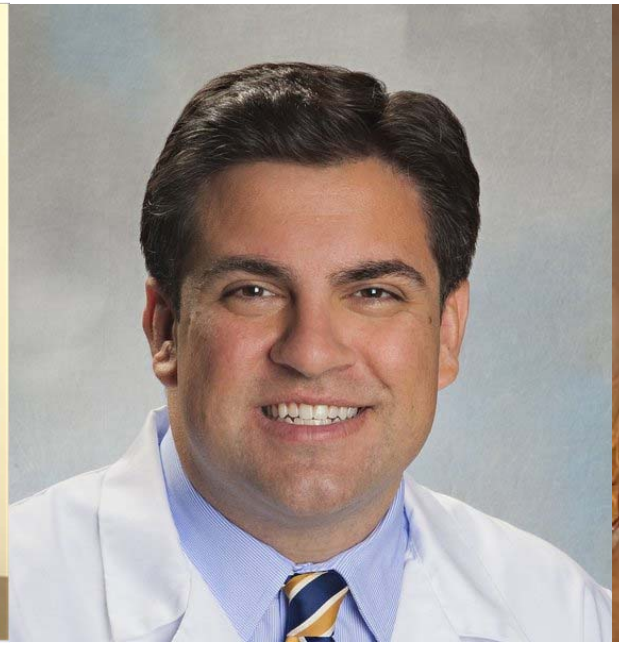
ASH ISTH NHF WFH 2021 Guidelines on the Diagnosis and Management of VWD

JOINT GUIDELINES ON THE DIAGNOSIS AND MANAGEMENT OF VWD

Joint Guidelines on the Diagnosis and Management of VWD



Jean Grow, PhD
Marquette University
(Emeritus)
GROW

Nathan T. Connell, MD, MPH
Brigham and Women's
Hospital Harvard University

Angela Weyand, MD
University of Michigan
Hospitals & Health
Center

ASH ISTH NHF WFH 2021 Guidelines on the Diagnosis and Management of VWD

CLINICAL GUIDELINES

blood advances

ASH ISTH NHF WFH 2021 guidelines on the diagnosis of von Willebrand disease

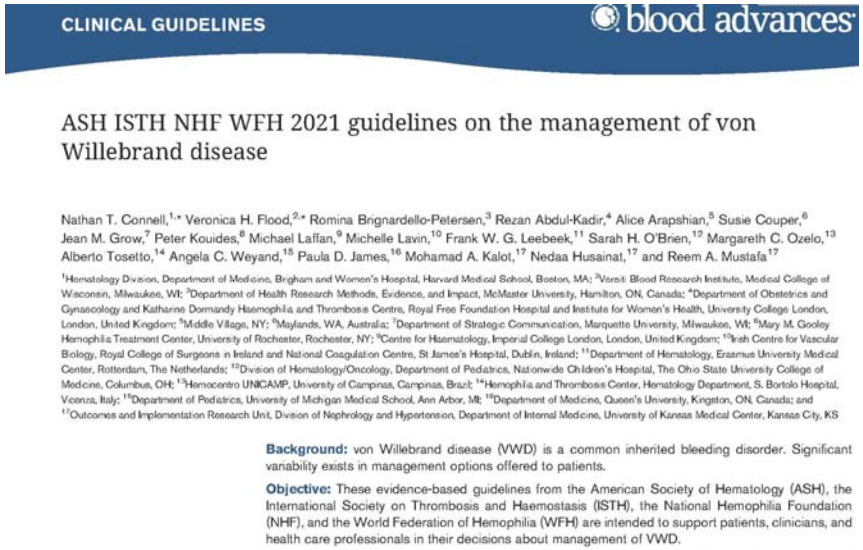
Paula D. James,[1] Nathan T. Connell,[2] Barbara Ameer,[3,4] Jorge Di Paola,[5] Jeroen Eikenboom,[6] Nicolas Giraud,[7] Sandra Haberichter,[8] Vicki Jacobs-Pratt,[9] Barbara Konkle,[10,11] Claire McLintock,[12] Simon McRae,[13] Robert R. Montgomery,[14] James S. O'Donnell,[15] Nikole Scappe,[16] Robert Sidonio Jr,[17] Veronica H. Flood,[14,18] Nedaa Husainat,[19] Mohamad A. Kalot,[19] and Reem A. Mustafa[19]

[1]Department of Medicine, Queen's University, Kingston, ON, Canada; [2]Brigham and Women's Hospital, Harvard Medical School, Boston, MA; [3]Pharmacology Consulting, Princeton Junction, NJ; [4]Rutgers–Robert Wood Johnson Medical School, New Brunswick, NJ; [5]Department of Pediatrics, Washington University in St. Louis, St. Louis, MO; [6]Division of Thrombosis and Hemostasis, Department of Internal Medicine, Leiden University Medical Center, Leiden, The Netherlands; [7]Marseille, France; [8]Diagnostic Laboratories, Versiti Blood Research Institute, Milwaukee, WI; [9]Auburn, ME; [10]Bloodworks Northwest, Seattle, WA; [11]Division of Hematology, University of Washington, Seattle, WA; [12]National Women's Health, Auckland City Hospital, Auckland, New Zealand; [13]Northern Cancer Service, Launceston General Hospital, Launceston, TAS, Australia; [14]Versiti Blood Research Institute, Milwaukee, WI; [15]Irish Centre for Vascular Biology, Royal College of Surgeons in Ireland, Dublin, Ireland; [16]Coraopolis, PA; [17]Aflac Cancer and Blood Disorders, Children's Healthcare of Atlanta, Emory University, Atlanta, GA; [18]Department of Pediatrics, Medical College of Wisconsin, Milwaukee, WI; and [19]Outcomes and Implementation Research Unit, Division of Nephrology and Hypertension, Department of Internal Medicine, University of Kansas Medical Center, Kansas City, KS

Background: von Willebrand disease (VWD) is the most common inherited bleeding disorder known in humans. Accurate and timely diagnosis presents numerous challenges.

Objective: These evidence-based guidelines of the American Society of Hematology (ASH), the International Society on Thrombosis and Haemostasis (ISTH), the National Hemophilia Foundation (NHF), and the World Federation of Hemophilia (WFH) are intended to support patients, clinicians, and other health care professionals in their decisions about VWD diagnosis.

www.bloodadvances.com



CLINICAL GUIDELINES

blood advances

ASH ISTH NHF WFH 2021 guidelines on the management of von Willebrand disease

Nathan T. Connell,[1,*] Veronica H. Flood,[2,*] Romina Brignardello-Petersen,[3] Rezan Abdul-Kadir,[4] Alice Arapshian,[5] Susie Couper,[6] Jean M. Grow,[7] Peter Kouides,[8] Michael Laffan,[9] Michelle Lavin,[10] Frank W. G. Leebeek,[11] Sarah H. O'Brien,[12] Margareth C. Ozelo,[13] Alberto Tosetto,[14] Angela C. Weyand,[15] Paula D. James,[16] Mohamad A. Kalot,[17] Nedaa Husainat,[17] and Reem A. Mustafa[17]

[1]Hematology Division, Department of Medicine, Brigham and Women's Hospital, Harvard Medical School, Boston, MA; [2]Versiti Blood Research Institute, Medical College of Wisconsin, Milwaukee, WI; [3]Department of Health Research Methods, Evidence, and Impact, McMaster University, Hamilton, ON, Canada; [4]Department of Obstetrics and Gynaecology and Katharine Dormandy Haemophilia and Thrombosis Centre, Royal Free Foundation Hospital and Institute for Women's Health, University College London, London, United Kingdom; [5]Middle Village, NY; [6]Maylands, WA, Australia; [7]Department of Strategic Communication, Marquette University, Milwaukee, WI; [8]Mary M. Gooley Hemophilia Treatment Center, University of Rochester, Rochester, NY; [9]Centre for Haematology, Imperial College London, London, United Kingdom; [10]Irish Centre for Vascular Biology, Royal College of Surgeons in Ireland and National Coagulation Centre, St James's Hospital, Dublin, Ireland; [11]Department of Hematology, Erasmus University Medical Center, Rotterdam, The Netherlands; [12]Division of Hematology/Oncology, Department of Pediatrics, Nationwide Children's Hospital, The Ohio State University College of Medicine, Columbus, OH; [13]Hemocentro UNICAMP, University of Campinas, Campinas, Brazil; [14]Hemophilia and Thrombosis Center, Hematology Department, S. Bortolo Hospital, Vicenza, Italy; [15]Department of Pediatrics, University of Michigan Medical School, Ann Arbor, MI; [16]Department of Medicine, Queen's University, Kingston, ON, Canada; and [17]Outcomes and Implementation Research Unit, Division of Nephrology and Hypertension, Department of Internal Medicine, University of Kansas Medical Center, Kansas City, KS

Background: von Willebrand disease (VWD) is a common inherited bleeding disorder. Significant variability exists in management options offered to patients.

Objective: These evidence-based guidelines from the American Society of Hematology (ASH), the International Society on Thrombosis and Haemostasis (ISTH), the National Hemophilia Foundation (NHF), and the World Federation of Hemophilia (WFH) are intended to support patients, clinicians, and health care professionals in their decisions about management of VWD.

AMERICAN SOCIETY OF HEMATOLOGY

ISTH International Society on Thrombosis and Haemostasis

NATIONAL HEMOPHILIA FOUNDATION *for all bleeding disorders*

WFH WORLD FEDERATION OF HEMOPHILIA FÉDÉRATION MONDIALE DE L'HÉMOPHILIE FEDERACIÓN MUNDIAL DE HEMOFILIA

HOUSEKEEPING

- Upon joining the webinar, you will see two audio options. You can opt to listen via the speakers on your computer OR by using your phone to call in. If the phone option is chosen, the webinar toolbar will provide you with the phone and access number and audio pin.
- All audio will be muted. At the end of the presentation there will be time for questions. To submit a written question, please use the “Questions” area of your toolbar. The presenters will respond to as many questions as time allows.
- Today’s webinar will last approximately 1 hour. Please note that this webinar will be recorded.

