acid	Hormonal therapy with oral contraceptives	Hormonal therapy with levonorgestrel-releasing intrauterine system	DDAVP
DESIRABLE EFFECTS	★★	★★★	★★★	★
UNDESIRABLE EFFECTS	★★★	★★	★★	★★★
BALANCE OF EFFECTS	★★	★★★	★★★	★
RESOURCES REQUIRED	★★★	★★	★★	★
COST EFFECTIVENESS				★★★
EQUITY	★★	★★★	★★★	★
ACCEPTABILITY	★★★	★★	★★	★
FEASIBILITY	★★★	★★	★★	★

★★★ Ranked as best option in the factor considered for making the recommendation
★★ Ranked as intermediate option in the factor considered for making the recommendation
★ Ranked as worst option in the factor considered for making the recommendation

CONCLUSIONS

Recommendation

The panel suggests using either hormonal therapy (combined hormonal contraception or levonorgestrel-releasing intrauterine system) or tranexamic acid over DDAVP to treat women with VWD with heavy menstrual bleeding who do not wish to conceive (conditional recommendation, based on very low-quality evidence).

The panel suggests using tranexamic acid over hormonal therapy and DDAVP to treat women with VWD and heavy menstrual bleeding who wish to conceive. (conditional recommendation based on very low-quality evidence).

Remarks:

- **This recommendation does not imply that the interventions considered can only be prescribed as monotherapy. In some cases, multiple options can be combined especially if control of heavy menstrual bleeding is less than optimal with the initial therapy**
- **Desmopressin will not be effective in type 3 and many type 2 VWD patients and should not be used in type 2B VWD.**
- **Women may require additional treatment directed at bleeding symptoms for the first several menstrual cycles after placement of a levonorgestrel-releasing intrauterine system.**

Good Practice Statements:

- **The panel encourages the development of multidisciplinary clinics in which gynecology and hematology see patients jointly to facilitate the management of heavy menstrual bleeding for patients with bleeding disorders.**
- **Decisions regarding the use of the levonorgestrel-releasing intrauterine system should be made in a setting of shared-decision making with multidisciplinary input (e.g. gynecology, hematology, and patients)**
- **In some patients, there may be other benefits to use of hormonal therapy such as treatment of oligomenorrhea due to polycystic ovary syndrome or menstrual-associated migraines.**
- **Patients with new onset heavy menstrual bleeding should be assessed and treated for iron deficiency and anemia.**
- **Women with known bleeding disorders and HMB should undergo gynaecological assessment that is recommended for women with HMB in the general population to rule out common pelvic pathologies such as fibroids and polyps, especially those not responding to first line treatment.**
- **Special consideration is required in terms of side effects of therapy for those who are at high risk of endometrial hyperplasia/malignancies such as women over 35, those with PCO, high BMI, women with comorbidities such as diabetes and hypertension.**

Justification

The recommendation for using hormonal therapy or Tranexamic Acid over DDAVP to treat women with VWD and heavy menstrual bleeding places a high value on the better balance of effects and the increase in health equity anticipated with hormonal therapy, as well as the best acceptability and feasibility of tranexamic acid.

The recommendation for women who wish to conceive derives from the previous recommendation, given than hormonal therapy is not an option for these women.

Subgroup considerations

Implementation considerations

Monitoring and evaluation

Research priorities

The panel suggested future research:

- **Studies on the use of combined therapy vs. single therapy (efficacy and safety of the combination of hormonal therapy with tranexamic acid);**
- **Studies assessing patients' values and preferences on the benefits and harms**
- **Prospective study of levonorgestrel-releasing intrauterine system in terms of acceptability rate, spotting rate and risk of expulsion and malposition;**

Table 2: Evidence profile. DDAVP compared to tranexamic acid for women with VWD with HMB

Certainty assessment							Summary of findings				
							Study event rates (%)			Anticipated absolute effects	
№ of participants (studies) Follow-up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty of evidence	With tranexamic acid	With DDAVP	Relative effect (95% CI)	Risk with tranexamic acid	Risk difference with DDAVP
Change in menstrual blood loss (follow up: 2 months; assessed with: Change from baseline on PBAC)											
116 (1 RCT)[1]	not serious [a]	not serious	serious [b]	not serious	none	⨁⨁⨁◯ MODERATE	MCh -105.7 (-130.5 to -81.0)	MCh -64.1 (-88.0 to -40.3)	-	The mean change in menstrual blood loss was **-105.7**	MD **41.6 higher** (19.6 higher to 63.6 higher)
Quality of life (follow up: 2 months; assessed with: Several scales (HRQoL, SF-36, CES-D, RUTA))											
116 (1 RCT)[1]	serious [c]	not serious	serious [b]	not serious	none	⨁⨁◯◯ LOW	The researchers do not provide an explicit comparison between the groups. Scores across instruments and domains suggested improvement for both interventions, but this was statistically significant only for domains/ instruments				
Side effects (follow up: 2 months; assessed with: Most common: headaches)											
232 (1 RCT)[1]	not serious [a]	not serious	serious [b]	serious [d]	none	⨁⨁◯◯ LOW	6/116 (5.2%)	7/116 (6.0%)	not estimable	52 per 1,000	NE [e]
Severe side effects (follow up: 2 months)											
232 (1 RCT)[1]	not serious [a]	not serious	serious [b]	serious [d]	none	⨁⨁◯◯ LOW	0/116 (0.0%)	2/116 (1.7%)	not estimable	0 per 1,000	NE [e]
Major bleeding - not reported											
-	-	-	-	-	-	-	-	-	-	-	-
Need for surgery - not reported											
-	-	-	-	-	-	-	-	-	-	-	-
Need for additional treatment - not reported											
-	-	-	-	-	-	-	-	-	-	-	-

Table 2: Evidence profile. DDAVP compared to tranexamic acid for women with VWD with HMB

Certainty assessment							Summary of findings				
Menstruation duration - not reported											
-	-	-	-	-	-	-	-	-	-	-	-
Absence from school, work, and other required activities - not reported											
-	-	-	-	-	-	-	-	-	-	-	-

CI: Confidence interval; **MD:** Mean difference

Explanations

a. Allocation sequence generation and concealment unclear in the publication. However, we clarified with the researchers the procedures they used
b. Patients analyzed had not responded to treatment with oral contraceptives. Patients seeking for first line treatment may be importantly different from those seeking second line treatment
c. Lack of blinding could have affected the reporting of this subjective outcome
d. Few events, results are likely to be fragile
e. Difference not estimable because RR could not be calculated. This cross-over study does not report an appropriately calculated RR

Table 3: Evidence Profile. DDAVP compared to hormonal therapy for women with VWD with HMB

Certainty assessment							Summary of findings				
							Study event rates (%)			Anticipated absolute effects	
№ of participants (studies) Follow-up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty of evidence	With hormonal therapy	With DDAVP	Relative effect (95% CI)	Risk with hormonal therapy	Risk difference with DDAVP
Effectiveness (follow up: median 30 months; assessed with: Alleviation of symptoms)											
36 (1 observational study) [2]	extremely serious [a]	not serious	not serious	serious [b]	none	⨁◯◯◯ VERY LOW	12/14 (85.7%)	17/22 (77.3%)	**RR 0.90** (0.66 to 1.23)	857 per 1,000	**86 fewer per 1,000** (from 291 fewer to 197 more)
Menstrual flow (follow up: median 30 months; assessed with: mean PBAC score over follow up)											
36 (1 observational study) [2]	extremely serious [a]	not serious	not serious	not serious	none	⨁◯◯◯ VERY LOW	14	22	-	The mean menstrual flow was **105.1** points	MD **0.9 points higher** (9.89 lower to 11.69 higher)
Adverse events (not serious) (follow up: median 30 months; assessed with: reported by patients)											
36 (1 observational study) [2]	extremely serious [a]	not serious	not serious	very serious [b]	none	⨁◯◯◯ VERY LOW	0/14 (0.0%)	4/22 (18.2%)	**RR 5.87** (0.34 to 101.31)	0 per 1,000	**180 more per 1,000** (from 0 fewer to 370 more) [c]
Major bleeding - not reported											
-	-	-	-	-	-	-	-	-	-	-	-
Need for surgery - not reported											
-	-	-	-	-	-	-	-	-	-	-	-

