

Searches Strategy for VWD Diagnosis guidelines

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We will combine these search terms to construct search strategies using **operators like AND and OR**.

We will use OR to combine the terms within each concept (e.g. Patients with VWD, bleeding assessment tools, VWF activity assays identified with a light grey shade in Table 1), to make sure we capture all the relevant articles to that specific concept, regardless of how the researchers labeled it. For example, when searching for articles about desmopressin trials, the search string will be “Deamino Arginine Vasopressin or desmopressin or DDAVP”.

We will use AND to combine different concepts, to make sure to capture articles that are addressing the questions of interest. For example, for the question regarding bleeding assessment tools, we will combine the concepts “patients with VWD AND intervention bleeding assessment tools”.

For some questions, the search will have both operators. For example, for the question regarding Patients with suspected Type 2A, 2B or 2M in need of additional testing, the strategy will combine patients with VWD AND (intervention VWF multimer testing) OR (intervention Collagen binding testing). Table 2 shows details of this.

We will also use other strategies for some concepts, such as **proximity of words**. For example, for patients with VWD, we will also search for abstracts that have the terms “Von Willebrand” close to the terms “disease OR disorder”.

In addition, we will use **truncations and wild cards**- which are illustrated in the table. A truncation searches for all terms that are the same to the one specified up to the truncation. For example, searching for “bleed*” and truncating it will search for bleed, bleeding, bleeder, etc.

Finally, we will use **study design filters** to only capture randomized clinical trials and any type of observational studies comparing at least 2 of the options of interest, in addition to a filter to only capture articles related to diagnosis.

We will not limit the search by outcomes measured in the studies, date, or language of publication.

Table 1: Search terms used for each of the concepts

Term	It also includes
Patients with VWD	
Von Willebrand Disease	
Von Willebrand Disorder	
VWD	
Intervention: Bleeding assessment tools	
Bleeding assessment tools	
Bleeding score	
Screening tool	
questionnaire	
Interview	
Intervention: VWF activity assays	
Von Willebrand Factor	
VWF	
Ristocetin cofactor	VWF:RCo
VWF:G1b	VWF:G1bM VWF:GP1bR
Assay	
Glycoprotein 1b	
Glycoprotein Ib	
Intervention: Diagnosis exclusion	
Phenotype	
Evolving	
Aging	
Intervention: VWF propeptide trial	
VWF Propeptide	
VWFpp	
Intervention: Desmopressin trial	
Desmopressin trial	
Desmopressin challenge	
DDVAP	
Deamino Arginine Vasopressin	
Intervention: VWF multimer testing	
multimer	
Intervention: Collagen binding testing	
Collagen binding	
VWF:CB	
Intervention: Ristocetin induced platelet binding(RIPA) testing	
Ristocetin induced platelet binding	
RIPA	
PT-VWD	
Intervention: Genetic testing	
Genetic test	Genetic Assay Genetic Screen Genetic Assessment
Mutation	
Variant	
Genotype	
Gene	

Inheritance	
Intervention: VWF:FVIII binding	
VWF:FVIII binding	
VWF:FVIII B binding	
Factor 8 binding	

Table 2: Concepts used for each question

Question	Concepts
BAT in patients suspected of VWD	patients with VWD AND Intervention Bleeding assessment tools
Patients suspected of VWD with negative BAT	patients with VWD AND intervention Bleeding assessment tools
Essays in patients with suspected VWD	patients with VWD AND intervention VWF activity assays
Patients with a historic diagnosis of VWD but who now have normal VWF levels	patients with VWD AND intervention Diagnosis exclusion
Patients with abnormal initial screen of VWF:Ag, VWF:RCo, and suspected Type 1 VWD cut-off values	patients with VWD AND intervention VWF activity assays
Propeptide levels and desmopressin trials in patients suspected of Type 1 VWD	patients with VWD AND (intervention VWF propeptide trial) OR (intervention Desmopressin trial)
Patients with abnormal initial screen of VWF:Ag, VWF:RCo and a low RCo:Ag ratio	patients with VWD AND intervention VWF activity assays
Patients with suspected Type 2A, 2B or 2M in need of additional testing	patients with VWD AND (intervention VWF multimer testing) OR (intervention Collagen binding testing)
Patients suspected to have Type 2B VWD	patients with VWD AND (intervention Ristocetin induced platelet binding) OR (intervention Genetic testing)
Patients suspected to have Type 2N in need of additional testing	patients with VWD AND (intervention VWF:FVIII binding) OR (intervention Genetic testing)

Example of search strategy: Bleeding assessment tools in patients suspected of VWD.