POLLING

- We will begin today's webinar first with two brief audience polls.
- First, we are interested in knowing more about you.
- Please select your response to the poll question now.

ASH ISTH NHF WFH 2021 Guidelines on the Diagnosis and Management of VWD

CLINCALGUIDELINES AND PEOPLE WITH VWD

Jean Grow, PhD

Professor of Advertising, Emeritus
Former Co-Director of the Institute for Women's Leadership
Marquette University Milwaukee, Wisconsin

Founder, GROW - a DEI consultancy
Milwaukee, Wisconsin

ASH ISTH NHF WFH VWD Management Guidelines panelist

DISCLOSURES FOR JEAN GROW, PHD

No financial disclosures related to this talk

ASH ISTH NHF WFH 2021 Guidelines on the Diagnosis and Management of VWD

CLINICAL GUIDELINES

blood advances

ASH ISTH NHF WFH 2021 guidelines on the diagnosis of von Willebrand disease

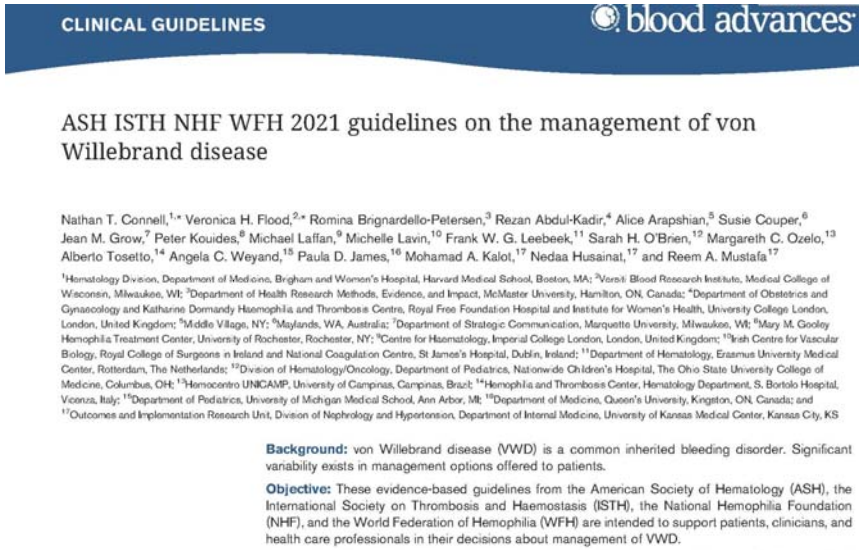
Paula D. James,[1] Nathan T. Connell,[2] Barbara Ameer,[3,4] Jorge Di Paola,[5] Jeroen Eikenboom,[6] Nicolas Giraud,[7] Sandra Haberichter,[8] Vicki Jacobs-Pratt,[9] Barbara Konkle,[10,11] Claire McLintock,[12] Simon McRae,[13] Robert R. Montgomery,[14] James S. O'Donnell,[15] Nikole Scappe,[16] Robert Sidonio Jr,[17] Veronica H. Flood,[14,18] Nedaa Husainat,[19] Mohamad A. Kalot,[19] and Reem A. Mustafa[19]

[1]Department of Medicine, Queen's University, Kingston, ON, Canada; [2]Brigham and Women's Hospital, Harvard Medical School, Boston, MA; [3]Pharmacology Consulting, Princeton Junction, NJ; [4]Rutgers–Robert Wood Johnson Medical School, New Brunswick, NJ; [5]Department of Pediatrics, Washington University in St. Louis, St. Louis, MO; [6]Division of Thrombosis and Hemostasis, Department of Internal Medicine, Leiden University Medical Center, Leiden, The Netherlands; [7]Marseille, France; [8]Diagnostic Laboratories, Versiti Blood Research Institute, Milwaukee, WI; [9]Auburn, ME; [10]Bloodworks Northwest, Seattle, WA; [11]Division of Hematology, University of Washington, Seattle, WA; [12]National Women's Health, Auckland City Hospital, Auckland, New Zealand; [13]Northern Cancer Service, Launceston General Hospital, Launceston, TAS, Australia; [14]Versiti Blood Research Institute, Milwaukee, WI; [15]Irish Centre for Vascular Biology, Royal College of Surgeons in Ireland, Dublin, Ireland; [16]Coraopolis, PA; [17]Aflac Cancer and Blood Disorders, Children's Healthcare of Atlanta, Emory University, Atlanta, GA; [18]Department of Pediatrics, Medical College of Wisconsin, Milwaukee, WI; and [19]Outcomes and Implementation Research Unit, Division of Nephrology and Hypertension, Department of Internal Medicine, University of Kansas Medical Center, Kansas City, KS

Background: von Willebrand disease (VWD) is the most common inherited bleeding disorder known in humans. Accurate and timely diagnosis presents numerous challenges.

Objective: These evidence-based guidelines of the American Society of Hematology (ASH), the International Society on Thrombosis and Haemostasis (ISTH), the National Hemophilia Foundation (NHF), and the World Federation of Hemophilia (WFH) are intended to support patients, clinicians, and other health care professionals in their decisions about VWD diagnosis.

www.bloodadvances.com



CLINICAL GUIDELINES

blood advances

ASH ISTH NHF WFH 2021 guidelines on the management of von Willebrand disease

Nathan T. Connell,[1,*] Veronica H. Flood,[2,*] Romina Brignardello-Petersen,[3] Rezan Abdul-Kadir,[4] Alice Arapshian,[5] Susie Couper,[6] Jean M. Grow,[7] Peter Kouides,[8] Michael Laffan,[9] Michelle Lavin,[10] Frank W. G. Leebeek,[11] Sarah H. O'Brien,[12] Margareth C. Ozelo,[13] Alberto Tosetto,[14] Angela C. Weyand,[15] Paula D. James,[16] Mohamad A. Kalot,[17] Nedaa Husainat,[17] and Reem A. Mustafa[17]

[1]Hematology Division, Department of Medicine, Brigham and Women's Hospital, Harvard Medical School, Boston, MA; [2]Versiti Blood Research Institute, Medical College of Wisconsin, Milwaukee, WI; [3]Department of Health Research Methods, Evidence, and Impact, McMaster University, Hamilton, ON, Canada; [4]Department of Obstetrics and Gynaecology and Katharine Dormandy Haemophilia and Thrombosis Centre, Royal Free Foundation Hospital and Institute for Women's Health, University College London, London, United Kingdom; [5]Middle Village, NY; [6]Maylands, WA, Australia; [7]Department of Strategic Communication, Marquette University, Milwaukee, WI; [8]Mary M. Gooley Hemophilia Treatment Center, University of Rochester, Rochester, NY; [9]Centre for Haematology, Imperial College London, London, United Kingdom; [10]Irish Centre for Vascular Biology, Royal College of Surgeons in Ireland and National Coagulation Centre, St James's Hospital, Dublin, Ireland; [11]Department of Hematology, Erasmus University Medical Center, Rotterdam, The Netherlands; [12]Division of Hematology/Oncology, Department of Pediatrics, Nationwide Children's Hospital, The Ohio State University College of Medicine, Columbus, OH; [13]Hemocentro UNICAMP, University of Campinas, Campinas, Brazil; [14]Hemophilia and Thrombosis Center, Hematology Department, S. Bortolo Hospital, Vicenza, Italy; [15]Department of Pediatrics, University of Michigan Medical School, Ann Arbor, MI; [16]Department of Medicine, Queen's University, Kingston, ON, Canada; and [17]Outcomes and Implementation Research Unit, Division of Nephrology and Hypertension, Department of Internal Medicine, University of Kansas Medical Center, Kansas City, KS

Background: von Willebrand disease (VWD) is a common inherited bleeding disorder. Significant variability exists in management options offered to patients.

Objective: These evidence-based guidelines from the American Society of Hematology (ASH), the International Society on Thrombosis and Haemostasis (ISTH), the National Hemophilia Foundation (NHF), and the World Federation of Hemophilia (WFH) are intended to support patients, clinicians, and health care professionals in their decisions about management of VWD.

AMERICAN SOCIETY OF HEMATOLOGY

ISTH International Society on Thrombosis and Haemostasis

NATIONAL HEMOPHILIA FOUNDATION *for all bleeding disorders*

WFH WORLD FEDERATION OF HEMOPHILIA FÉDÉRATION MONDIALE DE L'HÉMOPHILIE FEDERACIÓN MUNDIAL DE HEMOFILIA

VON WILLEBRAND DISEASE (VWD)

Most common inherited bleeding disorder:

- 1/1,000 to 1/10,000 people affected by symptomatic bleeding

Can cause unusual bleeding

- From small wounds or “minor” procedures
- Frequent nosebleeds and bruising
- Into joints

Inherited equally by men and women

Often impacts women disproportionally through

- Heavy or abnormal periods
- Post-partum bleeding

ASH ISTH NHF WFH 2021 Guidelines on the Diagnosis and Management of VWD
www.bloodadvances.com

NEED FOR VWD CLINICAL PRACTICE GUIDELINES

- Many patients go years without an accurate diagnosis, living with untreated bleeding
- Clinical complexity of VWD and absence of extensive evidence to guide decision making means that there is considerable variability in the clinical management of the disorder

Clinical practice guidelines are most needed in the context of inadequate awareness, variability in clinical practice, and a paucity of high-quality evidence in the published literature

HUMAN NEED FOR VWD GUIDELINES

- "Bruiser" the bleeder in a family of 7
- Age 5: nearly died from hemorrhage (sledding accident)
- 1974: "nonbleeding" tympanoplasty – post-operative diagnosis: VWD
- 3 generations contributed to many years of research (Dr Juan Chediak)
  - FDA approval of a plasma-derived FVIII/VWF
  - Spontaneous mutation
- Elective hysterectomy vs monthly hemorrhaging

HUMAN IMPACT OF INADEQUATE AWARENESS

Both children inherited VWD

- Son – largely unaffected

Daughter, experiences more symptoms

- Bruising – abuse concerns
  - Daycare provider, police
- 2019: miscarriage requiring dilation and curettage(D&C)
  - "No treatment required" – obstetrician+hematologist
  - Self-advocacy – cancelled procedure