Table 3: Evidence Profile. DDAVP compared to hormonal therapy for women with VWD with HMB

Certainty assessment							Summary of findings				
Need for additional treatment - not reported											
-	-	-	-	-	-	-	-	-	-	-	-
Menstruation duration - not measured											
-	-	-	-	-	-	-	-	-	-	-	-
Absence from school, work, or other required activities - not reported											
-	-	-	-	-	-	-	-	-	-	-	-

CI: Confidence interval; **RR:** Risk ratio; **MD:** Mean difference

Explanations

a. Assignment to treatment was done by clinician and patient preference. No matching or control of confounding
b. The CI suggests the possibility of appreciable benefit and appreciable harm. Small sample size.
c. Absolute effects calculated based on risk difference in this study

Table 4: Evidence profile. Hormonal therapy with levonorgestrel-releasing intrauterine system compared to other options for women with VWD with HMB

Certainty assessment							Summary of findings
№ of participants (studies) Follow-up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty of evidence	Impact
Control of heavy menstrual bleeding (assessed with: PBAC score)							
42 (2 observational studies)[6 7]	very serious [a]	not serious	not serious	serious [b]	none	⨁◯◯◯ VERY LOW	In one study with 16 women, the PBAC score changed from a range of 98 to 386 before the intervention, to 0 to 75 after the intervention. A second study with 26 women reported that the median (range) PBAC changed from 255 (134 to 683) before the intervention to 35 (0 to 89) after the intervention.
Health-related quality of life (assessed with: Kadir questionnaire)							
26 (1 observational study)[6]	very serious [a]	not serious	not serious	not serious	none	⨁◯◯◯ VERY LOW	In one study with 26 women, the median (range) QOL scores increased from 26 (13 to 48) to 52 (39 to 59)
Anemia (assessed with: number of women)							
23 (2 observational study)[7 8]	very serious [a]	not serious	not serious	very serious [b]	none	⨁◯◯◯ VERY LOW	in 1 study with 7 women, the proportion with anemia before or after the intervention was 0. In one study with 16 women, the proportion with anemia before was 12.5 and after the intervention was 0
Hemoglobin (assessed with: g/dL)							
61 (4 observational studies)[4-7]	very serious [a]	not serious	not serious	not serious	none	⨁◯◯◯ VERY LOW	There were 4 studies that reported this outcome, but the results were presented in a way that did not allow pooling. Overall levonorgestrel-releasing intrauterine system resulted in an improvement of hemoglobin. - In 1 study with 16 patients, 12.5% had hemoglobin <11g/dL before the intervention, and 0 after - In 1 study with 26 patients, Hb median (range) was 11.2 g/dL (9.7 to 13) before the intervention and 13.2g/dL (11.2- 14.3) after the intervention - In 1 study with 6 women, mean Hb was 12.2 g/dL before the intervention and 13 g/dL after the intervention - In 1 study with 13 women, mean (range) Hb level was 11.1 g/dL (3 to 15.9) before the intervention and 13.4 g/dL (12 to 14.8) after the intervention

Table 4: Evidence profile. Hormonal therapy with levonorgestrel-releasing intrauterine system compared to other options for women with VWD with HMB

Certainty assessment							Summary of findings
Menstruation duration (assessed with: several definitions)							
23 (2 observational studies) [7 8]	very serious [a]	not serious	not serious	serious [b]	none	⨁◯◯◯ VERY LOW	- Duration of menstrual bleeding reduced from 9 to 3 days (1 study, 7 patients) - Proportion of women in whom duration decreased, 71% (1 study, 7 women) - Reporting of periods "much better", 100% (1 study, 16 patients)
Complications (assessed with: Expulsion and malposition)							
20 (1 observational study) [4]	very serious [a]	not serious	not serious	serious [b]	none	⨁◯◯◯ VERY LOW	The proportion of women with expulsions was 15 % (3/20), and the proportion of women with malposition was 10% (2/10)
Absence from school, work, or other required activities (assessed with: periods affecting life)							
16 (1 observational study)[7]	very serious [a,c]	not serious	not serious	serious [b]	none	⨁◯◯◯ VERY LOW	In one study with 16 women, the proportion whose life was affected by the periods was 0. There was no data about the proportion before the intervention was administered
Adverse effects (assessed with: not defined)							
16 (1 observational study)[7]	very serious [a]	not serious	not serious	serious [b]	none	⨁◯◯◯ VERY LOW	In 1 study with 16 women, the proportion who experienced side effects was 0
Major bleeding - not reported							
-	-	-	-	-	-	-	
Need for surgery - not reported							
-	-	-	-	-	-	-	
Need for multiple treatments - not reported							
-	-	-	-	-	-	-	

Table 4: Evidence profile. Hormonal therapy with levonorgestrel-releasing intrauterine system compared to other options for women with VWD with HMB

Certainty assessment							Summary of findings
Transfusions - not reported							
-	-	-	-	-	-	-	

CI: Confidence interval

Explanations

a. These are case series, there is no comparison with the other options
b. Overall sample size is small
c. There is no comparison with a period without the intervention

Table 5: Panel members' experience

Total number of responses	14
Total number of women treated	1363
Total number of women with HMB	420

Outcome/ treatment	TxA (total=207)	Hormonal therapy (total= 265)	DDAVP (total=36)
Control of HMB	Median (IQR), 71 (45 to 81)% Mean (SD), 62 (32)%	Median (IQR), 74 (62 to 80)% Mean (SD), 73 (15)%	Median (IQR), 50 (50 to 100)% Mean (SD), 62 (39)%
Major bleeding	Median (IQR), 0 (0 to 17)% Mean (SD), 14 (29)%	Median (IQR), 4 (0 to 12)% Mean (SD), 7 (8.6)%	Median (IQR), 0 (0 to 0)% Mean (SD), 9 (19)%
Serious adverse events	Median (IQR), 0 (0 to 0)% Mean (SD), 4 (1.3)%	Median (IQR), 0 (0 to 0)% Mean (SD), 1 (3.7)%	Median (IQR), 0 (0 to 0)% Mean (SD), 5 (16)%
Need for surgery	Median (IQR), 0 (0 to 3)% Mean (SD), 8 (2)%	Median (IQR), 0 (0 to 13.3)% Mean (SD), 8.5 (11.3)%	Median (IQR), 0 (0 to 0)% Mean (SD), 0 (0)%
Need for multiple treatments	Median (IQR), 0 (0 to 25)% Mean (SD), 20 (33)%	Median (IQR), 4 (0 to 13.3)% Mean (SD), 10 (14)%	Median (IQR), 4 (0 to 9)% Mean (SD), 35 (47)%
Absence from school, work, or other required activities	Median (IQR), 15 (0 to 50)% Mean (SD), 30 (36)%	Median (IQR), 13 (0 to 20)% Mean (SD), 13 (14)%	Median (IQR), 50 (0 to 50)% Mean (SD), 39 (42)%
Acceptable HRQoL	Median (IQR), 88 (75 to 100)% Mean (SD), 77 (33)%	Median (IQR), 74 (60 to 93)% Mean (SD), 71 (25)%	Median (IQR), 70 (50 to 100)% Mean (SD), 67 (41)%
Transfusions	Median (IQR), 0 (0 to 0)% Mean (SD), 3.5 (11)%	Median (IQR), 0 (0 to 8)% Mean (SD), 5 (8)%	Median (IQR), 0 (0 to 0)% Mean (SD), 9 (19)%
Anemia/ iron deficiency	Median (IQR), 41 (20 to 67)% Mean (SD), 46 (32)%	Median (IQR), 25 (20 to 37)% Mean (SD), 28 (20)%	Median (IQR), 35 (0 to 50)% Mean (SD), 36 (42)%