1. exp von Willebrand Diseases/ or VWD.mp. or (von willebrand adj4 (disease or disorder)).mp.
2. (bleeding assess* tool* or bleed* score or screen* tool* or questionnaire* or interview).mp.
3. (bleed* adj4 (assess* or screen* or tool*)).mp.a
4. 2 or 3
5. 1 and 4

*The search strategy contains the following, which were not described above: “exp term /”, searches for all the terms indexed under the term (for example, exploding the term “Von Willebrand Diseases” searches also for VWD type 1, type 2, type 3 etc; “mp.”, searches for the term in multiples fields, including title, abstract, keywords, etc; “adj4”, is the tool to search for terms close to one another (in line 1, we searched for von willebrand term within 4 words of any of the 2 second terms (disease or disorder).

PICO 1: In Patients with suspected VWD - Using a bleeding assessment tool (any tool) to screen for VWD VS Non-standardized clinical assessment (not using a bleeding assessment tool)

Database(s): OVID Medline Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) 1946 to Present

Search Strategy:

#	Searches	Results
1	exp von Willebrand Diseases/ or VWD.mp. or (von willebrand adj4 (disease or disorder)).mp.	6470
2	(bleeding assess* tool* or bleed* score or screen* tool* or questionnaire* or interview).mp.	784636
3	(bleed* adj4 (assess* or screen* or tool*)).mp.	2740
4	2 or 3	787072
5	1 and 4	314

Database(s): **Embase** 1974 to 2018 December 13

Search Strategy:

#	Searches	Results
1	exp von Willebrand Disease/ or VWD.mp. or (von willebrand adj4 (disease or disorder)).mp.	10275
2	(bleeding assess* tool* or bleed* score or screen* tool* or questionnaire* or interview).mp.	1094952
3	(bleed* adj4 (assess* or screen* or tool*)).mp.	5047
4	2 or 3	1099275
5	1 and 4	853

PICO 2: Patients suspected of VWD with negative BAT (men and children) - Blood testing VS No blood testing

Database(s): OVID Medline Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) 1946 to Present

Search Strategy:

#	Searches	Results
1	exp von Willebrand Diseases/ or VWD.mp. or (von willebrand adj4 (disease or disorder)).mp.	6470
2	(bleeding assess* tool* or bleed* score or screen* tool* or questionnaire* or interview).mp.	784636
3	(bleed* adj4 (assess* or screen* or tool*)).mp.	2740
4	2 or 3	787072
5	(blood adj4 test*).mp.	67402
6	4 or 5	850438
7	1 and 6	913

Database(s): **Embase** 1974 to 2018 December 13

Search Strategy:

#	Searches	Results
1	exp von Willebrand Disease/ or VWD.mp. or (von willebrand adj4 (disease or disorder)).mp.	10275
2	(bleeding assess* tool* or bleed* score or screen* tool* or questionnaire* or interview).mp.	1094952
3	(bleed* adj4 (assess* or screen* or tool*)).mp.	5047
4	2 or 3	1099275
5	(blood adj4 test*).mp.	113728
6	4 or 5	1205027
7	1 and 6	1258

PICO 3: In Patients with suspected VWD - VWF:RCo (Automated and non-automated assays) VS Newer assays that reflect the platelet binding activity of VWF function (ie: VWF:G1bM, VWF:GP1bR).

Database(s): OVID Medline Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) 1946 to Present

Search Strategy:

#	Searches	Results
1	exp von Willebrand Diseases/ or VWD.mp. or (von willebrand adj4 (disease or disorder)).mp.	6470
2	exp von willebrand factor/ or VWF.mp. or ristocetin cofactor.mp. or GPIb*.mp. or glycoprotein 1b.mp. or glycoprotein Ib.mp. or assay*.mp. or activity.mp.	3448167
3	1 and 2	3376

Database(s): **Embase** 1974 to 2018 December 13

Search Strategy:

#	Searches	Results
1	exp von Willebrand Disease/ or VWD.mp. or (von willebrand adj4 (disease or disorder)).mp.	10275
2	exp von willebrand factor/ or (VWF or ristocetin cofactor or glycoprotein 1b or glycoprotein Ib or GPIb* or assay*).mp.	1602981
3	1 and 2	5758

PICO 4: Patients with a historic diagnosis of VWD but who now have normal VWF levels - Remove the diagnosis of VWD VS Reconsider another diagnosis

Database(s): OVID Medline Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) 1946 to Present

Search Strategy:

#	Searches	Results
1	exp von Willebrand Diseases/ or VWD.mp. or (von willebrand adj4 (disease or disorder)).mp.	6470
2	(Phenotype or evolving or aging).mp.	804294
3	1 and 2	461

