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► **To cite this version:**

Cécile V Denis, Sophie Susen, Peter J. Lenting. Von Willebrand Disease: What does the future hold?. Blood, 2021, 137 (17), pp.2299-2306. 10.1182/blood.2020008501 . hal-03267627

**HAL Id: hal-03267627**

**<https://hal.science/hal-03267627>**

Submitted on 22 Jun 2021

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# Von Willebrand Disease: What does the future hold?

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**Short title:** Von Willebrand disease: What does the future hold?

**Article type:** Perspective

Abstract: 242 words

Main text (without figure legends): 4000 words

Figures: 2

References: 86

1 **Abstract**

2 Von Willebrand disease (VWD) is characterized by its heterogeneous clinical manifestation,  
3 which complicates its diagnosis and management. The clinical management of VWD has  
4 remained essentially unchanged over the last 30 years or so, using von Willebrand factor (VWF)  
5 concentrates, desmopressin and anti-fibrinolytic agents as main tools to control bleeding. This  
6 is in contrast to hemophilia A, for which a continuous innovative path has led to novel  
7 treatment modalities.

8 Despite current VWD management being considered effective, quality-of-life studies  
9 consistently reveal a higher than anticipated burden of VWD on patients, which is particularly  
10 true for women. Apparently, despite our perceived notion of current therapeutic efficiency,  
11 there is space for innovation with the goal to reach superior efficacy. Developing innovative  
12 treatments for VWD is complex, especially given the heterogeneity of the disease and the  
13 multifunctional nature of VWF. In this perspective article, we describe several potential  
14 strategies that could provide the basis for future VWD treatments. These include genetic  
15 approaches such as gene therapy using dual-vector adeno-associated virus and transcriptional  
16 silencing of mutant alleles. Furthermore, protein-based approaches to increase FVIII levels in  
17 VWD-type 3 or 2N patients will be discussed. Finally, antibody-based options to interfere with  
18 VWF degradation (for congenital VWD-type 2A or acquired Von Willebrand syndrome-type 2A)  
19 or increase endogenous VWF levels (for VWD-type 1) will be presented. By highlighting these  
20 potential strategies, we hope to initiate an innovative path, which ultimately would allow us  
21 to better serve VWD patients and their specific needs.

22

23

1

## 2 **Introduction**

3 Von Willebrand disease (VWD) is an inherited bleeding disorder resulting from quantitative or  
4 qualitative deficiencies in von Willebrand factor (VWF), a plasma multimeric glycoprotein  
5 controlling platelet adhesion and aggregation.<sup>1</sup> Although VWD is expected to affect men and  
6 women equally, there are more women diagnosed with VWD due to gynecological-related  
7 hemostatic challenges. The real prevalence of VWD has been a matter of debate for many  
8 years, ranging from as high as 1.3% when taking into account epidemiological studies<sup>2</sup> to 100  
9 cases per million when considering patients with clinically relevant bleeding symptoms.<sup>3</sup>  
10 VWD is traditionally classified in three types. VWD-type 1 is characterized by a partial  
11 quantitative deficiency in VWF. VWD-type 2 refers to qualitative VWF defects with a number  
12 of subtypes (2A, 2B, 2N and 2M) according to the patients' functional defect. Finally, VWD-  
13 type 3, also called severe VWD, is manifested by a virtually complete deficiency in VWF.<sup>1</sup>  
14 Bleeding symptoms are usually considered less serious than hemophilia-related symptoms.  
15 Although that may be true for mild VWD patients, specific comparative studies revealed that  
16 the bleeding-profile between VWD-type 3 and severe hemophilia A is more similar than  
17 expected.<sup>4,5</sup> Nevertheless, prophylactic treatment remains relatively rare in VWD patients.  
18 To develop alternative treatments for managing VWD in the 21<sup>st</sup> century, it will be crucial to  
19 understand the challenges faced by VWD patients and to take into account the disease  
20 specificities.

21

## 22 **Challenges in the diagnosis of VWD**

23 Given the heterogeneity of the disease that is observed sometimes within the same family or  
24 even in the same patient throughout his/her lifetime, VWD has been and remains to this day,  
25 a complex entity to diagnose<sup>6</sup> and to manage, partially explaining the difference between  
26 prevalence and actually diagnosed patients. Laboratory testing of VWD outside highly  
27 specialized centers is a challenge in itself, and the link between mild phenotypes and a VWF  
28 defect is not always straightforward. In addition, bleeding history relies on a subjective  
29 interpretation by the patients, their parents as well as the clinician. This is particularly true  
30 with regard to menstrual bleeding, a subject not easily discussed both inside and outside the  
31 family circle. Drs. Weyand and James recently noted that while 76% of men with VWD are  
32 diagnosed by 10 years, 50% of the women are not diagnosed by 12 years of age.<sup>7</sup> Although

1 this could partially be explained by a first bleeding episode at different ages, it has also been  
2 shown that the diagnostic delay following the first bleeding episode is longer in women than  
3 men.<sup>8</sup> Delayed diagnosis may result in missed treatment opportunities and increased  
4 morbidity (both medical and psychological). It is thus important to increase knowledge and  
5 awareness of VWD among (general) clinicians and public.