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Appendix

Table 1: Characteristics of comparative studies

Study	Comparison	Study design	Recruitment	Country	Setting	HMB diagnosis	Others	Bleeding disorder distribution	Interventions	N baseline	Age distribution	PBAC
Kouides, 2009	DDAVP (IN) vs TxA	RCT (cross-over)	2001-2006	USA	Heamophilia treatment centre, bleeding disorders clinic, gynaecology care centre	PBAC >100	Patients chose not to use OC because they had not respoded well in the past	VWD, 7% Platelet aggregation/ release, 75% Prolonged closure time, 7% Subnormal coagulation factor level, 11%	DDAVP IN, 300ug on day 2 and 3 of MB TxA, 1g 4x per day during first 5 days of MB	116	Mean, 36	Median, 224
Amesse, 2005	DDAP (IN) vs OC	Retrospective cohort	1998-2002	USA	Hematology clinic, pedatric-adolescent gynecology clinic	PBAC >100	Explicitly acknowledges that treatment was determined by physician together with patient	VWD, 100% type 1, 98% type 2b, 2%	DDAVP IN, 1.5 mg/mL or 150 ug oer puff, based on body weight at onset and 2 more days OC, 0.15 mg desogestrel and 30 ug ethinyl estradiol daily	36	Median (range), 16 (9-18)	Mean (SD), 263.2 (171.4)

Table 2: Characteristics of case series of levonorgestrel-releasing intrauterine system

Author	Setting	Country	N	Bleeding disorder	Dx HMB	Length of use	Age	Outcomes	Comments
Lukes, 2008	Tertiary medical center	USA	7	4 with confirmed VWD	Focused history taking	9-28 months	Median (range), 38 (28 to 48)	Duration of MB reduced 6 days (from 9 to 3) Proportion with decrease in duration, 71% Failure of therapy, 29% Anemia, 0 before or after	Does not meet eligibility for high proportion w/ no VWD, and all of them had previous treatment with oral contraceptives
Kingman, 2004	Hemophilia Centre	England	16	13 with VWD, 2 with FXI deficiency, 1 with platelet disorder	Subjective menorrhagia	up to 9 months	Median (range), 31 (27 to 40)	PBAC range before, 98 to 386; after, 0 to 75. Reporting that periods were much better, 100% Hemoglobin < 11 g/dL, 2 before, 0 after Periods affecting life, 0 Side effects, 0	Does not meet eligibility because they failed previous treatment
Chi, 2011	Hemophilia Centre and Thrombosis Unit	England	26	50% with VWD, 23% platelet disorder, 23% carrier of hemophilia, 4% FVII deficiency	NR	<12 months	Median (range), 41 (18 to 53)	PBAC score median (range) decreased from 255 (134 to 683) to 35 (0-89) Hb median (range), 11.2 g/dL (9.7 to 13) before and 13.2 (11.2-14.3) after QoL outcomes reported too	Does not meet eligibility, 85% had received previous tmt that did not work
Rimmer 2013	Bleeding disorders clinic	Canada	20	60% with VWD, 20% hemophilia carriers, 15% platelet function defect, 5% combined VWD and HC	NR	NR	Median (range), 31 (18 to 43)	3 expulsions and 2 malpositions 6 women for Hb change	Inserted because of preference or failure of other therapies
Adeyemi-Fowode 2017	NR	USA	13	VWD and low VWF	NR	NR	Median (range), 10 (9-13)	Mean (SD) time to imptovement 94 (69) days Amenorrhea or ocassional spotting, 61% Increase in Hb	May not meet eligibility owing to population, also, 100% tried other treatments with no success

Figure 1: Risk of bias assessment for RCT

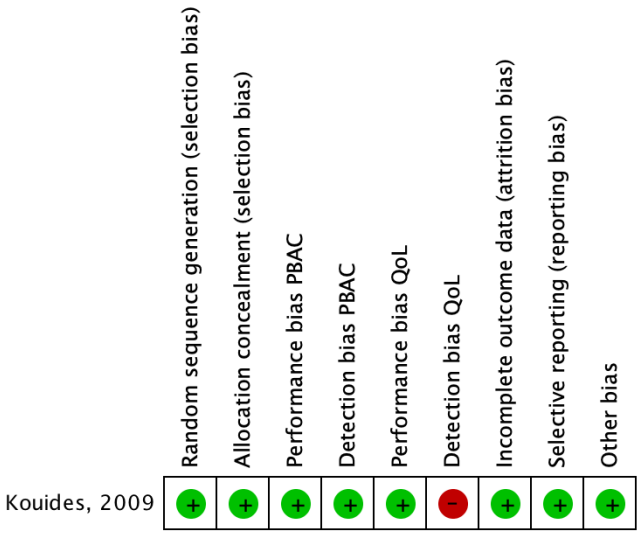
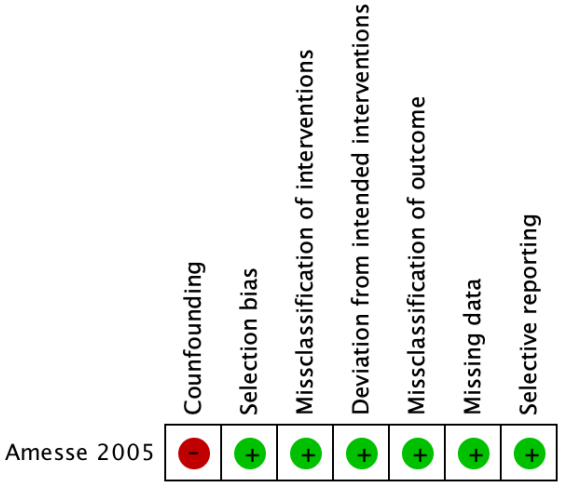


Figure 2: Risk of bias assessment for OS

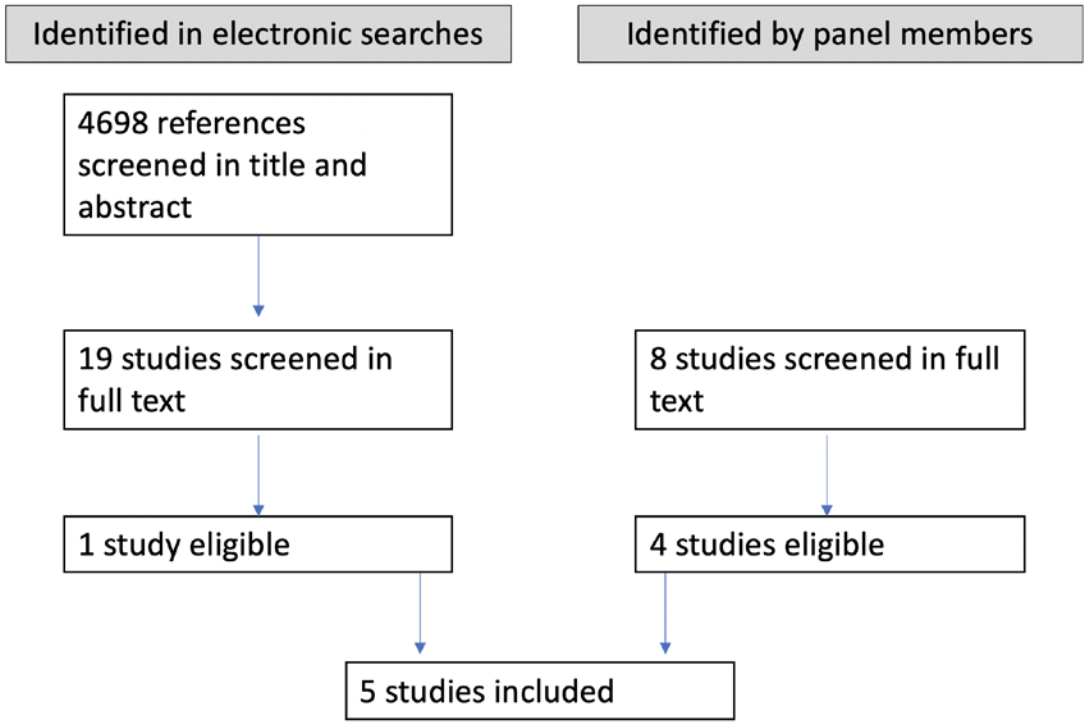


RQ7: In women with VWD who require or desire neuraxial anesthesia during labor, should we administer VWF concentrate to achieve VWF level of 50- 150 IU/dl or >150 IU/dl?

