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EDITORIAL

The 2021 von Willebrand disease guidelines: Clarity and controversy

1 | INTRODUCTION

Medicine is rapidly developing, and publications are produced at an enormous rate making it impossible for a single individual to remain up to date in all areas. As a result, clinical guidelines utilising all the evidence are now available in almost all areas of medicine. The Institute of Medicine defined clinical guidelines as "systematically developed statements to assist practitioner and patient decisions about appropriate health care for specific clinical circumstances[1]".

In 2021 the American Society for Haematology (ASH), the International Society for Thrombosis and Haemostasis (ISTH), the World Federation of Haemophilia (WFH) and the National Haemophilia Foundation (NHF) collaborated to produce two guidelines on the diagnosis and management of von Willebrand disease (VWD).[2,3] The published guidelines are comprehensive spanning 46 pages and were produced using the highest international standards with the process coordinated by a team from the University of Kansas. The target audience are clinicians, other health care professionals and patients.

Guidelines cannot provide an answer for every clinical scenario so at the start of the production process the questions to be tackled were decided on. The process of choosing the questions was aided by wide consultation during which 601 participant (49% patient or care giver and 51% healthcare professional) responses were received. The consultation process is addressed in a separate manuscript.[4] Once the questions were decided detailed systematic literature searches were performed and the results presented to the panellists for a decision. Only members of the panels without conflicts of interest were allowed to vote on the decisions. The panels made either strong or conditional decisions which are reflected in the manuscript as recommendations or suggestions, respectively. A recommendation implies that the evidence for the decision is strong and further evidence is unlikely to change the decision. In the two new VWD guidelines only three of the questions were given a recommendation with the rest being suggestions.

Most of the conclusions of these guidelines are as expected by practising clinicians and we do not plan to address all of them in any detail. We have summarised the conclusions of the guidelines in Table 1.

2 | USE OF BLEEDING ASSESSMENT TOOLS (BAT)

Over the last 10–15 years BATs have gained popularity because they remove the subjectivity of deciding if a patient does or does not have a bleeding history. They do have limitations such as when used in younger individuals or persons without haemostatic challenges. The new VWD guidelines make a strong recommendation for the use of BAT scores in primary care before a decision to refer the patient for investigation of VWD is made. For persons already referred to secondary care, a BAT score is not essential, but it can be useful in ongoing care.

3 | LABORATORY TESTING

The VWD guidelines suggest the use of the newer functional assays that measure binding of VWF to recombinant glycoprotein Ib (VWF:GPIbM and VWF:GPIbR) over the VWF ristocetin cofactor assay (VWF:RCo) because these assays show less variability and are more accurate at lower levels. Based on the evidence the panellists were presented with, we feel a strong recommendation for the use of these assays could have been made. We do wonder whether the decision not to make it a strong recommendation was influenced by the fact that most laboratories in the United States (US) are using the VWF:RCo and that the newer assays are not FDA approved. These assays, however, are approved and widely used in Europe and Australia. We believe that clinical practice should follow guidelines and not the other way round.

4 | DEFINITION OF TYPE 1 VWD

The most controversial decision made in the new VWD guideline documents is to reclassify patients with a bleeding phenotype and VWF activity levels of 0.30-0.50 IU/mL as having VWD. This is a significant change from the previous guideline which classified these individuals as having "low VWF" rather than "von Willebrand disease[5]". This decision medicalises a large number of individuals, many with blood group O who are likely to have levels < 0.50IU/mL as a variation of normal. By this decision, these normal individuals are labelled as having a bleeding disorder. Surprisingly this decision was given a strong recommendation, rather than a suggestion, which implies that major good evidence has become available for this decision to be made in comparison to the previous VWD guidelines. We are not aware of such evidence and wonder if the panellists were unduly influenced by the United States health care system where, giving persons with VWF of 0.30-0.50IU/mL the label of a disease allows them access to the federal haemophilia cen-