6

### 7 **VWD and quality of life**

8 What objective tools do we actually rely on to define that VWD is a mild bleeding disorder in  
9 most cases? First and primary is the clinical management of patients, since many VWD  
10 patients are followed in specialized hemophilia treatment centers. The health care  
11 professionals managing patients are highly-trained hematologists who have the necessary  
12 expertise to evaluate the disease burden. However and as stated maybe provocatively by Dr.  
13 Kouides “VWD on clinical grounds is primarily a disease of females”.<sup>9</sup> We are now increasingly  
14 learning how gender bias may have unwillingly affected patient’s care in many areas.<sup>10-12</sup>  
15 Whether such an issue has contributed to underestimate VWD severity in terms of physical  
16 and psychological consequences is unclear. Yet, there seems to be a parallel between the  
17 increasing number of female hematologists and the greater recognition of significant VWD-  
18 associated morbidities, especially when related to women reproductive health.<sup>13-15</sup>  
19 The second tool to evaluate disease severity are health-related quality of life (HR-QoL) studies,  
20 widely accepted as crucial instruments of patient-centered care.<sup>16</sup> For VWD, a few studies  
21 have addressed this issue using either 1) validated HR-QoL questionnaires, 2) questionnaires  
22 not officially validated or 3) through interviews. All studies have reported significantly  
23 decreased quality of life in VWD patients. The largest study (509 patients) was performed in  
24 the Netherlands using the generic Short Form (SF)-36 and reported decreased vitality (score  
25 measuring energy and fatigue) in both men and women with VWD.<sup>17</sup> Smaller studies  
26 performed in Canada (102 patients, SF-36 questionnaire), Finland (47 patients, Medical  
27 Outcomes Study-36 questionnaire), Sweden (30 female patients, SF-36 questionnaire),  
28 Canada again (28 patients, Health Utility Index Mark-2 and Mark-3) or United Kingdom (57  
29 female patients, general questionnaire) not only confirmed a lower quality of life for VWD  
30 patients compared to the general population, but for studies in which both men and women  
31 were included, most reported a difference between both genders.<sup>18-22</sup> Studies focusing  
32 primarily on women clearly indicate how the burden of VWD is borne disproportionately by

1 women. Heavy menstrual bleeding and its associated pain (observed in 32-100% of patients),<sup>23</sup>  
2 post-partum hemorrhage (in 15-60% of patients),<sup>13</sup> and hysterectomy (performed in 10-26%  
3 of patients),<sup>24</sup> are common in VWD women.<sup>15,25</sup> Qualitative interview-based studies about HR-  
4 QoL or lived experiences are even more striking with women reporting a considerable  
5 impairment in their lives.<sup>26-28</sup> Obviously not all VWD patients are affected by severe bleeding  
6 symptoms, a fact that can mitigate some of the HR-QoL studies where only a modest impact  
7 was reported, such as in the large Dutch study. Focusing on subgroups can probably give  
8 better ideas of the situation. A perfect example is illustrated in another Dutch study focusing  
9 on VWD patients with joint bleeds.<sup>29</sup> The authors show that 23% of patients from the Dutch  
10 VWD cohort self-reported joint bleeds. Not only is this percentage higher than anticipated,  
11 but joint bleeds were reported in VWD-type 1 as well as in VWD-type 2 or VWD-type 3, even  
12 if factor VIII (FVIII) levels exceeded 10%. Joint bleeds were associated with increased  
13 consumption of factor concentrates, joint pain and lower HR-QoL, suggesting a “significant  
14 burden of arthropathy in VWD”.<sup>29</sup>

15 Another factor that can impact the results of the HR-QoL studies is the absence of disease-  
16 specific instruments.<sup>23</sup> All the validated HR-QoL questionnaires used so far are generic  
17 instruments. A VWD-specific QoL has been developed,<sup>30</sup> but although it was mentioned that  
18 the questionnaire was validated in a German study (Wil-QoL) and a French study (WISH-QoL),  
19 no publications are yet available.

20 Altogether, these different studies illustrate the higher than anticipated burden of VWD on  
21 patients and suggest that VWD classification in types 1, 2 and 3, although crucial to understand  
22 the physiopathology of the disease is not always a good proxy for clinical severity. The actual  
23 patient’s phenotype is not only driven by the VWD phenotype, but also by burden in terms of  
24 hospitalizations, surgical interventions, drug consumption, gynecological visits, sick leaves and  
25 other objective parameters. This burden is only in part included in the bleeding score used to  
26 characterize the disease (Bleeding Assessment Tool of the International Society on  
27 Thrombosis and Hemostasis). However, this tool is cumulative and more adapted to diagnosis  
28 rather than reevaluation of the bleeding tendency. To better understand the evolution of the  
29 patient’s phenotype and associated burden, an alternative score could be designed to  
30 determine spontaneous symptomatology in the presence and absence of treatment.  
31 Undoubtedly, despite our perceived notion of therapeutic efficacy of current VWD treatments,

1 improved management of patients is necessary to address patient's needs in an optimal  
2 fashion.