P: women with VWD of any type, except for acquired; hemophilia, or inherited bleeding disorders who require/ desire neuraxial anesthesia during labor
I: VWF level 50-150 IU/dl
C: VWF level >150 IU/dl
O: Major bleeding, AE in mother (serious), spinal epidural hematoma, failed procedure, mortality, thrombotic events, transfusion

After title and abstract screening of 4698 references, and full text screening of 19 studies, we did not find any comparative studies. Thus, we decided to include case series to inform this question. We found 1 study through our screening. In addition, the panel brought up 8 studies that they believe presented relevant information, which were screened in full text. From these, 4 studies were eligible and were included. Figure 1 shows a summary of the screening process

Figure 1: Flow chart of study selection process



This evidence report contains evidence from 5 case series.[1-5] The main characteristics of these studies are presented in Table 1.

Study	Design	Country	Recruitment period	N	Bleeding disorders
Duggan 2017	Retrospective case series	NR	2006-2016	10	Haemophilia carriers
Kadir 1997	Case series	England	1985-1995	6	Haemophilia carriers
Kadir 1998	Retrospective case series	England	1980-1996	10 (8 with VWD and 2 with FXI deficiency)	VWD and factor XI deficiency
Chi 2008	Retrospective case series	England	1995-2005	25	Haemophilia carriers
Chi 2009	Retrospective case series	England	2000-2005	37 women, 41 pregnancies	Not reported for epidural, but of total sample 24% VWD, 25% hamophilia carriers, 30% factor XI deficiency

In addition, we systematically collected the experience of the panel when facing this clinical scenario.

Table 2 presents the Evidence to Decision framework for this question; Table 3 presents the Evidence Profile; Table 4 summarizes the panel's experience. The appendix presents relevant figures.

TABLE 2: EVIDENCE TO DECISION FRAMEWORK QUESTION 7

Should VWF levels 50-150 IU/dl vs. VWF levels >150 IU/dl be used for women with VWD in labour who require/ desire neuraxial anesthesia?	
POPULATION:	women with VWD in labour who require/ desire neuraxial anesthesia
INTERVENTION:	VWF levels 50-150 IU/dl
COMPARISON:	VWF levels >150 IU/dl
MAIN OUTCOMES:	Complications of neuraxial anesthesia; Failed procedure; Major bleeding; Adverse events in mother; Spinal hematoma; Mortality; Thrombotic events; Transfusion;
SETTING:	High Income Healthcare Setting
PERSPECTIVE:	Clinical
CONFLICT OF INTERESTS:	The ASH conflict of interest policy for clinical practice guidelines was applied.

ASSESSMENT

Problem
Is the problem a priority?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ● **Yes** ○ Varies ○ Don't know		Neuraxial anesthesia use is varied in practice and sometimes withheld from VWD patients. Currently, there are no explicit recommendations or guidelines on target VWF levels for VWD patients who require or desire neuraxial anesthesia. This question was prioritized among several other questions to be addressed in these guidelines.

Desirable Effects
How substantial are the desirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Trivial ○ Small ○ Moderate ○ Large ○ Varies ● **Don't know**	The following is a summary of the evidence found. Table 3 present details.	During the meeting the panel discussed the lack of evidence available to make judgments about how the desirable effects of the options compare. Therefore, the panel decided to make a judgment of **Don't Know.** The panel also discussed the following: - Recent research suggest targeting higher VWF levels may be beneficial in preventing postpartum hemorrhage (PPH)[6]. There is, however, a lack of evidence on neuraxial anesthesia outcomes. Moreover, while higher factor levels may reduce PPH, some indirect data suggest correlation between the presence of an epidural itself and higher risk of PPH. [7]

Outcomes	**Impact**
Complications of epidural assessed with: Number of events/ administration	The pooled proportion of complications of epidural was 6% (5/83 deliveries). In 4 studies the types of complications were not reported. In one of the studies the complications reported were hypotension, accidental dural puncture, inadequate analgesia, bloody tap with no further complications, and failed block requiring general anesthesia
Failed procedure assessed with:	In the study that reported this outcome, the proportion of deliveries in which it occurred was 2.4% (1/41 deliveries)

	Number of events/ administration	
	Outcomes / **Importance** / **Certainty of the evidence (GRADE)**	
	Complications of epidural assessed with: Number of events/ administration — CRITICAL — ⨁◯◯◯ VERY LOW[a,b]	
	Failed procedure assessed with: Number of events/ administration — CRITICAL — ⨁◯◯◯ VERY LOW[a,b]	
	a. No control group b. Very few events and patients	

- Desirable effects of increasing VWF levels when administering neuraxial anesthesia is avoiding spinal hematoma. However, limitation of data makes the risk of spinal Hematoma impossible to assess in patients with bleeding disorders.

- Studies have shown that in patients with type 2 and 3 VWD, restoration of normal hemostasis is not reliably achievable even following replacement therapy, and correcting VWF levels does not necessarily confer normal primary hemostasis despite a normal VWF activity level. [8]

Undesirable Effects

How substantial are the undesirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Large ○ Moderate ○ Small ○ Trivial ○ Varies ● **Don't know**	See box above	During the meeting the panel discussed the lack of evidence available to make judgments about how the desirable effects of the options compare. Therefore, the panel decided to make a judgment of **Don't Know.** The panel also discussed the following: - Women who have neuraxial anesthesia are more likely to have a longer second stage of labour, increased need for oxytocin and higher rate of instrumental deliveries. - There may be a larger potential risk of thrombosis when VWF levels are >150 IU/dl than when they are 50-150 IU/dl

Certainty of evidence

What is the overall certainty of the evidence of effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
● **Very low** ○ Low ○ Moderate ○ High ○ No included studies	The quality of the evidence is very low, mainly owing to the extremely serious risk of bias from case series that provide information about only one of the alternatives	None

Values

Is there important uncertainty about or variability in how much people value the main outcomes?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Important uncertainty or variability ● **Possibly important uncertainty or variability** ○ Probably no important uncertainty or variability ○ No important uncertainty or variability	No research evidence found.	In a survey to panel members before the meeting, some commented that women are more likely to place a higher value on a potential reduction of bleeding than the risk of thrombosis. The panel discussion reflected the variability on how patients trade-off the potential benefits and side effects. Some panelists placed a high value on avoiding bleeding while others placed a high value on avoiding thrombotic complications. Thus, the panel judged that there is possibly important uncertainty or variability in patient values and preferences. The panel also discussed the following: - Values may vary in patients with more significant bleeding phenotypes and certain VWD subtypes, particularly type 2 and 3.

Balance of effects

Does the balance between desirable and undesirable effects favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ○ Varies ● **Don't know**		Based on the uncertainty of desirable and undesirable effects, the panel judged the balance as **Don't Know.**

Resources required

How large are the resource requirements (costs)?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Large costs ○ Moderate costs ○ Negligible costs and savings ● **Moderate savings** ○ Large savings ○ Varies ○ Don't know	No research evidence found	In a survey to panel members before the meeting, costs were described as high by the panel. While this may not be an issue in settings in which the treatment cost is completely covered by government or insurers, some panel members highlighted that targeting levels to > 150 IU/dL is considerably more expensive than targeting levels of 50-150 IU/dL.

Certainty of evidence of required resources

What is the certainty of the evidence of resource requirements (costs)?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Very low ○ Low ○ Moderate ○ High ● **No included studies**	No research evidence found	None

Cost effectiveness

Does the cost-effectiveness of the intervention favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ○ Varies ● **No included studies**	No research evidence found	None

Equity

What would be the impact on health equity?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Reduced ○ Probably reduced ○ Probably no impact ● **Probably increased** ○ Increased ○ Varies ○ Don't know	No research evidence found	The panel discussed recommending neuraxial anesthesia with VWF levels to 50-150 IU/dL will **probably increase** equity to patients who require or desire neuraxial anesthesia during labor as targeting higher levels would require more treatment for patients, which may be expensive and/or difficult to procure.