Reached out to trusted hematologist
Faxed recommendation
Re-scheduled procedure with necessary medication

Critical need: increased awareness and understanding of VWD amongst <u>all</u> healthcare professionals and society as a whole

ASH ISTH NHF WFH 2021 Guidelines on the Diagnosis and Management of VWD
www.bloodadvances.com

ASH ISTH NHF WFH 2021 Guidelines on the Diagnosis and Management of VWD

CLINICAL GUIDELINES

blood advances

ASH ISTH NHF WFH 2021 guidelines on the diagnosis of von Willebrand disease

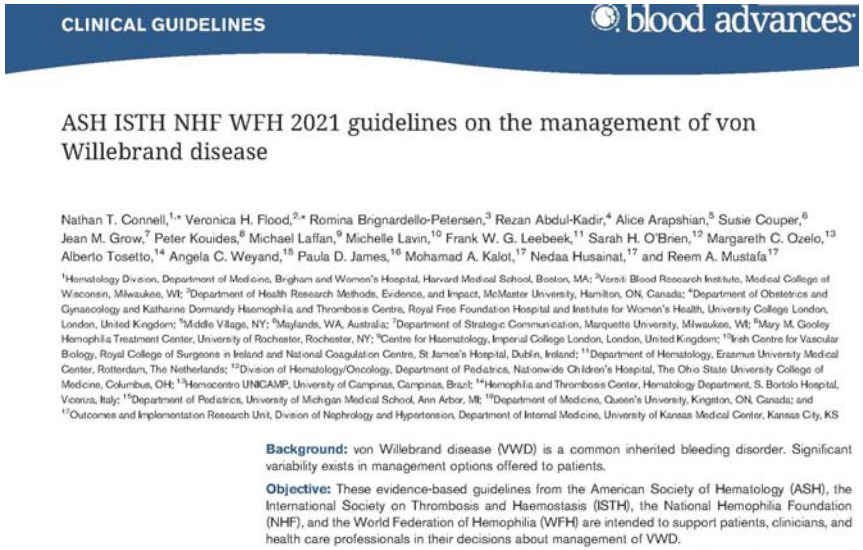
Paula D. James,[1] Nathan T. Connell,[2] Barbara Ameer,[3,4] Jorge Di Paola,[5] Jeroen Eikenboom,[6] Nicolas Giraud,[7] Sandra Haberichter,[8] Vicki Jacobs-Pratt,[9] Barbara Konkle,[10,11] Claire McLintock,[12] Simon McRae,[13] Robert R. Montgomery,[14] James S. O'Donnell,[15] Nikole Scappe,[16] Robert Sidonio Jr,[17] Veronica H. Flood,[14,18] Nedaa Husainat,[19] Mohamad A. Kalot,[19] and Reem A. Mustafa[19]

[1]Department of Medicine, Queen's University, Kingston, ON, Canada; [2]Brigham and Women's Hospital, Harvard Medical School, Boston, MA; [3]Pharmacology Consulting, Princeton Junction, NJ; [4]Rutgers–Robert Wood Johnson Medical School, New Brunswick, NJ; [5]Department of Pediatrics, Washington University in St. Louis, St. Louis, MO; [6]Division of Thrombosis and Hemostasis, Department of Internal Medicine, Leiden University Medical Center, Leiden, The Netherlands; [7]Marseille, France; [8]Diagnostic Laboratories, Versiti Blood Research Institute, Milwaukee, WI; [9]Auburn, ME; [10]Bloodworks Northwest, Seattle, WA; [11]Division of Hematology, University of Washington, Seattle, WA; [12]National Women's Health, Auckland City Hospital, Auckland, New Zealand; [13]Northern Cancer Service, Launceston General Hospital, Launceston, TAS, Australia; [14]Versiti Blood Research Institute, Milwaukee, WI; [15]Irish Centre for Vascular Biology, Royal College of Surgeons in Ireland, Dublin, Ireland; [16]Coraopolis, PA; [17]Aflac Cancer and Blood Disorders, Children's Healthcare of Atlanta, Emory University, Atlanta, GA; [18]Department of Pediatrics, Medical College of Wisconsin, Milwaukee, WI; and [19]Outcomes and Implementation Research Unit, Division of Nephrology and Hypertension, Department of Internal Medicine, University of Kansas Medical Center, Kansas City, KS

Background: von Willebrand disease (VWD) is the most common inherited bleeding disorder known in humans. Accurate and timely diagnosis presents numerous challenges.

Objective: These evidence-based guidelines of the American Society of Hematology (ASH), the International Society on Thrombosis and Haemostasis (ISTH), the National Hemophilia Foundation (NHF), and the World Federation of Hemophilia (WFH) are intended to support patients, clinicians, and other health care professionals in their decisions about VWD diagnosis.

www.bloodadvances.com



CLINICAL GUIDELINES

blood advances

ASH ISTH NHF WFH 2021 guidelines on the management of von Willebrand disease

Nathan T. Connell,[1,*] Veronica H. Flood,[2,*] Romina Brignardello-Petersen,[3] Rezan Abdul-Kadir,[4] Alice Arapshian,[5] Susie Couper,[6] Jean M. Grow,[7] Peter Kouides,[8] Michael Laffan,[9] Michelle Lavin,[10] Frank W. G. Leebeek,[11] Sarah H. O'Brien,[12] Margareth C. Ozelo,[13] Alberto Tosetto,[14] Angela C. Weyand,[15] Paula D. James,[16] Mohamad A. Kalot,[17] Nedaa Husainat,[17] and Reem A. Mustafa[17]

[1]Hematology Division, Department of Medicine, Brigham and Women's Hospital, Harvard Medical School, Boston, MA; [2]Versiti Blood Research Institute, Medical College of Wisconsin, Milwaukee, WI; [3]Department of Health Research Methods, Evidence, and Impact, McMaster University, Hamilton, ON, Canada; [4]Department of Obstetrics and Gynaecology and Katharine Dormandy Haemophilia and Thrombosis Centre, Royal Free Foundation Hospital and Institute for Women's Health, University College London, London, United Kingdom; [5]Middle Village, NY; [6]Maylands, WA, Australia; [7]Department of Strategic Communication, Marquette University, Milwaukee, WI; [8]Mary M. Gooley Hemophilia Treatment Center, University of Rochester, Rochester, NY; [9]Centre for Haematology, Imperial College London, London, United Kingdom; [10]Irish Centre for Vascular Biology, Royal College of Surgeons in Ireland and National Coagulation Centre, St James's Hospital, Dublin, Ireland; [11]Department of Hematology, Erasmus University Medical Center, Rotterdam, The Netherlands; [12]Division of Hematology/Oncology, Department of Pediatrics, Nationwide Children's Hospital, The Ohio State University College of Medicine, Columbus, OH; [13]Hemocentro UNICAMP, University of Campinas, Campinas, Brazil; [14]Hemophilia and Thrombosis Center, Hematology Department, S. Bortolo Hospital, Vicenza, Italy; [15]Department of Pediatrics, University of Michigan Medical School, Ann Arbor, MI; [16]Department of Medicine, Queen's University, Kingston, ON, Canada; and [17]Outcomes and Implementation Research Unit, Division of Nephrology and Hypertension, Department of Internal Medicine, University of Kansas Medical Center, Kansas City, KS

Background: von Willebrand disease (VWD) is a common inherited bleeding disorder. Significant variability exists in management options offered to patients.

Objective: These evidence-based guidelines from the American Society of Hematology (ASH), the International Society on Thrombosis and Haemostasis (ISTH), the National Hemophilia Foundation (NHF), and the World Federation of Hemophilia (WFH) are intended to support patients, clinicians, and health care professionals in their decisions about management of VWD.