TABLE 1 The decisions on the questions addressed by the VWD panels

Diagnostic guideline
1. ***Recommendation*** for use of BAT in primary care
2. Suggestion for no need for BAT in patients referred to a specialist
3. ***Recommendation*** for no need for BAT in patients with a family history of VWD
4. Suggestion for use of the newer VWF activity assays (VWF:GP1bM, VWF:GP1bR) over the VWF:RCo assay
5. Suggestion for reconsideration of the diagnosis as opposed to removing it in persons with previous VWD type 1 whose levels normalised with age
6. ***Recommendation*** to label persons as having type 1 VWD, if they have VWF < 0.30IU/mL regardless of bleeding or 0.30-0.50IU/mL with abnormal bleeding
7. Suggestion for a desmopressin trial with 1 and 4 h testing rather than VWFpp/VWF:Ag ratio in patients with suspected type 1 VWD with increased clearance
8. Suggestion for VWF:Ac/VWF:Ag ratio cut-off of 0.7 rather than 0.5 for diagnosis of type 2 VWD
9. Suggestion for use of multimer analysis or VWF:CB/VWF:Ag for type 2 VWD subtyping
10. Suggestion for genetic testing over low dose RIPA for type 2B VWD
11. Suggestion for either VWF:FVIIIB or genetic testing for type 2N VWD
Management guideline
1. Suggestion for use of long-term prophylaxis in patients with VWD with a history of severe and frequent bleeds
2a. Suggestion to perform a trial of desmopressin in patients with VWF of < 0.30IU/mL
2b. Suggestion against treating with desmopressin in the absence of a desmopressin trial
3. Suggestion for using over not using antiplatelet and anticoagulant therapy in patients with VWD and cardiovascular disease
4a. Suggestion to target both FVIII and VWF:Ac of > 0.50IU/mL for at least 3 days in the setting of major surgery
4b. Suggestion against the use of only FVIII of > 0.50IU/mL for 3 days in the setting of major surgery
5a. Suggestion to raise VWF:Ac with desmopressin or concentrate and use tranexamic acid for minor surgery
5b. Suggestion to use tranexamic acid for minor surgery
6a. Suggestion for use of hormonal therapy (contraceptive pill or Mirena coil) or tranexamic acid rather than desmopressin in women with heavy menstrual bleeding who do not wish to conceive
6b. Suggestion to use tranexamic acid over desmopressin in women with heavy menstrual bleeding who wish to conceive
7. Suggestion to use a target of VWF:Ac of 0.50-1.50IU/mL over >1.50 IU/mL for neuraxial anaesthesia during labour of pregnancy
8. Suggestion to use tranexamic acid for 10–14 days during the post-partum period

tres. Although treating patients with low VWF and bleeding is similar to type 1 VWD, we feel that low VWF should for the time be considered as a distinct clinical and pathological entity.

5 | REMOVAL OF A DIAGNOSIS

A very welcome area addressed by the guidelines is what to do with patients who have been diagnosed as having VWD but whose VWF levels normalise as they get older. VWF levels increase with age, so this is not a rare event especially in those individuals where the VWF was only mildly reduced in the first place. The guideline suggests that before removal of the diagnosis, the original diagnosis is reconsidered and reviewed as to whether other bleeding disorders have been excluded at the time of the original diagnosis. Finally, if it looks like the diagnosis can be removed, it is suggested that this is delayed until an invasive or surgical procedure is carried out without any haematological intervention and the diagnosis is only removed if there is no excessive bleeding at the time of the procedure. If bleeding is observed despite normal VWF levels, a diagnosis of unclassified bleeding disorder may be more appropriate.

6 | USE OF PROPHYLAXIS

Prophylactic treatment is the standard of care for patients with severe and sometimes moderate haemophilia A and B. The VWD guidelines now suggest the use of prophylaxis with VWF concentrate for patients with frequent bleeds. In practice most of these patients will have type 3 VWD disease or 2 with gastrointestinal bleeding.[6] This recommendation will be particularly useful in the United States, but this practice has been part of routine care in Europe for many years.

Although the guidelines were performed under the names of some international societies such as the ISTH and WFH, many of the recommendations are based on resources available in high income countries and will be a challenge to implement in low or middle income countries. They are currently only available in the English language but hopefully the key elements can be translated for local use in other geographies.

High quality guideline production is expensive and time consuming, so the number of questions tackled remained limited and some important issues were not addressed.

The availability of the VWD guidelines should allow clinicians to provide the best evidence-based care to their patients. The open publication will hopefully allow affected individuals to know what to expect and what the most up to date evidence suggests.

DATA AVAILABILITY STATEMENT

Not relevant as no original data.

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