3

#### 4 **Current treatment**

5 Over the last 30 years, many reviews related to the clinical management of VWD have been  
6 published (see *eg.* <sup>1,24,31-38</sup>) and guidelines were recently published.<sup>39</sup> Without extensively  
7 revisiting the topic, some relevant issues can be highlighted.

8 The most relevant message is that the toolkit for the treatment of VWD has remained  
9 essentially unchanged over these 30 years. Already in 1991, Dr. Aledort described the use of  
10 intermediate-purity factor concentrates and desmopressin as main approaches for the  
11 management of VWD, as well as adjunctive anti-fibrinolytic and estrogenic therapy.<sup>31</sup> It then  
12 took until 2005 for the development of a purer plasma-derived VWF concentrate, poor in FVIII  
13 activity.<sup>40</sup> As for the first recombinant VWF concentrate, it is only since 2015 that it became  
14 available in the USA and 2017 in Europe.<sup>41</sup>

15 When establishing a parallel with progresses made in the clinical management of hemophilia  
16 A over the same period of time, the contrast is particularly striking (Figure 1). While a parallel  
17 development was observed in terms of intermediate-purity concentrates (which contain both  
18 VWF and FVIII) and desmopressin in the 1980s, a real divergence started in the 1990s with the  
19 development of monoclonal antibody-purified and recombinant FVIII concentrates. At that  
20 time, who would have guessed that it would take another 20 years for comparable products  
21 to be available for VWD? But research did not stand still in the hemophilia field and while  
22 VWD management was only trying to fill the gap, nothing short of a revolution was looming  
23 on the other side of the VWF/FVIII partnership. Indeed, during the last decade, hemophilia A  
24 treatment has soared with several novel therapeutic strategies being available or in late  
25 clinical development.<sup>42-45</sup> In particular, gene therapy is reaching maturity and therefore for  
26 the first time in history, a real cure for the disease is within sight.

27 Thus, innovation in VWD treatment has basically stopped and the limitations of current  
28 treatments have not been addressed. Of course, the arrival of a recombinant VWF  
29 concentrate is an important step forward. However, without neglecting its specific merits, the  
30 availability of this recombinant VWF concentrate is not changing the essentials of VWD  
31 management, and prophylactic treatment will still require multiple intravenous infusions *per*  
32 week. The invasive nature of intravenous administration is associated with an increased risk

1 of infections, it is inconvenient, and it is challenging in the very young and old to find adequate  
2 venous access for repeated injections. Furthermore, prophylactic treatment using  
3 concentrates is expensive and not affordable world-wide. Finally, a major hindrance to the  
4 use of prophylaxis is that the criteria for introduction of prophylaxis for VWD patients  
5 (particularly women with heavy menstrual bleeding) are not as well defined as for patients  
6 with hemophilia. As a consequence, the benefit or need for prophylaxis are less well  
7 recognized.<sup>46</sup>

8 The advantages of desmopressin are numerous, and validate its status as the “treatment of  
9 choice” in VWD-type 1 patients. It can be administered in different ways (IV, subcutaneous or  
10 intranasal), is relatively cheap, and without risk of transmittable disease. It will transiently  
11 achieve adequate post-treatment levels of VWF and FVIII in 80% of cases.<sup>47,48</sup> However, there  
12 are also some limitations. It has variable effectiveness in type 2A & 2M, and is usually  
13 considered for minor bleeding/surgery.<sup>47</sup> Moreover, this medication is contra-indicated for  
14 VWD-type 2B, while its application in VWD-type 3 is ineffective since no FVIII or VWF is  
15 released from the endothelial storage-organelles.<sup>47</sup> Importantly, desmopressin is primarily a  
16 antidiuretic, with VWF release being an off-target effect. A number of side-effects  
17 concomitant to desmopressin use have also been reported (transient headaches, facial  
18 flushing, hypotension, hyponatremia and mild tachycardia), which are generally mild and well-  
19 tolerated.<sup>49,50</sup> Nevertheless, a recent VWD coping survey presented by Kalot *et al.* revealed  
20 that patients/caregivers display more concern about the side effect profile of desmopressin  
21 compared to health care professionals, and seem to prefer a prophylactic approach.<sup>51</sup>  
22 Furthermore, the repetitive use of desmopressin may result in reduced responsiveness  
23 (tachyphylaxis) due to exhaustion of the VWF storage-organelles.<sup>52</sup> Finally, it is relevant to  
24 mention that desmopressin is a monopolized product by Ferring Pharmaceuticals, which could  
25 compromise availability in case of production issues (see eg.  
26 [https://www.ferringusa.com/press/ferring-us-issues-voluntary-nationwide-recall-of-ddavp-  
27 nasal-spray-10-mcg-0-1ml-desmopressin-acetate-nasal-spray-10-mcg-0-1ml-stimate-nasal-  
28 spray-1-5-mg-ml-due-to-superpotency/](https://www.ferringusa.com/press/ferring-us-issues-voluntary-nationwide-recall-of-ddavp-nasal-spray-10-mcg-0-1ml-desmopressin-acetate-nasal-spray-10-mcg-0-1ml-stimate-nasal-spray-1-5-mg-ml-due-to-superpotency/)).