Acceptability

Is the intervention acceptable to key stakeholders?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ○ Yes ● **Varies** ○ Don't know	No research evidence found	In a survey to panel members, responses varied when asked if it would it be acceptable to pregnant women to target levels >150 IU/dL. Many panel members said yes, if it was recommended by their physician, and given that they are more likely to place a high value on preventing bleeding regardless of a potential increase on the risk of thrombosis. One panel member highlighted that women are likely to care more about the effect of the intervention on the outcome than the intervention itself. In addition, most panel members said that it would not be acceptable to clinicians to always target a level >150 IU/dL. Threats to the acceptability of this option is the potential increased risk of thrombosis, highlighted by several panel members. Other panel members mentioned that the evidence supporting this option should be sound for clinicians to accept it. The panel also discussed the following: - The panel agreed that VWF levels of 50- 150 IU/dl and >150 IU/dl are both acceptable. - Psychosocial considerations about death due to bleeding versus the risk of thrombosis creates a dichotomy among patients leading to a variability in the acceptability of VWF level of 50- 150 IU/dl vs. >150 IU/dl.

Feasibility

Is the intervention feasible to implement?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ● **Yes** ○ Varies ○ Don't know	No research evidence found	In a survey to panel members before the meeting, responses varied when asked if it is feasible to always increase the levels to >150 IU/dL. Threats to feasibility of this option highlighted by the panel included the amount of VWF concentrate needed and the time necessary to raise the levels to a higher target. In addition, responses varied across panel members when asked if all women would be able to receive any of the options if they were recommended. Feasibility of providing either option seems to depend on the place of delivery (those delivering at HTCs are more likely to be able to receive any option, but those in community hospital may not have the same level of access to the treatment options). Cost of the product may also threaten feasibility.

SUMMARY OF JUDGEMENTS

	JUDGEMENT						
PROBLEM	No	Probably no	Probably yes	**Yes**		Varies	Don't know
DESIRABLE EFFECTS	Trivial	Small	Moderate	Large		Varies	**Don't know**
UNDESIRABLE EFFECTS	Large	Moderate	Small	Trivial		Varies	**Don't know**
CERTAINTY OF EVIDENCE	**Very low**	Low	Moderate	High			No included studies
VALUES	Important uncertainty or variability	**Possibly important uncertainty or variability**	Probably no important uncertainty or variability	No important uncertainty or variability			
BALANCE OF EFFECTS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	**Don't know**
RESOURCES REQUIRED	Large costs	Moderate costs	Negligible costs and savings	**Moderate savings**	Large savings	Varies	Don't know
CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	Very low	Low	Moderate	High			**No included studies**
COST EFFECTIVENESS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	**No included studies**
EQUITY	Reduced	Probably reduced	Probably no impact	**Probably increased**	Increased	Varies	Don't know
ACCEPTABILITY	No	Probably no	Probably yes	Yes		**Varies**	Don't know
FEASIBILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know

TYPE OF RECOMMENDATION

Strong recommendation against the intervention	Conditional recommendation against the intervention	Conditional recommendation for either the intervention or the comparison	**Conditional recommendation for the intervention**	Strong recommendation for the intervention
○	○	○	●	○

CONCLUSIONS

Recommendation

In women with VWD deemed suitable for neuraxial anesthesia during labor, the panel suggests targeting VWF levels to 50-150 IU/dL over targeting a level of >150 IU/dL to allow neuraxial anesthesia. (Conditional, Very Low Certainty of Evidence)

Remarks:

- **This recommendation focused on the outcomes of the anesthesia procedure itself, and not on the effects of the levels on postpartum hemorrhage (PPH) in which VWF levels of >150 IU/dL may be advised in some situations.**
- **Individual risk assessment should be performed, taking into account patient diagnosis and history, and for this reason the panel advocates for a third trimester visit where VWF and FVIII levels can be checked and a prospective plan formed for delivery.**
- **This recommendation is intended for women who desire or require neuraxial anesthesia and does not address safety.**
- **VWF levels should be maintained while the epidural is in place and for at least 6 hours following removal.**
- **Patients should also be assessed for thrombotic risk post-delivery, and treatment (such as compression stockings) provided when needed.**

Good practice statement: Decisions regarding anesthesia and delivery should be made in the context of a multi-disciplinary discussion with input from anesthesia, hematology, and obstetrics, and these discussions should take place well in advance of the patient's due date.

Justification

Given that there is no evidence to support a judgment on how the options compare with regards to their effects on epidural health outcomes, the recommendation for targeting VWF levels of 50-150 IU/dL over targeting a level of >150 IU/dL in women with VWD in labor who require or desire epidural places a high value on increasing health equity and the lower costs of targeting levels of 50-150 IU/dL.

Subgroup considerations

Implementation considerations

Monitoring and evaluation

Research priorities

The panel suggested future research:

- Studies evaluating why patients with Type 2 and 3 VWD do not completely correct hemostatic defects in spite of receiving VWF concentrates and whether there are differences in this correction between plasma-derived and recombinant VWF replacement therapies
- The role of platelet-derived VWF in hemostasis during pregnancy, particularly in the setting of labor, delivery, and postpartum hemorrhage
- Development and evaluation of clinical testing to ensure adequate primary hemostasis and whether therapy can be guided by these tests to improve outcomes
- Studies to directly compare delivery and neurologic outcomes in women with VWD who are treated to different target VWF and FVIII levels, specifically evaluating the difference between a target level of 50 IU/dL versus 150 IU/dL

Table 3: VWF levels 50-150 IU/dl compared to VWF levels >150 IU/dl in women with VWD in labour who require/ desire neuraxial anesthesia

Certainty assessment							Summary of findings
№ of participants (studies) Follow-up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty of evidence	Impact
Complications of epidural (assessed with: Number of events/ administration)							
83 (5 observational studies)[1-5]	extremely serious [a]	not serious	not serious	serious [b]	none	⨁◯◯◯ VERY LOW	The pooled proportion of complications of epidural was 6% (5/83 deliveries). In 4 studies the types of complications were not reported. In one of the studies the complications reported were hypotension, accidental dural puncture, inadequate analgesia, bloody tap with no further complications, and failed block requiring general anesthesia
Failed procedure (assessed with: Number of events/ administration)							
41 (1 observational study)[4]	extremely serious [a]	not serious	not serious	serious [b]	none	⨁◯◯◯ VERY LOW	In the study that reported this outcome, the proportion of deliveries in which it occurred was 2.4% (1/41 deliveries)
Major bleeding - not reported							
-	-	-	-	-	-	-	-
Adverse events in mother - not reported							
-	-	-	-	-	-	-	-
Spinal hematoma - not reported							
-	-	-	-	-	-	-	-
Mortality - not reported							
-	-	-	-	-	-	-	-
Thrombotic events - not reported							

Table 3: VWF levels 50-150 IU/dl compared to VWF levels >150 IU/dl in women with VWD in labour who require/ desire neuraxial anesthesia

Certainty assessment							Summary of findings				
-	-	-	-	-	-	-	-	-	-	-	-

Transfusion - not reported

-	-	-	-	-	-	-	-	-	-	-	-

CI: Confidence interval

Explanations

a. No control group
b. Very few events and patients

Table 4: Panel members' experience

	Women with VWD who desire/require neuraxial anesthesia, whose levels were increased to 50-150 IU/dL*		**Women with VWD who desire/require neuraxial anesthesia, whose levels were increased to >150 IU/dL***	
	N with level 50-150/all those with epidural 110/143 = 78% (SD 0.32) (weighted mean 76.5%)		N with level >150/all those with epidural 34/143 = 24% (SD 0.31) (weighted mean 23%)	
	Events/110 pts (average, SD)	**Proportion (average proportion, SD)**	**Events/34 pts (average, SD)**	**Proportion (average proportion, SD)**
Able to receive the epidural anesthesia (opposite of failed procedure):	110 (10, 10.7)	100% (100%,0%)	34 (100%,0%)	100% (100%,0%)
Major bleeding:	3 (0.3, 0.9)	2.7% (1.2%, 3.8%)	0 (0%)	0%
Serious adverse events affecting the mother:	3 (0.3, 0.9)	2.7% (1.2%,3.8%)	0 (0%)	0%
Spinal hematoma:	0 (0,0)	0%	0 (0%)	0%
Postpartum hemorrhage:	19 (1.7,2.1)	17% (17.6%, 17.1%)	2 (0.2, 0.6)	5.9% (4%, 8.9%)
Mortality:	0 (0,0)	0%	0 (0,0)	0%
Thrombotic events:	0 (0,0)	0%	0 (0,0)	0%
Transfusions (any type, including infusion):	11 (1, 1.3)	10% (20.5%, 32.1%)	0 (0,0)	0%
Adverse effects in child:	0 (0,0)	0%	0 (0,0)	0%
Hospitalization**				