AMERICAN SOCIETY OF HEMATOLOGY

ISTH International Society on Thrombosis and Haemostasis

NATIONAL HEMOPHILIA FOUNDATION *for all bleeding disorders*

WFH WORLD FEDERATION OF HEMOPHILIA FÉDÉRATION MONDIALE DE L'HÉMOPHILIE FEDERACIÓN MUNDIAL DE HEMOFILIA

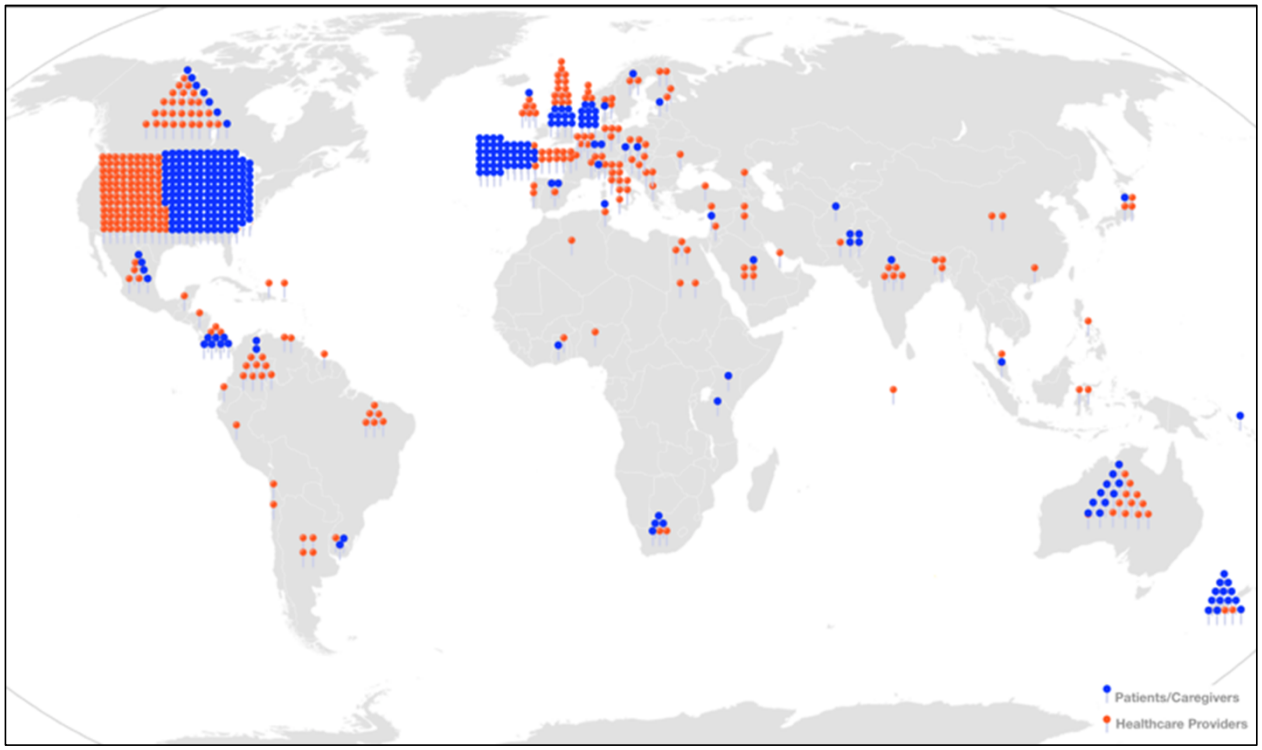
VWD PATIENT INTEGRATION IN DEVELOPMENT

- Initiative born out of patient and healthcare professional needs identification
- Strong organizational collaboration (ASH, ISTH, NHF, WFH)
- Panel composition – 25% patients as full voting members
- International stakeholder survey to inform guideline priorities
- Ranking and drafting guideline questions
- Identification of patient-important outcomes (PICOs)
- Targeted training and workshops to empower patient panelists
- Patient preferences sought throughout
- Patient-inclusive open comment period
- Patient involvement in education and dissemination

INTERNATIONAL SURVEY TO INFORM PRIORITIES

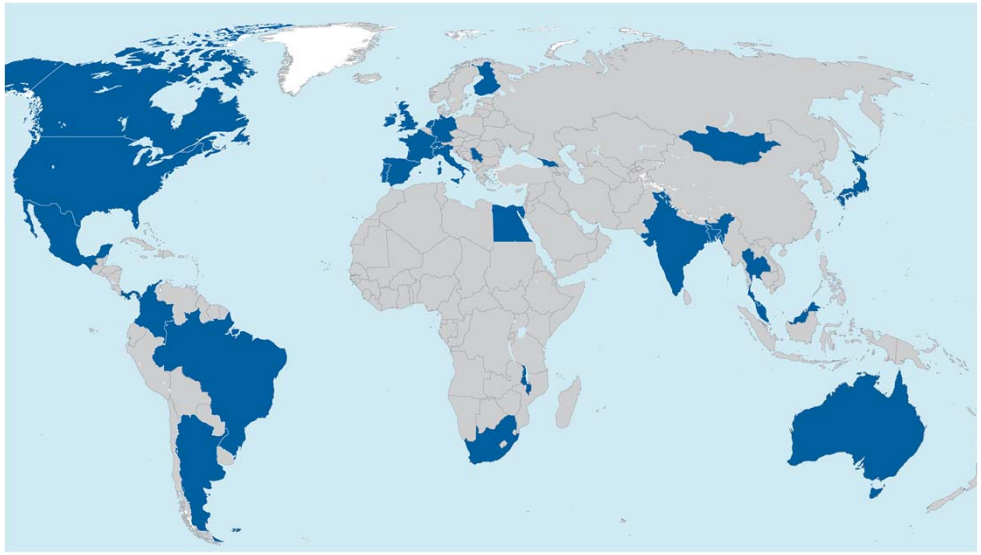
Participant Characteristics

- 71 countries
  6 continents
- 601 participants responses
  9,500 discrete comments
- 51% patients / caregivers
  49% healthcare providers
- 21% male
  54% female
  26% no gender identified
- 18% low / middle-income
  82% high-income countries
- 59% receive / provide care at HTC

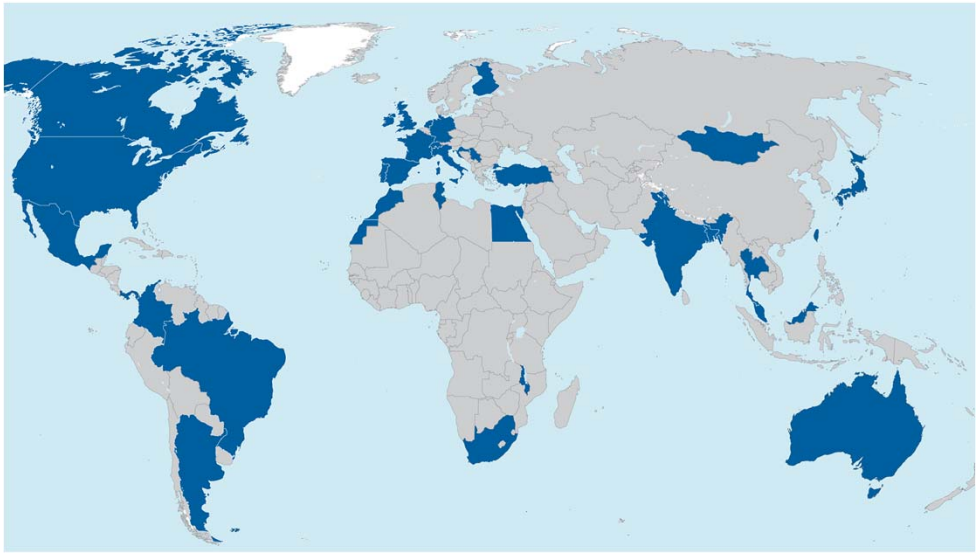


Kalot, MA, et al; An international survey to inform priorities for new guidelines on von Willebrand disease. *Haemophilia*. 2020; 26: 106– 116

PUBLIC COMMENT RESPONSE DISTRIBUTION



Diagnosis



Management

More than 100 people commented from 38 countries

~15% from patients!

ASH ISTH NHF WFH 2021 Guidelines on the Diagnosis and Management of VWD

www.bloodadvances.com

GUIDELINES WE CAN TRUST

Collaborative, inclusive, rigorous development process yielded guidelines that we can feel confident

- Are based on the best available evidence and patient, caregiver, and healthcare provider knowledge, attitudes, expectations moral and ethical values, and beliefs
- Take into consideration patient goals for life and health
- Will serve people with VWD and those who care for them well in the shared decision making and advocacy essential to improving the diagnosis and management of VWD

Guidelines 2.0 – CMAJ 2013

ASH ISTH NHF WFH 2021 Guidelines on the Diagnosis and Management of VWD

Nathan T Connell, MD, MPH

Assistant Professor of Medicine,
Harvard Medical School

Associate Physician, Hematology Division, Brigham and Women's Hospital

Boston, Massachusetts

ASH ISTH NHF WFH VWD Diagnosis and Management Guidelines Panels
Clinical Vice-Chair

DISCLOSURES FOR NATHAN CONNELL, MD, MPH

No financial disclosures related to this talk

GUIDELINE DEVELOPMENT PROCESS

VWD Guideline Collaboration Objectives

- Facilitate clinical decision-making regarding the diagnosis and management of von Willebrand disease to contribute to ***better health outcomes, quality of life, and health equity***
- Increase ***access*** to appropriate diagnostic testing and therapeutic options
- Identify ***research priorities***
- Guide healthcare providers, patients, payers, and other stakeholders as to ***priority focus areas*** in VWD