29 Hormonal treatment is commonly used to reduce heavy menstrual bleeding in VWD. However,  
30 as for desmopressin, increased VWF/FVIII levels are a mere secondary effect of hormonal  
31 treatment, which in itself has its own side effects and contra-indications. These are not always



1 minor, as for example the use of progesterone has been associated with an increased risk of  
2 sphenoidal osteomeningiomas.

3 In conclusion, YES there are some efficient treatments for VWD, but NO this does not mean  
4 that we should stop trying to improve these treatments with the goals of reaching superior  
5 efficacy, improving quality of life of the patients and finally curing the disease.

6

### 7 **The challenge of innovation in VWD management**

8 What can be done to improve VWD treatment? Unsurprisingly, there is not a simple answer  
9 to that question. Increasing prophylactic treatment would be a first step, as the introduction  
10 of prophylaxis for VWD patients appears to significantly reduce the rate of bleeding episodes  
11 and the need for hospitalization.<sup>53,54</sup> Nevertheless, prophylactic treatment did not fully  
12 prevent against the occurrence of bleeding episodes.<sup>54</sup> In addition, the current concentrates  
13 have similar issues as the FVIII concentrates that spurred the development of novel treatment  
14 strategies for hemophilia, including a relatively short half-life requiring multiple intravenous  
15 infusions *per week*. Designing VWF variants with a prolonged half-life could be an option to  
16 reduce infusion frequency. Such a strategy would not be such a major challenge to implement  
17 but besides an abstract published in 2006 which showed its validity, no follow-up  
18 development has been put in place.<sup>55</sup>

19 However, to be truly innovative, we as a scientific community need to think of alternative  
20 ways that are adapted to the patients' situation, rather than being limited to VWF  
21 concentrates or desmopressin. It is with such novel mindset that we will be able to break the  
22 glass ceiling and come up with the VWD-specific equivalents of fitusiran or emicizumab. In  
23 order to move in this direction, we first need to identify the patients who will better benefit  
24 from a more personalized approach, a concept increasingly recognized as relevant.<sup>37,56</sup> As part  
25 of this identification process, we should realize that severe VWD is not necessarily restricted  
26 to VWD-type 3. Patients with VWD-type 1 or 2 may sometimes experience bleeding  
27 phenotypes similar in severity than some VWD-type 3 patients.<sup>57</sup> Knowing the VWD subtype  
28 of the patients will be crucial to adapt treatment but should not represent a limit in our  
29 perception and appreciation of disease severity. There are patients who experience major  
30 bleeds and some who have frequent minor bleeds and our challenge is to address the different  
31 needs of the bleeders.

1 In the following sections, we will describe a number of potential approaches that could change  
2 the current paradigm of how VWD is treated or can be treated in the upcoming years. Of note,  
3 we will not address specifically the platelet dysfunction described in some patients with VWD-  
4 type 2B<sup>58</sup> since targeting the VWF gene defect would also resolve the platelet phenotype.

5

## 6 **Novel strategies: genetic approaches**

### 7 *Gene therapy*

8 To really cure VWD, gene therapy represents the ultimate goal, especially as it seems to be  
9 successful for both hemophilia A and B. However, the challenges to express VWF via gene  
10 therapy appear quite daunting. A first obstacle relates to its multimerization. Several mouse  
11 studies have shown that functional VWF can be efficiently expressed in hepatocytes of VWF-  
12 deficient mice, either transiently<sup>59-62</sup> or for long-term expression.<sup>63,64</sup> However, hepatocytes  
13 are not well-equipped to produce sufficiently multimerized VWF, and over time the  
14 hemostatically active VWF multimers seem to disappear.<sup>63</sup> So targeting the endothelium will  
15 be necessary for efficient protein processing.

16 Size represents a second hurdle: the VWF cDNA is too large to be incorporated in adeno-  
17 associated viruses (AAV), the type of vectors most used in clinical trials. Successful  
18 incorporation into lentiviruses has been reported, but data on efficient *in vivo* expression is  
19 yet lacking.<sup>65,66</sup>

20 In an attempt to overcome both obstacles, our team in collaboration with Federico Mingozzi's  
21 team has designed a dual-AAV vector approach, in which the cDNA of VWF is divided over two  
22 AAV-particles, which in turn are adapted to specifically target endothelial cells. We show that  
23 such an approach is technically feasible although the current expression levels are too low to  
24 be clinically meaningful.<sup>67</sup>