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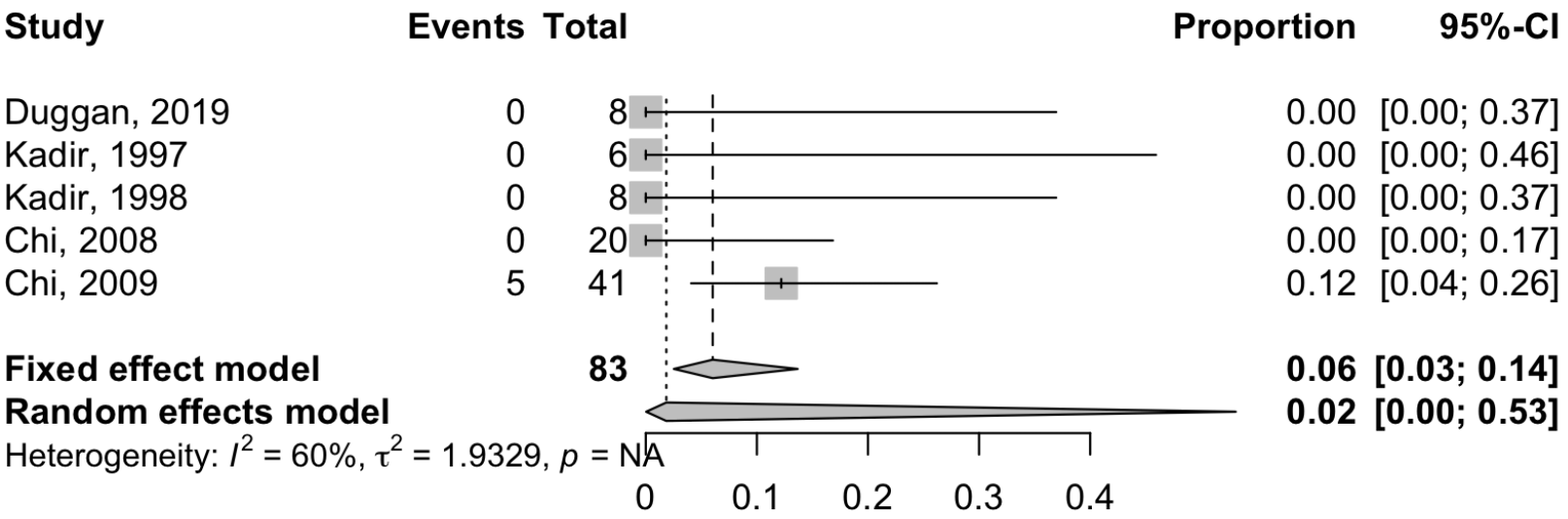
Appendix

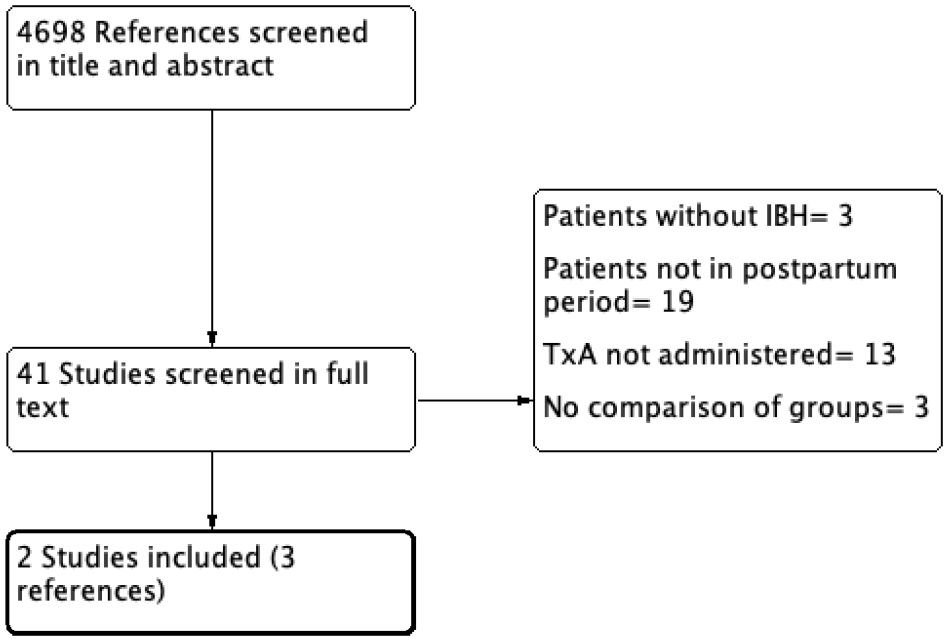
Figure 1: Forest plot analysis complications of epidural



RQ8: In women with type 1 VWD or low VWF level (may include type 2 and 3 VWD), should we prescribe tranexamic acid (or not) during the postpartum period?

The main eligibility criteria for selecting the evidence to inform this recommendation were:
P: Women with VWD all types, except for acquired; hemophilia, and inherited bleeding disorders. In the postpartum period (up to 6 weeks after giving birth)
I: Tranexamic acid (any type and dose) or any other antifibrinolytic
C: No intervention
O: Major bleeding, Primary PPH, Secondary PPH, AEs in mother, Need for other medical procedures, Blood loss, Mortality, Transfusion
S: Randomized Clinical Trials, Comparative observational studies

After title and abstract screening of 4698 references, and full text screening of 41 studies, we found and included 2 studies[1 2] (Figure 1)



This evidence report includes evidence from 2 comparative studies, both retrospective cohorts. Table 1 summarizes their main characteristics

Table 1: Main characteristics of the included studies

Study	Design	Country	Recruitment period	N	Bleeding disorder distribution	TxA Regimen
Govorov 2016	Retrospective cohort	Sweden	1995-2012	34 women, 59 delieveries	Type 1, 62%; type 2, 26%; type 3, 9%; unknownk rest	NR
Hawke 2016	Retrospective cohort	Canada	2002-2015	33 women, 62 pregnancies	Type 1 VWD, 39 (63%); type 2 VWD, 7 (11.5%); type 3 VWD, 1 (1.5%); hemophilia A carriers, 11 (18%); based on deliveries	Median (range) duration, 3 weeks (5 days to 6 weeks)

We present the Evidence to Decision Framework in Table 2 and the Evidence Profile in Table 3. The appendix presents figures for detailed assessments of risk of bias and forest plots.

TABLE 2: EVIDENCE TO DECISION FRAMEWORK RECOMMENDATION QUESTION 8

Should Tranexamic acid vs. no tranexamic acid be used for women with VWD in the postpartum period?	
POPULATION:	Women with VWD in the postpartum period
INTERVENTION:	Tranexamic acid
COMPARISON:	No tranexamic acid
MAIN OUTCOMES:	Severe primary postpartum hemorrhage; Primary postpartum hemorrhage; Secondary postpartum hemorrhage; Blood transfusion; Vaginal hematoma; Adverse events in mother- Thrombotic complications; Blood loss; Major bleeding; Need for other medical procedures; Mortality;
SETTING:	High income healthcare setting
PERSPECTIVE:	Clinical
CONFLICT OF INTERESTS:	The ASH conflict of interest policy for clinical practice guidelines was applied.