AMERICAN SOCIETY OF HEMATOLOGY ®

ISTH

NATIONAL HEMOPHILIA FOUNDATION
for all bleeding disorders

WFH
WORLD FEDERATION OF HEMOPHILIA
FÉDÉRATION MONDIALE DE L'HÉMOPHILIE
FEDERACIÓN MUNDIAL DE HEMOFILIA

KU MEDICAL CENTER
The University of Kansas

Guideline Development Process

CLINICAL QUESTIONS

10 to 20 **clinically-relevant questions** generated in **PICO format**

EVIDENCE SYNTHESIS

Evidence summary generated for each PICO question via systematic review

EVIDENCE TO DECISION

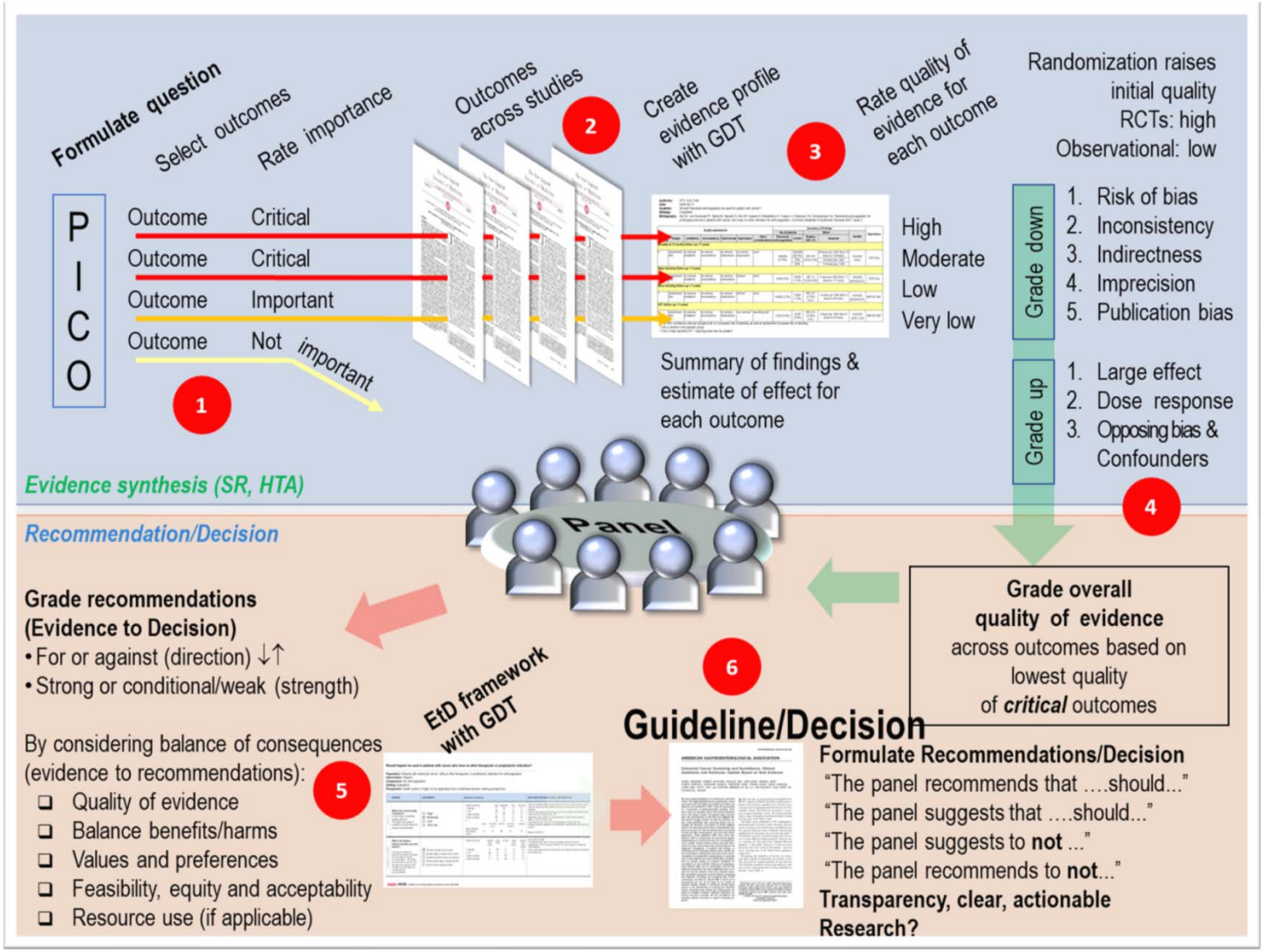
Evidence summaries incorporated into **Evidence to Decision (EtD) frameworks**:

- Resource use
- Feasibility
- Acceptability
- Equity
- Patient values and preferences

MAKING RECOMMENDATIONS

Recommendations made by guideline panel members based on EtD frameworks.

PICO: population, intervention, comparator, outcome



Slide Courtesy RA Mustafa

HOW PATIENTS AND CLINICIANS SHOULD USE THESE RECOMMENDATIONS

	STRONG Recommendation	CONDITIONAL Recommendation
For patients	Most individuals would want the intervention.	A majority would want the intervention, but many would not.
For clinicians	Most individuals should receive the intervention.	Different choices will be appropriate for different patients, depending on their values and preferences. Use shared decision making.
For policy makers	The recommendation can be adapted as a policy in most situations	There is a need for substantial debate and involvement of stakeholders

CONTEXT

Panels took the perspective of a **high-resource setting**

- Important to understand what might be the goal of optimal care
- Advocacy efforts and policy work
- Adolopment (adaptation, adoption, *de novo* development)

Patient panelists were full voting members

VWD DIAGNOSIS PANEL

Paula D. James
Nathan T. Connell
Barbara Ameer
Jorge Di Paola
Jeroen Eikenboom
Nicolas Giraud
Sandra Haberichter
Vicki Jacobs-Pratt
Barbara Konkle
Claire McLintock
Simon McRae
Robert R. Montgomery
James S. O'Donnell
Nikole Scappe
Robert Sidonio
Veronica H. Flood
Nedaa Husainat
Mohamad A. Kalot
Reem A. Mustafa

ASH ISTH NHF WFH 2021 Guidelines on the Diagnosis and Management of VWD
www.bloodadvances.com

Slide Courtesy RA Mustafa

VWD MANAGEMENT PANEL

Nathan T. Connell
Veronica H. Flood
Romina Brignardello-Petersen
Rezan Abdul-Kadir
Alice Arapshian
Susie Couper
Jean M. Grow
Peter Kouides
Michael Laffan
Michelle Lavin
Frank W. G. Leebeek
Sarah H. O'Brien
Margareth C. Ozelo
Alberto Tosetto
Angela C. Weyand
Paula D. James
Mohamad A. Kalot
Nedaa Husainat
Reem A. Mustafa

ASH ISTH NHF WFH 2021 Guidelines on the Diagnosis and Management of VWD
www.bloodadvances.com

Slide Courtesy RA Mustafa

METHODOLOGY TEAM

- Mohamad Kalot
- Nedaa Husainat
- Omar Abughanimeh
- Yazan Aljabiri
- Alec Britt
- Osama Diab
- Ahmad Dimassi
- Abdallah El-Alayli
- Hussein El-Khechen
- Bader Madoukh
- Shahrzad Motaghi
- John Roller
- Shaneela Shahid
- Sammy Tayiem
- Hani Turkmani
- Aref Qureini
- Romina Brignardello-Petersen
- Reem A. Mustafa

Slide Courtesy RA Mustafa

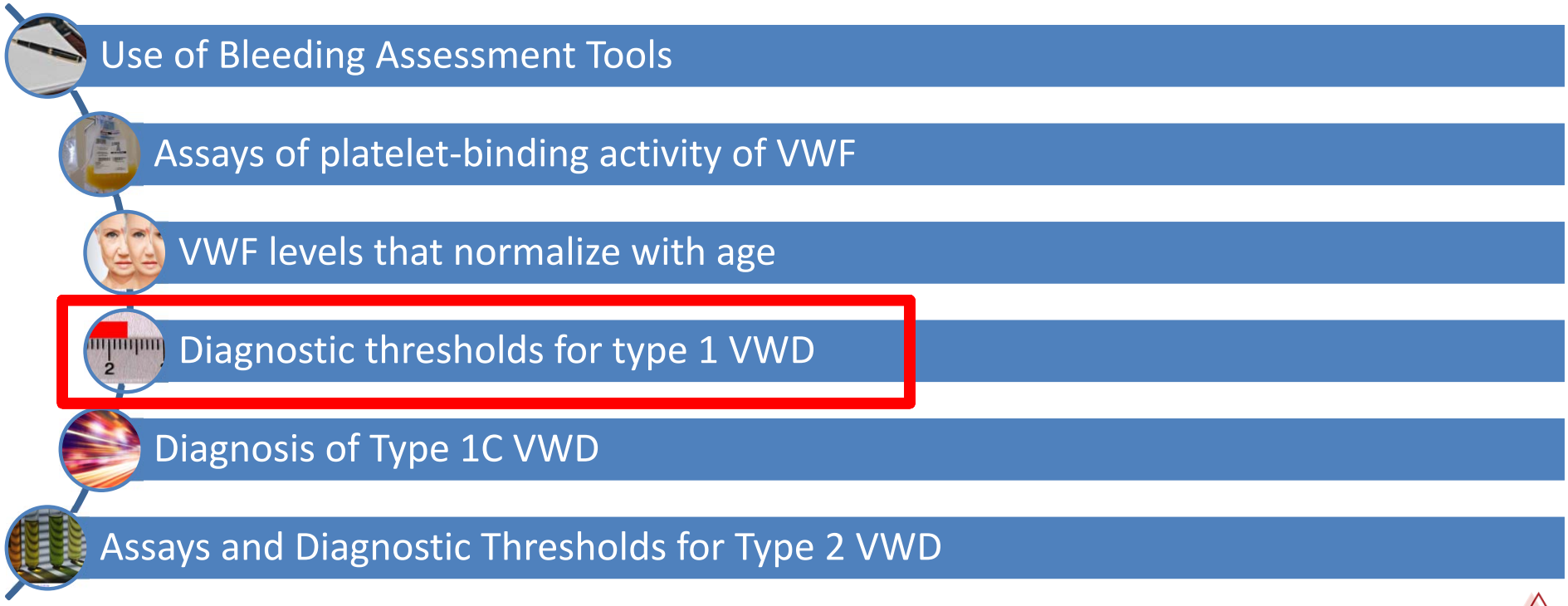
DIAGNOSIS OF VON WILLEBRAND DISEASE

ASH ISTH NHF WFH 2021 Guidelines on the Diagnosis and Management of VWD

www.bloodadvances.com

DIAGNOSIS OF VWD

James PD et al. Blood Adv. (2021)



ASH ISTH NHF WFH 2021 Guidelines on the Diagnosis and Management of VWD

www.bloodadvances.com

James PD et al. Blood Adv. (2021)

DIAGNOSIS: DIAGNOSTIC THRESHOLDS

For patients with an abnormal initial VWD screen (low VWF:Ag and/or platelet-dependent VWF activity) suspected of type 1 VWD, should the diagnostic cutoff be at VWF:Ag and/or VWF platelet-dependent activity <0.30 IU/mL or <0.50 IU/mL?

Recommendation 6. The panel *recommends* a VWF level of <0.30 IU/mL regardless of bleeding, and for patients with abnormal bleeding, a VWF level of <0.50 IU/mL to confirm the diagnosis of type 1 VWD

Strong recommendation based on low certainty in the evidence of effects ⊕⊕◯◯

Ag: antigen, IU: international unit

James PD et al. Blood Adv. (2021)

DIAGNOSIS: DIAGNOSTIC THRESHOLDS

Recommendation 6. The panel recommends a VWF level of <0.30 IU/mL regardless of bleeding, and for patients with abnormal bleeding, a VWF level of <0.50 IU/mL to confirm the diagnosis of type 1 VWD

Remarks:

- VWF level(s) refers to VWF:Ag and/or platelet-dependent VWF activity (eg, VWF:GPIbM).
- The lower limit of the normal range as determined by the local laboratory should be used if it is <0.50 IU/mL. ABO-specific reference ranges are not required.
- VWF is an acute-phase reactant that increases in response to a variety of stimuli (e.g., bleed, trauma, pregnancy). VWD diagnostic testing should be performed when patients are at a baseline state of health.