25 But even if we overcome these obstacles, there is another hurdle that we cannot ignore: if  
26 VWF is finally expressed at reasonable levels in the endothelial cells of the patient, how can  
27 we avoid the incorporation of dominant-negative mutants into the VWF multimer, when being  
28 expressed in the same cells as the transgene VWF? Indeed, Bowman *et al.* reported that the  
29 inheritance pattern for VWD-type 3 proved co-dominant in approximately 50% of the families  
30 included in their study.<sup>68</sup>

31 Perhaps expression of full-length VWF is not always necessary. In VWD-type 2N, and also some  
32 VWD-type 3 patients, the bleeding complications are associated with the low levels of FVIII,

1 and increasing FVIII levels would help to reduce bleeding in joints and soft tissues. For those  
2 patients, a gene therapy approach using the N-terminal portion of VWF (D1-D2-D'-D3 domains)  
3 would result in normalization of FVIII levels, as the presence of the dimeric D'D3-fragment  
4 protects FVIII from degradation and premature clearance.<sup>69</sup> Advantage of this approach is that  
5 multimerization is not a requirement, the cDNA (about 3.8 kb) easily fits into the AAV-vector  
6 and the protein can be expressed in hepatocytes. Preliminary studies in mice showed that  
7 such an approach is viable from a technical point of view.<sup>69</sup>

8

### 9 *Transcriptional silencing/gene-editing*

10 Rather than trying to express functional VWF, another approach would be to silence  
11 expression of mutant VWF. This makes even more sense given the dominant-negative  
12 character of many of the VWF mutations. A first example of this approach was reported by  
13 Casari *et al.*, who demonstrated that siRNA-mediated targeting of the mRNA breakpoint of an  
14 in-frame deletion mutant improved protein expression and multimerization.<sup>70</sup> Recently, we  
15 applied this siRNA-approach to a mouse model of VWD and confirmed the restoration of VWF  
16 multimers in plasma by silencing the dominant-negative allele.<sup>71</sup> To find a broader application  
17 for this technology, de Jong *et al.* designed siRNAs targeting common single-nucleotide  
18 polymorphisms in the *VWF* mutant allele, while leaving expression of the wild-type allele  
19 unaffected.<sup>72</sup>

20 Alternatively, another option could be to correct the *VWF* gene itself, using gene-editing  
21 approaches such as Crispr-Cas9. Little information on this approach in view of VWD currently  
22 exists, with the exception of a study investigating the bi-allelic deletion of the *VWF* gene in  
23 endothelial colony forming cells (ECFCs, also known as blood outgrowth endothelial cells).<sup>73</sup>

24 Both siRNA and gene-editing approaches are attractive, but one of the technical difficulties  
25 includes the specific targeting of sufficient numbers of endothelial cells. Currently, we do not  
26 know how many endothelial cells would need to be targeted to achieve sufficient production  
27 of functional VWF multimers. Additional research on these promising strategies is clearly  
28 needed at this point.

29

### 30 *Cellular therapy*

31 *Ex vivo* cellular therapy represents another method to introduce cells expressing functional  
32 VWF. This method was previously described by De Meyer and colleagues.<sup>65</sup> Briefly, canine

1 ECFCs were transduced using lentiviral vectors containing the human VWF cDNA. One day  
2 after transduction, cells indeed expressed functional multimerized VWF at levels 3-fold higher  
3 compared to normal ECFCs. However, expression levels to decreased 7-fold over a 4-week  
4 period during the expansion phase, which could be due to *in vitro* culturing of these cells.  
5 While a similar approach could also be applied using endothelial cells derived from induced  
6 pluripotent stem cells, human somatic cell therapy approaches are currently limited by the  
7 ability to generate sufficient amounts of cells to achieve physiological relevant expression  
8 levels after transplantation, the uncertain life-span of transplanted cells and the occurrence  
9 of genetic changes in the cells.<sup>74</sup> Progress on cellular therapies in other disease will certainly  
10 be helpful for the future development of this approach regarding VWD.

11

## 12 **Novel strategies: protein-based strategies**

### 13 *Compensating FVIII-deficiency in VWD*

14 Some of the bleeding complications in VWD-type 2N and type 3 patients are related to low  
15 FVIII levels, and improving FVIII levels could thus be beneficial. Infusing standard recombinant  
16 FVIII is not a viable option, since FVIII will be extremely-short lived in the absence of protection  
17 conferred by VWF. On the other hand, using FVIII/VWF concentrates in type 2N patients could  
18 lead to an excess of VWF, potentially posing a thrombotic risk.<sup>75,76</sup> An alternative solution may  
19 soon become available with the development of BIVV001, a novel FVIII-fusion variant which  
20 circulates independently of endogenous VWF, having a half-life 3-4 times longer than  
21 recombinant FVIII.<sup>77,78</sup> Although being developed for hemophilia A, this molecule could  
22 provide a novel treatment option for VWD-type 2N patients to correct FVIII-deficiency without  
23 increasing VWF levels.