ASSESSMENT

Problem
Is the problem a priority?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ● **Yes** ○ Varies ○ Don't know		This question was judged to be a priority among many candidate questions to address in these guidelines.

Desirable Effects
How substantial are the desirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Trivial ○ Small ○ Moderate ● **Large** ○ Varies ○ Don't know	The following is a summary of the Evidence Profile. Details are presented in Table 3	The evidence suggests that treating women with Type 1 VWD or low VWF during the postpartum period would provide **large desirable effects** such as a reduction in primary postpartum hemorrhage. The panel also discussed that there is a large body of evidence in the general population that shows that tranexamic acid reduces post-partum hemorrhage. However, these benefits may not be experienced by patients with VWD Type 2 and 3, who are likely to require additional treatment such as factor replacement.

Outcomes	Importance	Certainty of the evidence (GRADE)
Severe primary postpartum hemorrhage assessed with: Number of events/ deliveries	CRITICAL	⨁◯◯◯ VERY LOW[a,b]
Primary postpartum hemorrhage assessed with: Number of events/ deliveries	CRITICAL	⨁◯◯◯ VERY LOW[a,b]

Secondary postpartum hemorrhage assessed with: Number of events/ deliveries	CRITICAL	⨁◯◯◯ VERY LOW[a]
Blood transfusion assessed with: Number of events/ deliveries	CRITICAL	⨁◯◯◯ VERY LOW[a,b]
Vaginal hematoma assessed with: Number of events/ deliveries		⨁◯◯◯ VERY LOW[a,b]
Adverse events in mother- Thrombotic complications assessed with: Number of events/ deliveries	IMPORTANT	⨁◯◯◯ VERY LOW[a,c]
Blood loss assessed with: Median per group	CRITICAL	⨁◯◯◯ VERY LOW[a,d]

a. No adjustment for any potential confounder
b. Very small number of patients and events, the CI suggests appreciable benefit in one extreme and appreciable harm in the other
c. No events for this outcome
d. Very small number of patients

Outcomes	With no tranexamic acid	with tranexamic acid	Difference	Relative effect (95% CI)
Severe primary postpartum hemorrhage assessed with: Number of events/ deliveries	313 per 1,000	**112 per 1,000** (16 to 809)	**200 fewer per 1,000** (297 fewer to 497 more)	**RR 0.36** (0.05 to 2.59)
Primary postpartum hemorrhage assessed with: Number of events/ deliveries	438 per 1,000	**109 per 1,000** (18 to 766)	**328 fewer per 1,000** (420 fewer to 328 more)	**RR 0.25** (0.04 to 1.75)
Secondary postpartum hemorrhage assessed with: Number of events/ deliveries	381 per 1,000	**160 per 1,000** (76 to 347)	**221 fewer per 1,000** (305 fewer to 34 fewer)	**RR 0.42** (0.20 to 0.91)
Blood transfusion assessed with:	188 per 1,000	**45 per 1,000** (2 to 793)	**143 fewer per 1,000**	**RR 0.24** (0.01 to 4.23)

Number of events/ deliveries			(186 fewer to 606 more)	
Vaginal hematoma assessed with: Number of events/ deliveries	125 per 1,000	**43 per 1,000** (3 to 799)	**82 fewer per 1,000** (123 fewer to 674 more)	**RR 0.34** (0.02 to 6.39)
Adverse events in mother- Thrombotic complications assessed with: Number of events/ deliveries	0 per 1,000	**0 per 1,000** (0 to 0)	**0 fewer per 1,000** (0 fewer to 0 fewer)	not estimable
Blood loss assessed with: Median per group	The median (range) blood loss after deliveries in people who received TxA was 400 (270 to 1470) ml, and it was 425 (200 to 6000) in people who did not receive TxA			

Undesirable Effects

How substantial are the undesirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Large ○ Moderate ● **Small** ○ Trivial ○ Varies ○ Don't know	See box above	The panel agreed that the potential undesirable effects of tranexamic acid are very small.

Certainty of evidence

What is the overall certainty of the evidence of effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
● **Very low** ○ Low ○ Moderate ○ High ○ No included studies	The quality of the evidence for all outcomes is very low. The main concerns are risk of bias (body of evidence from observational studies with extremely serious risk of bias) and imprecision (small number of participants)	None

Values

Is there important uncertainty about or variability in how much people value the main outcomes?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Important uncertainty or variability ○ Possibly important uncertainty or variability ● **Probably no important uncertainty or variability** ○ No important uncertainty or variability	No research evidence found.	In a survey to panel members before the meeting, some described that patients may place a high value on the effects of tranexamic acid on breastfeeding. Others mentioned that the GI side effects may be an outcome important to patients. The panel discussion did not reflect any large uncertainty or variability on how patients and physicians trade-off the potential benefits and side-effects as most panel members considered it a safe drug.

Balance of effects

Does the balance between desirable and undesirable effects favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ● **Probably favors the intervention** ○ Favors the intervention ○ Varies ○ Don't know		Based on the likelihood of desirable effects on postpartum hemorrhage and hemostasis as well as the low potential of side effects, and the little variability and uncertainty in patients' values and preferences, the panel judged the balance of effects as **probably favors** the use of tranexamic Acid.

Resources required

How large are the resource requirements (costs)?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Large costs ○ Moderate costs ● **Negligible costs and savings** ○ Moderate savings ○ Large savings ○ Varies ○ Don't know	No research evidence found	In a survey to panel members before the meeting, all of them said that the costs of tranexamic acid is small. Specific amounts estimated ranged between 125 to 1000 USD approximately, or approximately 8 USD per tablet. Panel members considered that this option is affordable by most patients who have to pay for it. Who pays for the treatment depends on the setting. In some, like the UK, it is covered by the NHS. In others, third party payors may cover the cost with or without a significant copay for the patient.

Certainty of evidence of required resources

What is the certainty of the evidence of resource requirements (costs)?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Very low ○ Low ○ Moderate ○ High ● **No included studies**	No research evidence found	None

Cost effectiveness

Does the cost-effectiveness of the intervention favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ○ Varies ● **No included studies**	No research evidence found	None

Equity

What would be the impact on health equity?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Reduced ○ Probably reduced ○ Probably no impact ● **Probably increased** ○ Increased ○ Varies ○ Don't know	No research evidence found	The panel discussed that recommending tranexamic acid would **probably increase** equity because it a safe and inexpensive drug and the recommendation may also increase the use of tranexamic acid in patients with VWD who had bleeding symptoms but may not have completed a formal evaluation of VWD.

Acceptability

Is the intervention acceptable to key stakeholders?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ● **Probably yes** ○ Yes ○ Varies ○ Don't know	No research evidence found	In a survey to panel members before the meeting, all of them said that tranexamic acid is a treatment that patients would accept. However, they highlighted that women may be concerned about the potential side effects of tranexamic acid on breastfeeding (this may be the major threat to acceptability), and that patients need to be reassured that tranexamic acid is safe in this situation[3 4]. One patient commented that it would not be acceptable (it would be scary) to not receive clotting factor postpartum.

Feasibility

Is the intervention feasible to implement?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no	No research evidence found	Based on their experience, the panel members judged that tranexamic acid in the postpartum setting is feasible to

○ Probably yes ● **Yes** ○ Varies ○ Don't know		implement.