Ag: antigen, GPIbM: glycoprotein Ib mutant, IU: international unit

James PD et al. Blood Adv. (2021)

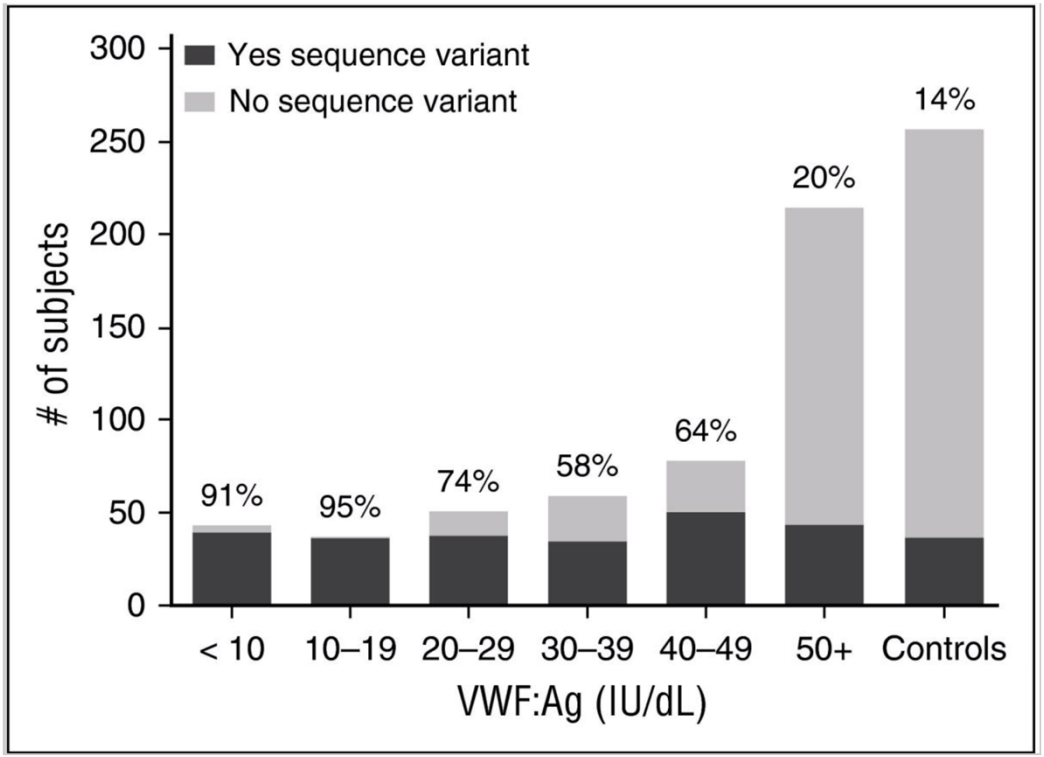
EVIDENCE TO DECISION (ETD)

Nine studies:

- 4 – mutation detection
- 2 – correlation between VWF levels and bleeding score
- 4 – likelihood ratios (2) & two odds ratios (2)
- 2 – prospective evaluation of patients (diagnostic accuracy)

Flood VH et al. Blood. (2016)

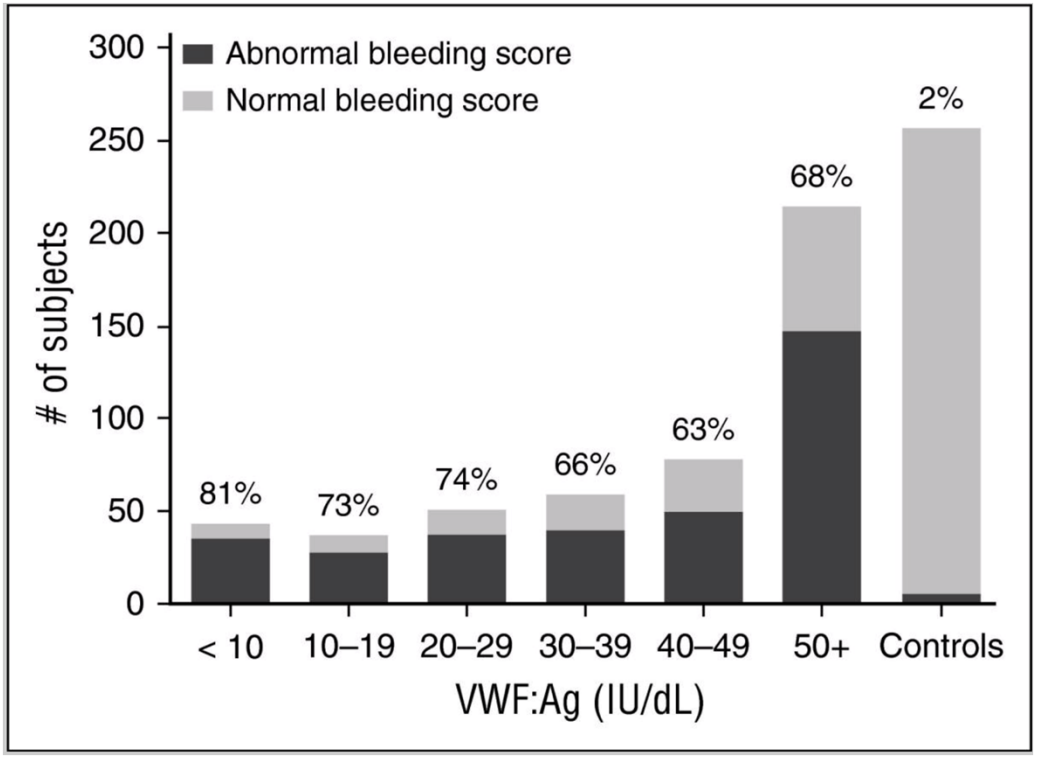
SEQUENCE VARIANT FREQUENCY



Ag: antigen, IU: international unit

Flood VH et al. Blood. (2016)

BLEEDING RATES AT VWF LEVELS



Ag: antigen, IU: international unit

LIKELIHOOD RATIOS

	VWF < 20	VWF 20 - 30	VWF 30 - 40	VWF 41 - 50	VWF 51 - 60
Bucciarelli 2015			∞	0.73	0.33
	VWF < 20	VWF 20 - 40		VWF 40 - 60	
Tosetto 2007	375	95		1.82	

High LR
Low LR

The panel considered setting cut-off at 40

James PD et al. Blood Adv. (2021)

KEY CONSIDERATIONS

The panel placed high value on:

- not missing the diagnosis, especially in those patients who bleed
- avoiding overdiagnosis in patients who do not bleed

Despite the low certainty in the evidence, the panel decided on a strong recommendation for 2 reasons:

- a high value was placed on an explicit diagnosis to ensure access to care for those with a bleeding phenotype, and
- to ensure international uniformity in diagnostic criteria and the avoidance of center-specific thresholds based on a conditional recommendation

James PD et al. Blood Adv. (2021)

OTHER KEY DIAGNOSTIC RECOMMENDATIONS

For patients with a low probability of VWD (e.g., seen in the primary care setting), the panel **recommends using a validated bleeding-assessment tool (BAT) as an initial screening test** to determine who needs specific blood testing over nonstandardized clinical assessment

- Strong recommendation based on moderate certainty in the evidence from diagnostic accuracy studies

  ⊕⊕⊕◯

The panel **suggests newer assays that measure the platelet-binding activity of VWF (eg, VWF:GPIbM, VWF:GPIbR) over the VWF ristocetin cofactor assay (VWF:RCo)** (automated or nonautomated assay) for the diagnosis of VWD

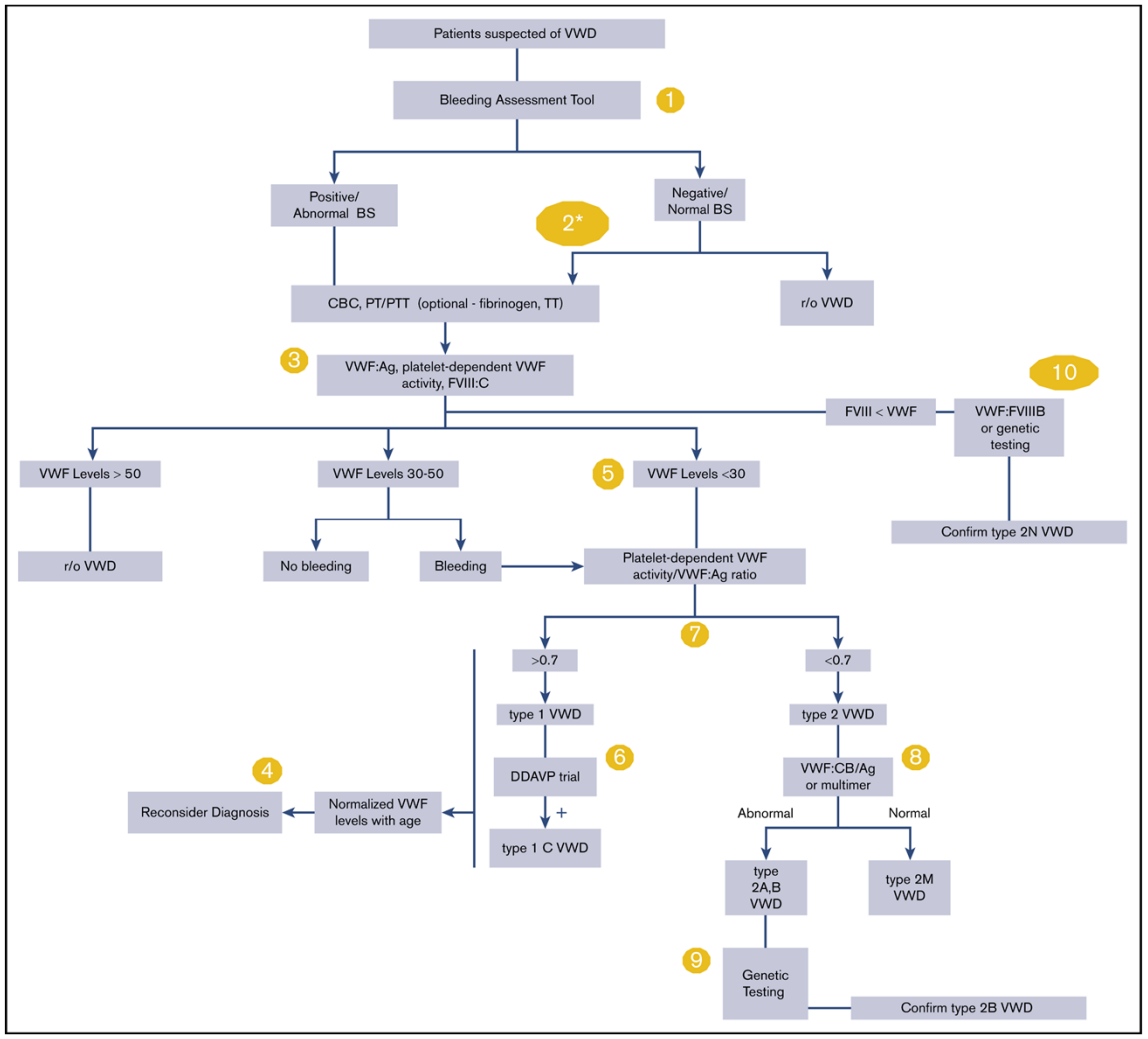
- Conditional recommendation based on low certainty in the evidence from diagnostic accuracy studies