24 Another approach was described by Weyand and colleagues, related to a VWD-type 3 patient  
25 who had developed allo-antibodies against both FVIII and VWF and experienced recurrent  
26 bleeding episodes.<sup>79</sup> To compensate for FVIII-deficiency in this patient, treatment with  
27 emicizumab was initiated. Emicizumab is a bispecific antibody that mimics to some extent the  
28 cofactor function of FVIII.<sup>43,80</sup> Emicizumab prophylaxis resulted in improved bleed prevention  
29 and reduced treatment burden.<sup>79</sup>

30

### 31 *Increasing endogenous VWF levels*

1 Desmopressin is often the first choice of treatment in VWD-type 1, as it will temporarily  
2 normalize endogenous levels of the otherwise functional VWF molecule. Due to the  
3 limitations associated with desmopressin detailed earlier, it would be of interest to develop  
4 novel strategies to increase endogenous VWF levels in a more sustainable approach. Various  
5 options could be designed in this respect. For instance, after the discovery that interleukin-11  
6 infusion was associated with an increase in VWF levels in both mouse and canine models, its  
7 clinical benefit was evaluated in two Phase II studies.<sup>81-84</sup> Although some clinical benefit  
8 following subcutaneous application was observed, the increase in VWF levels was modest  
9 (1.1-1.5 fold).<sup>83,84</sup> No additional clinical studies seem to be registered at Clinicaltrials.gov.  
10 Another strategy includes the use of single-domain antibodies (nanobodies) fused to an  
11 albumin-binding moiety (*eg.* peptide or nanobody), for instance, a VWF-binding nanobody  
12 that is fused to an albumin-binding peptide.<sup>85</sup> In this approach, such fusion protein would  
13 bridge circulating VWF to albumin, taking advantage of the long albumin half-life, and induce  
14 a prolonged half-life for VWF and consequently, increase VWF levels. Preliminary mouse  
15 studies revealed that pre-incubating VWF with a VWF-binding nanobody fused to an albumin-  
16 binding peptide (KB-VWF-013-ABP) resulted in a 7-fold increased VWF half-life. Moreover,  
17 subcutaneous application of this fusion protein was associated with a 4-8 fold increase in  
18 VWF- and FVIII-levels over a period of 7 days.<sup>85</sup> This approach thus holds great promises but  
19 needs to be further confirmed in different preclinical models.

20

### 21 *Preventing VWF degradation*

22 Excessive degradation of VWF is a particular problem in congenital VWD-type 2A(IIA), but also  
23 in some variants of acquired von Willebrand syndrome (aVWs), for instance in those having  
24 severe aortic stenosis or patients requiring mechanical circulatory support. While congenital  
25 VWD-type 2A could be treated using VWF concentrates, this is trickier in aVWs since it seems  
26 conceivable that the infused VWF will also be susceptible to degradation while passing  
27 through the pumps. To reduce VWF degradation, antibodies can be used to interfere with  
28 ADAMTS13-VWF interactions. Importantly, inhibition of VWF degradation should be limited  
29 to avoid thrombotic side effects as seen in thrombotic thrombocytopenic purpura. A few years  
30 ago, we described an anti-VWF antibody (Mab508) targeting the ADAMTS13-docking site at  
31 the VWF-D4 domain.<sup>86</sup> This antibody interferes with excessive VWF degradation, while leaving  
32 basal degradation intact. Indeed, the presence of Mab508 led to the conservation of high

1 molecular weight-multimers in *ex vivo* whole-blood perfusions systems.<sup>86</sup> Given the  
2 advantages of antibody-based treatment over concentrate-based treatments (*eg.* long half-  
3 life, eventual subcutaneous administration), such antibodies could be valuable assets in  
4 managing patients characterized by excessive VWF degradation.

5

#### 6 **Forward-looking perspective**

7 The heterogeneous nature of VWD implies that a “one size fits all” approach will never have  
8 the potential to address all the patients’ needs. However, the management of VWD patients  
9 currently follows such a trend. As highlighted in the last few paragraphs, research has not  
10 stood still and various solutions have been or are under investigation, although more could  
11 definitely be done in this regard. The main roadblock, in our view, appears at the next level,  
12 the translation of research results in potential industrial partnerships, allowing development  
13 of future treatments. So what are the biggest obstacles? Market size is certainly a major hurdle  
14 with few patients likely to benefit from each of the approaches highlighted previously.  
15 Another difficulty comes from the difference in perception of disease burden between health  
16 care professionals and the patients themselves. Maybe it is time to stop comparing bleeding  
17 in hemophilia and bleeding in VWD. All HR-QoL studies tell us that VWD patients have a  
18 significantly impaired quality of life. Patient’s advocacy has therefore a critical role to play in  
19 order to bring all stakeholders around the same table in order to prepare the future. No  
20 patient should be left behind. Our main aspiration is that ten years from now, if we were to  
21 write a review about VWD management, such a review will be quite different than the ones  
22 published for the last 30 years.

23

#### 24 **Acknowledgements:**

25 Financial support by the Agence Nationale de la Recherche (ANR-17-RHUS-0011) is gratefully  
26 acknowledged. This perspective could not have been written without the input of Dr. Olivier  
27 Christophe and Dr. Caterina Casari.