SUMMARY OF JUDGEMENTS

	JUDGEMENT						
PROBLEM	No	Probably no	Probably yes	**Yes**		Varies	Don't know
DESIRABLE EFFECTS	Trivial	Small	Moderate	**Large**		Varies	Don't know
UNDESIRABLE EFFECTS	Large	Moderate	**Small**	Trivial		Varies	Don't know
CERTAINTY OF EVIDENCE	**Very low**	Low	Moderate	High			No included studies
VALUES	Important uncertainty or variability	Possibly important uncertainty or variability	**Probably no important uncertainty or variability**	No important uncertainty or variability			
BALANCE OF EFFECTS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	**Favors the intervention**	Varies	Don't know
RESOURCES REQUIRED	Large costs	Moderate costs	**Negligible costs and savings**	Moderate savings	Large savings	Varies	Don't know
CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	Very low	Low	Moderate	High			**No included studies**
COST EFFECTIVENESS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	**No included studies**
EQUITY	Reduced	Probably reduced	Probably no impact	**Probably increased**	Increased	Varies	Don't know
ACCEPTABILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know
FEASIBILITY	No	Probably no	Probably yes	**Yes**		Varies	Don't know

TYPE OF RECOMMENDATION

Strong recommendation against the intervention	Conditional recommendation against the intervention	Conditional recommendation for either the intervention or the comparison	**Conditional recommendation for the intervention**	Strong recommendation for the intervention
○	○	○	●	○

CONCLUSIONS

Recommendation

The Panel suggests for the use of tranexamic acid over not using it in women with type 1 VWD or low VWF level (may include type 2 and 3 VWD) during the postpartum period (conditional recommendation/ based on low certainty evidence)

Good Practice Statements:
- Tranexamic acid may be given systemically via oral or intravenous routes.
- Patients who intend to breastfeed should be provided education about the safety of tranexamic acid during breastfeeding in conjunction with its benefits in reducing bleeding

There was a vote among panel members to make this recommendation a strong recommendation, based on the large body of indirect evidence showing benefits on postpartum hemorrhage, and the potentially catastrophic consequences of this outcome in women with VWD. Out of the 13 panel members who voted (those without conflicts of interest), 7 panel members voted to make this a strong recommendation. This did not meet the threshold of 80% necessary to make this a strong recommendation.

Justification

The recommendation for using tranexamic acid in women with Type I VWD or low VWF during the postpartum period places a high value on the benefits of prevention and treatment during significant life-threatening hemorrhages and the small harms of the intervention. The intervention is not costly, and it is acceptable to key stakeholders and feasible to implement.

Subgroup considerations

Implementation considerations

Monitoring and evaluation

Research priorities

The panel suggested future research:

- **A clinical trial on managing patients with postpartum hemorrhage;**
- **Basic science research on understanding Fibrinolysis in women during the post-partum period;**
- **Research on the utility of tranexamic acid in women with type 1 VWD or low VWF level during the postpartum period is required to determine how significant a benefit is derived from treatment with tranexamic acid;**
- **Research on the efficacy of TXA in the prevention and treatment of PPH in women with VWD, including the optimal duration of therapy.**

Table 3: Evidence profile. Tranexamic acid compared to no tranexamic acid for women with VWD in the postpartum period

Certainty assessment							Summary of findings				
							Study event rates (%)			Anticipated absolute effects	
№ of participants (studies) Follow-up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty of evidence	With no tranexamic acid	With Tranexamic acid	Relative effect (95% CI)	Risk with no tranexamic acid	Risk difference with Tranexamic acid
Severe primary postpartum hemorrhage (assessed with: Number of events/ deliveries)											
25 (1 observational study)[1]	extremely serious [a]	serious [b]	not serious	very serious [c]	none	⨁◯◯◯ VERY LOW	5/16 (31.3%)	1/9 (11.1%)	**RR 0.36** (0.05 to 2.59)	313 per 1,000	**200 fewer per 1,000** (from 297 fewer to 497 more)
Primary postpartum hemorrhage (assessed with: Number of events/ deliveries)											
25 (1 observational study)[1]	extremely serious [a]	serious [b]	not serious	very serious [c]	none	⨁◯◯◯ VERY LOW	7/16 (43.8%)	1/9 (11.1%)	**RR 0.25** (0.04 to 1.75)	438 per 1,000	**328 fewer per 1,000** (from 420 fewer to 328 more)
Secondary postpartum hemorrhage (assessed with: Number of events/ deliveries)											
87 (2 observational studies)[1 2]	extremely serious [a]	serious [b]	not serious	not serious	none	⨁◯◯◯ VERY LOW	16/42 (38.1%)	7/45 (15.6%)	**RR 0.42** (0.20 to 0.91)	381 per 1,000	**221 fewer per 1,000** (from 305 fewer to 34 fewer)
Blood transfusion (assessed with: Number of events/ deliveries)											
25 (1 observational study)[1]	extremely serious [a]	not serious	not serious	very serious [c]	none	⨁◯◯◯ VERY LOW	3/16 (18.8%)	0/9 (0.0%)	**RR 0.24** (0.01 to 4.23)	188 per 1,000	**143 fewer per 1,000** (from 186 fewer to 606 more)

Table 3: Evidence profile. Tranexamic acid compared to no tranexamic acid for women with VWD in the postpartum period

Certainty assessment							Summary of findings				
Vaginal hematoma (assessed with: Number of events/ deliveries)											
25 (1 observational study)[1]	extremely serious [a]	not serious	not serious	very serious [c]	none	⨁◯◯◯ VERY LOW	2/16 (12.5%)	0/9 (0.0%)	**RR 0.34** (0.02 to 6.39)	125 per 1,000	**82 fewer per 1,000** (from 123 fewer to 674 more)
Adverse events in mother- Thrombotic complications (assessed with: Number of events/ deliveries)											
36 (1 observational study)[2]	extremely serious [a]	not serious	not serious	serious [d]	none	⨁◯◯◯ VERY LOW		0/36 (0.0%)	-	-	-
Blood loss (assessed with: Median per group)											
25 (1 observational study)[1]	extremely serious [a]	serious [b]	not serious	serious [e]	none	⨁◯◯◯ VERY LOW	The median (range) blood loss after deliveries in people who received TxA was 400 (270 to 1470) ml, and it was 425 (200 to 6000) in people who did not receive TxA				
Major bleeding - not reported											
-	-	-	-	-	-	-	-	-	-	-	-
Need for other medical procedures - not reported											
-	-	-	-	-	-	-	-	-	-	-	-
Mortality - not reported											
-	-	-	-	-	-	-	-	-	-	-	-

CI: Confidence interval; **RR:** Risk ratio

Explanations

a. No adjustment for any potential confounder
b. The panel raised applicability concerns regarding the method for outcome measurement.

c. Very small number of patients and events, the CI suggests appreciable benefit in one extreme and appreciable harm in the other
d. No events for this outcome
e. Very small number of patients

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Appendix

Figure 1: Risk of bias assessment

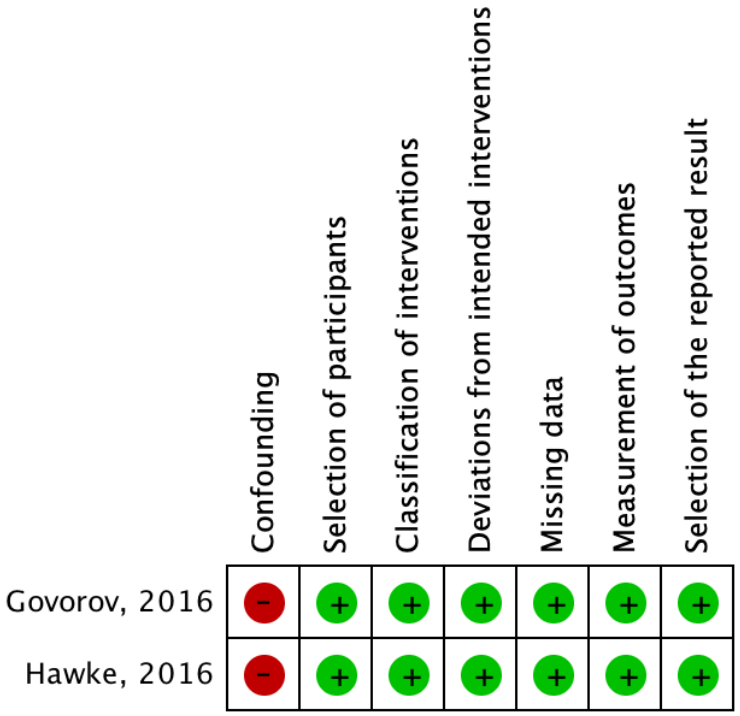

Figure 2: Forest plot analysis secondary postpartum hemorrhage