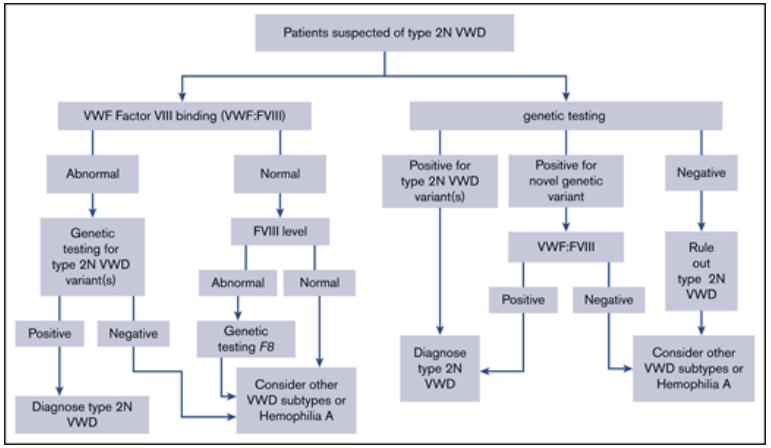
  ⊕⊕◯◯

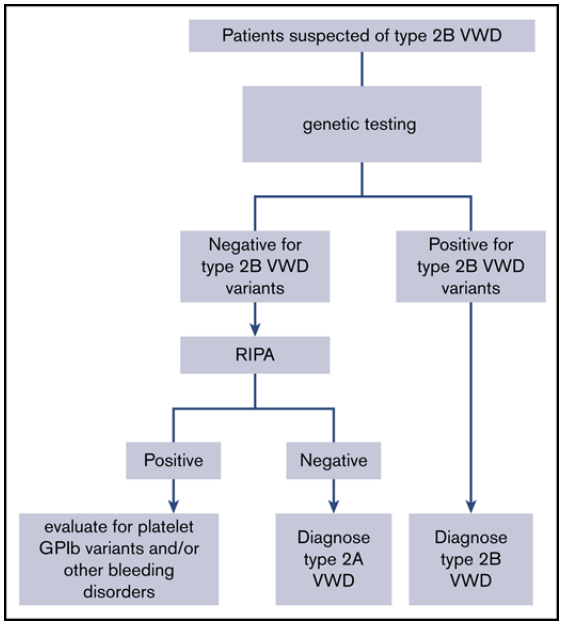
RESEARCH PRIORITIES

The panel identified the following research priorities:

- Detailed data for patients with VWF levels between 0.30 – 0.60 IU/mL, including:
  - Outcomes for bleeding with procedures
  - Prevalence of a concomitant bleeding disorder
- Correlation with bleeding symptoms and information about family members of patients with type 1 VWD







James PD et al. Blood Adv. (2021)

ASH ISTH NHF WFH 2021 Guidelines on the Diagnosis and Management of VWD

MANAGEMENT GUIDELINES

Angela Weyand, MD

Assistant Professor of Pediatric Hematology and Oncology
University of Michigan, Ann Arbor, Michigan

ASH ISTH NHF WFH VWD Management Guidelines panelist

DISCLOSURES FOR ANGELA WEYAND, MD

No relevant disclosures

MANAGEMENT: OVERVIEW

Connell NT and Flood VH et al. Blood Adv. (2021)

- Prophylaxis
- Desmopressin Challenge/Trial
- Antithrombotic Therapy
- Major and Minor Surgery
- Gynecology: Heavy Menstrual Bleeding
- Obstetrics: Neuraxial Anesthesia and Postpartum Management

Connell NT and Flood VH et al. Blood Adv. (2021)

MINOR SURGERIES

In patients with VWD undergoing minor surgery or minor invasive procedures, should the VWF level be increased to ≥0.50 IU/mL (with use of either VWF concentrate or desmopressin), should tranexamic acid monotherapy be used, or should combination therapy by increasing the VWF level to ≥0.50 IU/mL (with use of either VWF concentrate or desmopressin) in conjunction with tranexamic acid be used?

IU: international unit

Connell NT and Flood VH et al. Blood Adv. (2021)

MINOR SURGERIES

5a. In patients undergoing minor surgery or minor invasive procedures, the panel suggests increasing VWF activity levels to ≥0.50 IU/mL with desmopressin or factor concentrate with the addition of tranexamic acid over raising VWF levels to ≥0.50 IU/mL with desmopressin or factor concentrate alone

(conditional recommendation based on very low certainty in the evidence of effects ⊕◯◯◯).

IU: international unit

Connell NT and Flood VH et al. Blood Adv. (2021)

MINOR SURGERIES

5b. The panel suggests giving tranexamic acid alone over increasing VWF activity levels to ≥0.50 IU/mL with any intervention in patients with type 1 VWD with baseline VWF activity levels of >0.30 IU/mL and a mild bleeding phenotype undergoing minor mucosal procedures

(conditional recommendation based on very low certainty in the evidence of effects ⊕◯◯◯).

IU: international unit

Connell NT and Flood VH et al. Blood Adv. (2021)

REMARKS

- Individualized plans should consider bleeding risk for specific procedure
- Patients with type 3 VWD and many with type 2 will require VWF concentrate
- For patients at higher risk of thrombosis, it may be desirable to avoid the combination of extended increased VWF and FVIII levels (>1.50 IU/mL) and extended use of tranexamic acid
- Dental proceduralists may consider use of local hemostatic measures

FVIII: factor VIII, IU: international unit

EVIDENCE TO DECISION (ETD)

2 randomized trials comparing factor to factor plus TXA

8 case series of factor alone

4 case series of TXA alone

TXA: tranexamic acid

Connell NT and Flood VH et al. Blood Adv. (2021)

EVIDENCE TO DECISION (ETD)

Randomized clinical trials

- Factor concentrate or desmopressin alone associated with RR of 6.29 for postoperative bleeding compared with combination therapy including TXA
- Mean blood loss of 84.1mL compared to 61.2mL

Case Series

- 11% of patients treated with factor concentrate or desmopressin alone experienced bleeding compared to 14% of those treated with TXA alone

RR: risk ratio, TXA: tranexamic acid

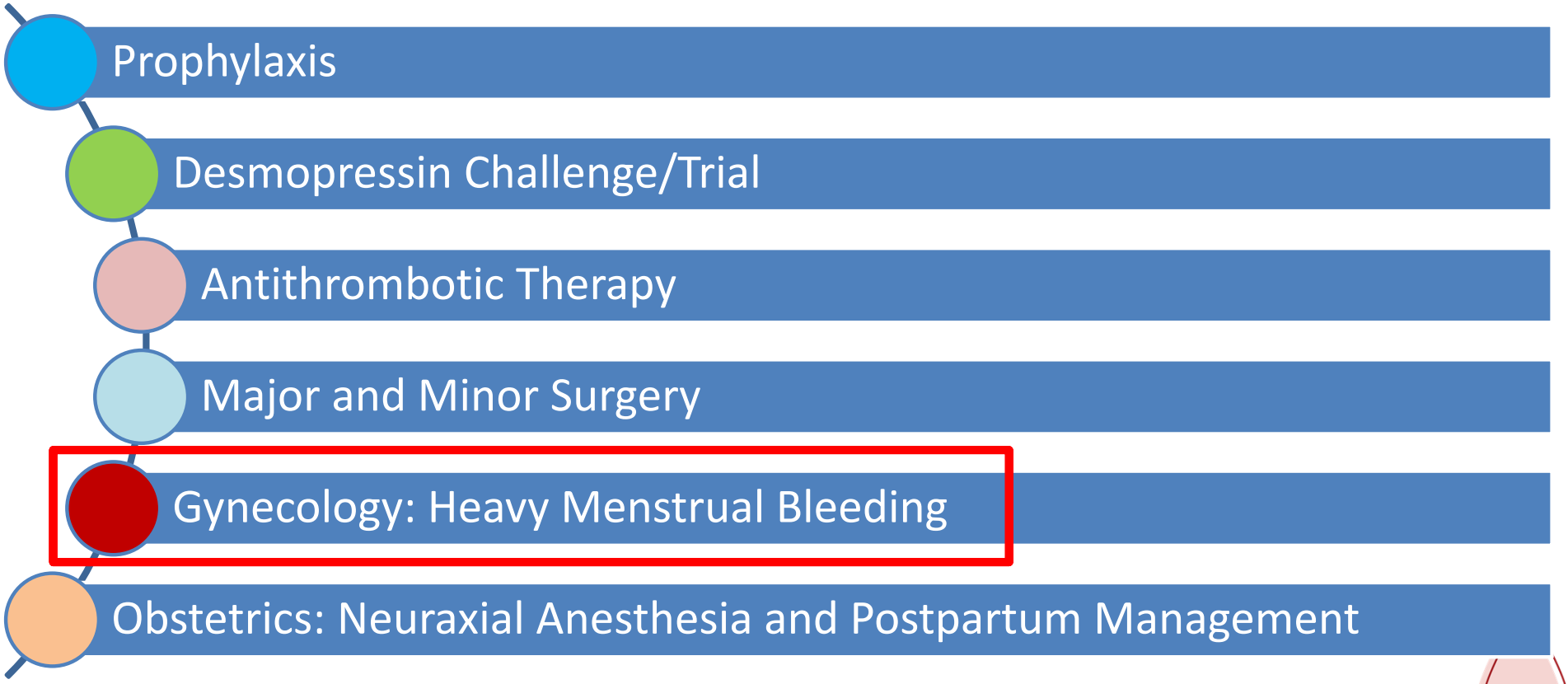
FUTURE RESEARCH

1. Use of TXA versus no TXA for certain procedures
2. Determination of differences in outcome based on procedure, anatomic site, TXA formulation or VWD subtype

TXA: tranexamic acid

MANAGEMENT: OVERVIEW

Connell NT and Flood VH et al. Blood Adv. (2021)



ASH ISTH NHF WFH 2021 Guidelines on the Diagnosis and Management of VWD

www.bloodadvances.com

Connell NT and Flood VH et al. Blood Adv. (2021)

HEAVY MENSTRUAL BLEEDING

In women with VWD with heavy menstrual bleeding, should tranexamic acid, hormonal therapy (ie, levonorgestrel-releasing intrauterine system or hormonal contraceptives), or desmopressin be prescribed?