28

#### 29 **Author contributions:**

30 All authors contribution to the conception, writing and editing of this manuscript.

31

#### 32 **Disclosures:**

1 CVD, SS and PJJ are inventors on patents owned by Inserm related to bleeding disorders. CVD,  
2 SS and PJJ are co-founders of Laelaps Therapeutics.

3

#### 4 **Legends**

##### 5 **Figure 1: Evolution of treatment modalities for hemophilia A and VWD**

6 A schematic overview of when novel treatment options became available for hemophilia A  
7 and VWD. High-purity and recombinant concentrates (orange) arrived 20 years later for VWD  
8 compared to hemophilia A. Extended half-life variants, non-factor therapies and gene therapy  
9 (red) have found their way to the clinic or are in late-stage clinical development for hemophilia  
10 A, whereas they are not yet at the horizon with regard to VWD.

11

12

##### 13 **Figure 2: Potential avenues to enrich the arsenal of treatment options for VWD**

14 Examples of potential novel genetic- or protein-based strategies for the management of VWD  
15 are highlighted. Some approaches could be used to serve all VWD patients, whereas others  
16 will be type-specific. Abbreviations used in the figure: AAV: adeno-associated virus; ECs:  
17 endothelial cells; ECFCs: endothelial colony forming cells (also referred to as blood outgrowth  
18 endothelial cells); ECMO: extra-corporal membrane oxygenation; FVIII: factor VIII; IL-11:  
19 interleukin-11; LVAD: left ventricular assist device; TALENs: transcription activator-like  
20 effector nucleases; VWD: von Willebrand disease; VWs: von Willebrand syndrome. Portions  
21 of this figure were created using Biorender.com.

22

23

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Figure 1: Evolution of treatment modalities for hemophilia A and von Willebrand disease

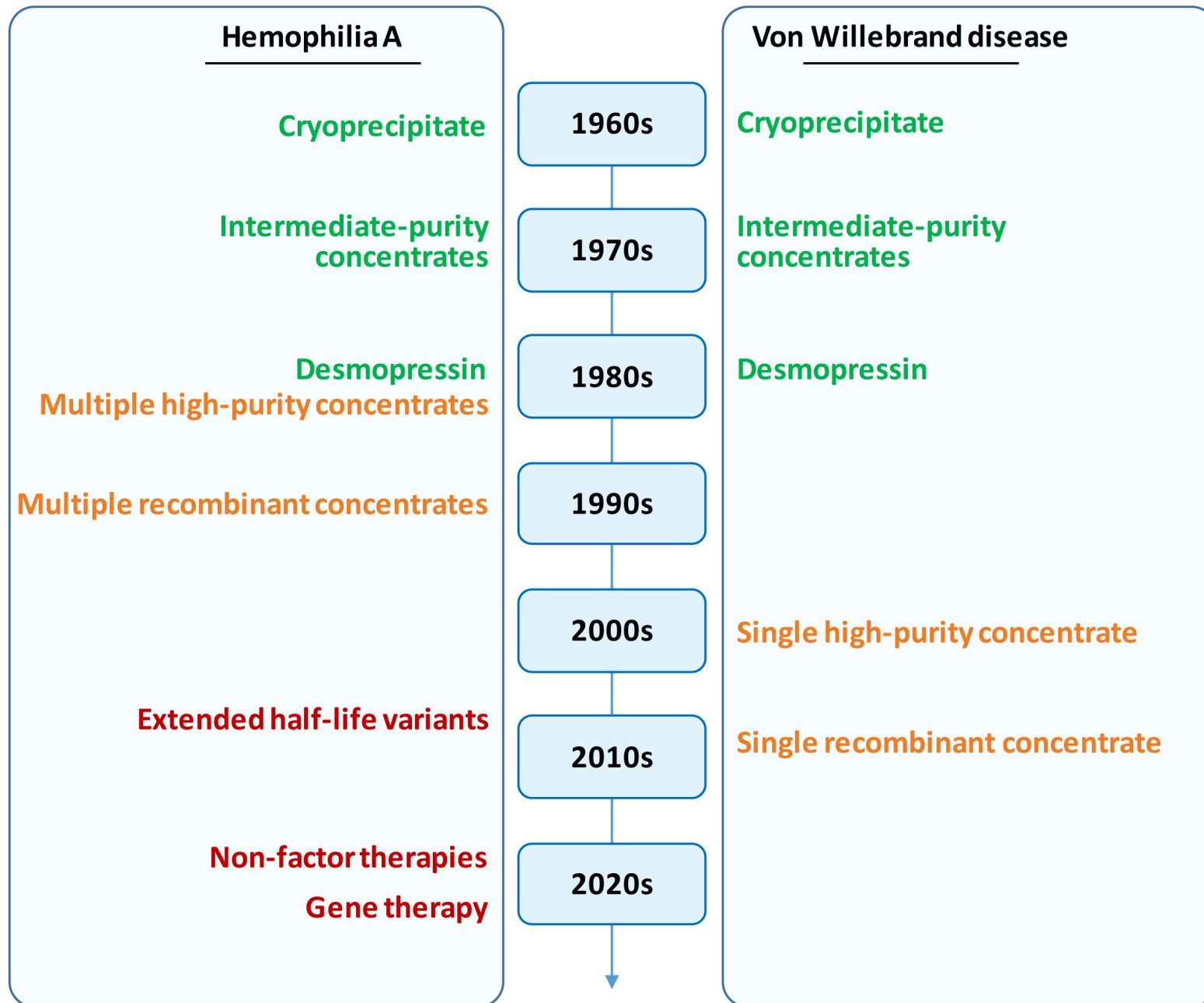
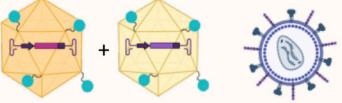
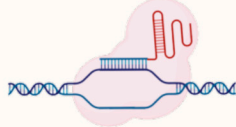
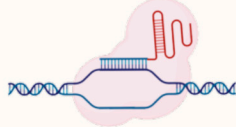
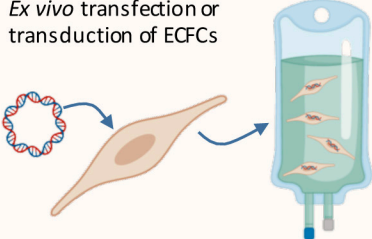
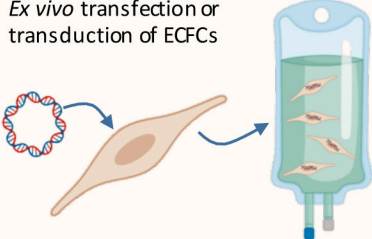