Database(s): **Embase** 1974 to 2018 December 13

Search Strategy:

#	Searches	Results
1	exp von Willebrand Disease/ or VWD.mp. or (von willebrand adj4 (disease or disorder)).mp.	10275
2	(Phenotype or evolving or aging).mp.	1189124
3	1 and 2	1034

Notes: Subgroup: Bleeding phenotype

PICO 5: Patients with abnormal initial screen of VWF:Ag, VWF:RCo, and suspected Type 1 VWD - Diagnosis of Type 1 VWD at VWF:Ag and/or VWF:RCo < 0.30 IU/mL VS Diagnosis of Type 1 VWD at VWF :Ag and/or VWF:RCo < the reference range of your lab which is usually 0.50 IU/mL

Database(s): OVID Medline Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) 1946 to Present

Search Strategy:

#	Searches	Results
1	exp von Willebrand Diseases/ or VWD.mp. or (von willebrand adj4 (disease or disorder)).mp.	6470
2	exp von willebrand factor/ or VWF.mp. or ristocetin cofactor.mp. or GPIb*.mp. or glycoprotein 1b.mp. or glycoprotein Ib.mp. or assay*.mp. or activity.mp.	3448167
3	1 and 2	3376

Database(s): **Embase** 1974 to 2018 December 13

Search Strategy:

#	Searches	Results
1	exp von Willebrand Disease/ or VWD.mp. or (von willebrand adj4 (disease or disorder)).mp.	10275
2	exp von willebrand factor/ or (VWF or ristocetin cofactor or glycoprotein 1b or glycoprotein Ib or GPIb* or assay*).mp.	1602981
3	1 and 2	5758

Notes: VWF:RCo means activity essays in general (ie: VWF:G1bM, VWF:GP1bR)

PICO 6: Patients suspected of Type 1 VWD – VWFpp VS Desmopressin trial with 1 and 4 hour bloodwork

Database(s): OVID Medline Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) 1946 to Present

Search Strategy:

#	Searches	Results
1	exp von Willebrand Diseases/ or VWD.mp. or (von willebrand adj4 (disease or disorder)).mp.	6470
2	(propeptide or VWFpp).mp.	5897
3	Deamino Arginine Vasopressin/ or desmopressin.mp. or DDAVP.mp.	5690
4	(challenge or trial).mp.	1383647
5	3 and 4	736
6	2 or 5	6625
7	1 and 6	182

Database(s): **Embase** 1974 to 2018 December 13

Search Strategy:

#	Searches	Results
1	exp von Willebrand Disease/ or VWD.mp. or (von willebrand adj4 (disease or disorder)).mp.	10275
2	(propeptide or VWFpp).mp.	7864
3	"argipressin[1 deamino]"/ or desmopressin.mp. or DDAVP.mp.	13200
4	(challenge or trial).mp.	2282560
5	3 and 4	2119
6	2 or 5	9976
7	1 and 6	535

PICO 7: Patients with abnormal initial screen of VWF:Ag, VWF:RCo and a low RCo:Ag ratio - RCo:Ag <0.5 VS Other cut-offs (ie: 0.6 or 0.7)

Database(s): OVID Medline Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) 1946 to Present

Search Strategy:

#	Searches	Results
1	exp von Willebrand Diseases/ or VWD.mp. or (von willebrand adj4 (disease or disorder)).mp.	6470
2	exp von willebrand factor/ or VWF.mp. or ristocetin cofactor.mp. or GPIb*.mp. or glycoprotein 1b.mp. or glycoprotein Ib.mp. or assay*.mp. or activity.mp.	3448167
3	1 and 2	3376

Database(s): **Embase** 1974 to 2018 December 13

Search Strategy:

#	Searches	Results
1	exp von Willebrand Disease/ or VWD.mp. or (von willebrand adj4 (disease or disorder)).mp.	10275
2	exp von willebrand factor/ or (VWF or ristocetin cofactor or glycoprotein 1b or glycoprotein Ib or GPIb* or assay*).mp.	1602981
3	1 and 2	5758

Notes: VWF:RCo means activity essays in general (ie: VWF:G1bM, VWF:GP1bR)

PICO 8: Patients with suspected Type 2A, 2B or 2M in need of additional testing - VWF multimer analysis VS VWF:CB

Database(s): OVID Medline Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) 1946 to Present

Search Strategy:

#	Searches	Results
1	exp von Willebrand Diseases/ or VWD.mp. or (von willebrand adj4 (disease or disorder)).mp.	6470
2	(multimer or Collagen binding or VWF:CB).mp.	3926
3	1 and 2	477

Database(s): **Embase** 1974 to 2018 December 13

Search Strategy:

#	Searches	Results
1	exp von Willebrand Disease/ or VWD.mp. or (von willebrand adj4 (disease or disorder)).mp.	10275
2	(multimer or Collagen binding or VWF:CB).mp.	5457
3	1 and 2	941

PICO 9: Patients suspected to have Type 2B VWD - Ristocetin induced platelet binding(RIPA) VS Genetic testing (mutation analysis)

Database(s): OVID Medline Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) 1946 to Present

Search Strategy:

#	Searches	Results
1	exp von Willebrand Diseases/ or VWD.mp. or (von willebrand adj4 (disease or disorder)).mp.	6470
2	(ripa or ristocetin induced platelet binding or PT-VWD).mp.	501
3	((genetic or mutation or variant or genotype or gene or inheritance) adj4 (test* or assay* or screen* or assess*)).mp.	163485
4	2 or 3	163976
5	1 and 4	275

Database(s): **Embase** 1974 to 2018 December 13

Search Strategy:

#	Searches	Results
1	exp von Willebrand Disease/ or VWD.mp. or (von willebrand adj4 (disease or disorder)).mp.	10275
2	(ripa or ristocetin induced platelet binding or PT-VWD).mp.	873
3	((genetic or mutation or variant or genotype or gene or inheritance) adj4 (test* or assay* or screen* or assess*)).mp.	206516
4	2 or 3	207360
5	1 and 4	517

PICO 10: Patients suspected to have Type 2N in need of additional testing - VWF:FVIII binding VS Genetic testing.

Database(s): OVID Medline Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) 1946 to Present

Search Strategy:

#	Searches	Results
1	exp von Willebrand Diseases/ or VWD.mp. or (von willebrand adj4 (disease or disorder)).mp.	6470
2	((factor VIII or VWF:FVIII or factor 8) adj4 binding).mp.	323
3	((genetic or mutation or variant or genotype or gene or inheritance) adj4 (test* or assay* or screen* or assess*)).mp.	163485
4	2 or 3	163802
5	1 and 4	253

Database(s): **Embase** 1974 to 2018 December 13

Search Strategy:

#	Searches	Results
1	exp von Willebrand Disease/ or VWD.mp. or (von willebrand adj4 (disease or disorder)).mp.	10275
2	((factor VIII or VWF:FVIII or factor 8) adj4 binding).mp.	426
3	((genetic or mutation or variant or genotype or gene or inheritance) adj4 (test* or assay* or screen* or assess*)).mp.	206516
4	2 or 3	206925
5	1 and 4	436

Study Design Filters

Database(s): OVID Medline Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) 1946 to Present

Search Strategy:

#	Searches	Results
29	limit 28 to human	3276
30	(randomized controlled trial or controlled clinical trial).pt. or (randomized or placebo).ab. or drug therapy.fs. or (randomly or trial or groups).ab.	4337050
31	epidemiologic studies/ or exp case control studies/ or exp cohort studies/ or Cross-sectional studies/	2225583
32	case control.tw.	111970
33	(cohort adj (study or studies)).tw.	166398
34	cohort analy\$.tw.	6624
35	(Follow up adj (study or studies)).tw.	46061
36	(Observational adj (study or studies)).tw.	87158
37	(longitudinal or retrospective or cross sectional).tw.	921384
38	or/31-36	2366260
39	(registr* or database).mp.	468967
40	(sensitiv: or diagnos:).mp. or di.fs.	5730164
41	30 or 38 or 39 or 40	10134762
42	29 and 41	1939

Database(s): **Embase** 1974 to 2018 December 13

Search Strategy:

#	Searches	Results
29	limit 28 to human	5475
30	di.fs. or predict:.tw. or specificity.tw.	4873662
31	random*.ab. or random*.ti. or (clinical adj trial*).hw,ab,ti. or exp 'health care quality'/	4680717
32	exp disease course/ or risk:.mp. or diagnos:.mp. or follow-up.mp. or ep.fs. or outcome.tw.	11189515
33	30 or 31 or 32	14073954
34	29 and 33	3781

Decisions about PICO question 3

- For the VWD Diagnosis Panel PICO questions, we will focus one question on the platelet-dependent function of VWF. In this question, the VWF:RCO is compared to newer assays such as VWF:G1bM. We did not include the VWF:CB assay in this question as the collagen binding activity of VWF is quite different than its ability to bind platelets and we do not believe one should substitute for the other. Clinically, the bleeding phenotype is more impacted by VWF-platelet dependent function as patients with only collagen binding defects generally have milder symptoms. Recognizing that many labs are offering VWF:CB, we included it where we felt it fit best, in the PICO question about the VWF multimer assay as these two assays are generally congruent in what they are measuring.