HEAVY MENSTRUAL BLEEDING

Recommendation 6a

The panel suggests using either hormonal therapy (CHC or levonorgestrel-releasing intrauterine system) or tranexamic acid (TXA) over desmopressin to treat women with VWD with heavy menstrual bleeding who do not wish to conceive(conditional recommendation based on very low certainty in the evidence of effects ⊕◯◯◯).

Recommendation 6b

The panel suggests using tranexamic acid over desmopressin to treat women with VWD and heavy menstrual bleeding who wish to conceive (conditional recommendation based on very low certainty in the evidence ⊕◯◯◯).

CHC: combined hormonal contraception, TXA: tranexamic acid

REMARKS

This recommendation does not imply that the interventions considered can be prescribed only as monotherapy.

Desmopressin is not effective in type 3 and many type 2 VWD patients and contraindicated in type 2B VWD.

Women may require additional treatment for the first several menstrual cycles after placement of IUS.

Good practice statement: When feasible, the panel encourages the development of multidisciplinary clinics in which gynecologists and hematologists see patients jointly.

IUS: intrauterine system

Connell NT and Flood VH et al. Blood Adv. (2021)

EVIDENCE TO DECISION (ETD)

2 comparative studies

- Randomized clinical trial comparing desmopressin and TXA
- Observational study comparing hormonal therapy to desmopressin

5 case series about levonorgestrel intrauterine system (IUS)

TXA: tranexamic acid

Connell NT and Flood VH et al. Blood Adv. (2021)

EVIDENCE TO DECISION (ETD)

Randomized clinical trial

- TXA vs desmopressin
- Greater decrease with TXA
- Adverse effect differences not estimable
- QoL increased in both groups

Observational Study

- CHC vs desmopressin
- No difference in effectiveness

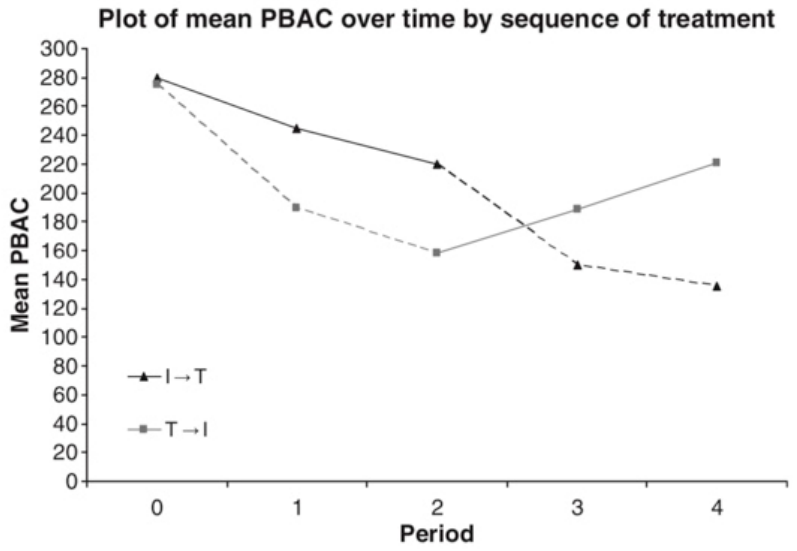


Fig 4. Plot of mean pictorial blood assessment chart (PBAC) over time by sequence of treatment. I = intranasal desmopressin (IN-DDAVP), T = tranexamic acid (TA).

CHC: combined hormonal contraception, QoL: quality of life, TXA: tranexamic acid

Connell NT and Flood VH et al. Blood Adv. (2021)

EVIDENCE TO DECISION (ETD)

5 case series totaling 82 patients (56 VWD)

Suggest control of heavy menstrual bleeding

- PBAC score
- Health related quality of life
- Hemoglobin
- Duration of bleeding

Expulsion 15%, Malposition 10%

PBAC: pictorial blood assessment chart

Connell NT and Flood VH et al. Blood Adv. (2021)

FUTURE RESEARCH

1. Studies on the use of combined therapy vs single therapy
   (efficacy and safety of the combination of hormonal therapy with tranexamic acid)

2. Studies assessing patients' values and preferences regarding the benefits and harms of various contraceptive methods

3. A prospective study of a levonorgestrel-releasing intrauterine system in terms of acceptability rates, spotting rate, and risk of expulsion or malposition

Connell NT and Flood VH et al. Blood Adv. (2021)

OTHER KEY MANAGEMENT RECOMMENDATIONS

Recommendation 1

In patients with VWD with a history of severe and frequent bleeds, the guideline panel suggests using long-term prophylaxis rather than no prophylaxis

(conditional recommendation based on low certainty in the evidence of effects ⨁⨁◯◯).

Recommendation 2a

In patients for whom desmopressin is a valid treatment option (primarily type 1 VWD) and who have a baseline VWF level of <0.30 IU/mL, 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 recommendation based on very low certainty in the evidence of effects ⨁◯◯◯).

IU: international unit

EDUCATION, DISSEMINATION, IMPLEMENTATION

www.hematology.org/VWDguidelines

www.isth.org/page/VWDGuidelines

www.hemophilia.org/bleeding-disorders-a-z/types/von-willebrand-disease

www.wfh.org/VWDGuidelines

- Webinars
- Snapshots
- Pocket guide
- Translations
- Patient materials
- More …

ASH ISTH NHF WFH 2021 Guidelines on the Diagnosis and Management of VWD
www.bloodadvances.com

ASH ISTH NHF WFH 2021 Guidelines on the Diagnosis and Management of VWD

QUESTIONS?

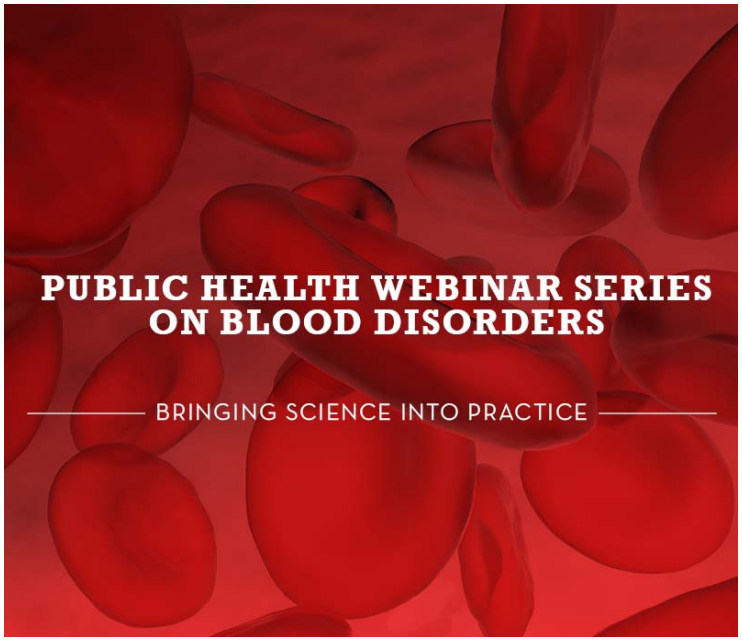
- www.hematology.org/VWDguidelines
- www.isth.org/page/VWDGuidelines
- www.hemophilia.org/bleeding-disorders-a-z/types/von-willebrand-disease
- www.wfh.org/VWDGuidelines

AMERICAN SOCIETY OF HEMATOLOGY

ISTH International Society on Thrombosis and Haemostasis

NATIONAL HEMOPHILIA FOUNDATION *for all bleeding disorders*

WFH
WORLD FEDERATION OF HEMOPHILIA
FÉDÉRATION MONDIALE DE L'HÉMOPHILIE
FEDERACIÓN MUNDIAL DE HEMOFILIA



This webinar was brought to you by CDC's Division of Blood Disorders. We thank the Hemophilia Federation of America for hosting today's webinar.

Hemophilia Federation of America™

Questions about this webinar series? Please contact Cynthia Sayers at CSayers@cdc.gov.

CDC Webinar Archive: https://www.cdc.gov/blooddisorderswebinars/

PUBLIC HEALTH WEBINAR SERIES ON BLOOD DISORDERS

BRINGING SCIENCE INTO PRACTICE

Multidisciplinary Care for Acute Pulmonary Embolism: The Pulmonary Embolism Response Team

March 11, 2021, 2 to 3 pm Eastern

Rachel P. Rosovsky, MD, MPH
Director, Thrombosis Research, Division of Hematology
Massachusetts General Hospital
Assistant Professor of Medicine, Harvard Medical School

More information, contact Cynthia Sayers; CSayers@cdc.gov