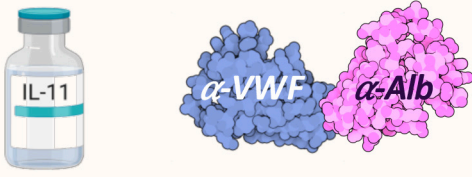
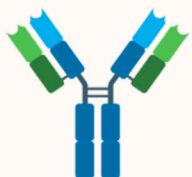


Figure 2: Potential avenues to enrich the arsenal of treatment options for VWD

### Genetic approaches

<p><b>Somatic gene therapy</b></p>  <p>EC-specific dual-vector AAV + Lentivirus targeting ECs</p> <ul style="list-style-type: none"> <li>• Expression of full-length VWF in ECs to ensure optimal multimerization</li> <li>• All VWD-types, but absence of dominant-negative mutants in host cells is obligatory</li> </ul> <hr/>  <p>Hepatocyte-specific AAV</p> <ul style="list-style-type: none"> <li>• Expression of VWF D1-D2-D'-D3 fragment in hepatocytes to normalize FVIII levels</li> <li>• VWD-type 2N &amp; type 3</li> </ul>	<p><b>Gene editing</b></p>  <p>Crispr-Cas9 TALENs Zinc-finger nucleases</p> <ul style="list-style-type: none"> <li>• Mono-allelic gene editing for dominant-negative mutants</li> <li>• Bi-allelic gene editing for recessive mutants</li> <li>• All types of VWD</li> </ul>
<p><b>Transcriptional silencing</b></p>  <p>siRNA</p> <ul style="list-style-type: none"> <li>• Silencing of mutant alleles</li> <li>• All types of VWD</li> </ul>	<p><b>Cellular therapy</b></p>  <p>Ex vivo transfection or transduction of ECFCs</p> <ul style="list-style-type: none"> <li>• Expression of full-length VWF in ECs to ensure optimal multimerization</li> <li>• No co-multimerization with mutant VWF, but co-existence in circulation</li> <li>• All types of VWD</li> </ul>

### Protein-based therapies

<p><b>Compensating FVIII deficiency</b></p>  <p>BIVV001      emicizumab</p> <ul style="list-style-type: none"> <li>• BIVV001 is a FVIII-variant that circulates independently of endogenous VWF</li> <li>• Emicizumab is a bispecific antibody mimicking FVIII-cofactor function &amp; can be given subcutaneously</li> <li>• VWD-type 2N and type 3</li> </ul>	<p><b>Increasing endogenous VWF levels</b></p>  <p>Interleukin-11      bispecific nanobodies</p> <ul style="list-style-type: none"> <li>• IL-11 stimulates synthesis of VWF, resulting in a modest rise of VWF levels (1.1-1.5-fold)</li> <li>• can be given subcutaneously</li> <li>• Bispecific nanobodies may delay clearance of endogenous VWF &amp; can be given subcutaneously</li> <li>• VWD-type 1 and type 2M</li> </ul>	<p><b>Preventing excessive VWF degradation</b></p>  <p>Mab508</p> <ul style="list-style-type: none"> <li>• Mab508 impairs VWF-ADAMTS13 interactions, thereby conserving high-molecular weight multimers</li> <li>• VWD-type 2A (IIA)</li> <li>• Acquired VWs-type 2A (including severe aortic stenosis, LVAD, ECMO,...)</li> </ul>
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