Introduction to the Review Series. A century after Erik von Willebrand

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As in many other cases in the history of medical advances, a natural experiment was at the origin of the first description of von Willebrand disease (VWD), the most frequent inherited bleeding disorder. VWD is caused by quantitative and/or qualitative defects of von Willebrand factor (VWF), a huge multimeric glycoprotein produced by endothelial cells and megakaryocytes and endowed with multiple functions in primary and secondary hemostasis. The first case was published in 1926 in Swedish language by Erik von Willebrand, professor of medicine at Helsinki University in Finland. In the century since his first description of a new disease (that he called hereditary pseudohemophilia and distinguished from hemophilia), a large number of publications fostered the understanding of this complex and common bleeding disorder. The clinical and molecular heterogeneity of VWD and knowledge on the multiple biological functions of VWF witnessed dramatic advances, which are featured in the frame of a review series by means of the following articles and authors:

- Riitta Lassila and Erik Berntorp, "The landmark contribution by Erik von Willebrand";[1]
- Sandra Haberichter and S. James O'Donnell, "Structure and multiple functions of von Willebrand factor";[2]
- Alberto Tosetto and Jeroen Eikenboom, "Clinical and laboratory diagnosis of von Willebrand disease";[3]
- Giancarlo Castaman and Augusto Federici, "Von Willebrand disease: classification and epidemiology";[4]
- Omid Seidizadeh and David Lillicrap, "Molecular genetic testing in von Willebrand disease: past, present and beyond";[5]
- Caterina Casari, Frank Leebeek and Flora Peyvandi, "Historical, recent and future treatments for von Willebrand disease";[6]
- Rezan Abdul-Kadir and Margaret Ragni, "Gynecologic and obstetric management of girls and women with von Willebrand disease".[7]

For the first article of the review series we chose Erik Berntorp from Malmo and Riitta Lassila from Helsinki in order to emphasize and celebrate at the same time Finland, as the country of the author of the first description of VWD, as well as Sweden, where the pioneering work of Inge Maria Nilsson and Margareta Blombäck contributed enormously to knowledge about the disease and early treatment. The article reiterates the features of the index case, i.e., Hjordis Sundblom, a young woman from Föglö in the Åland island archipelago. Incidentally, a few years ago we both visited the cemetery of Föglö, which contains Hjordis' grave, as well as the house where she lived with her large family including at least seven additional bleeders, some of whom died prematurely of catastrophic hemorrhages.[8] Hjordis suffered from type 3 VWD, a form compatible with such a severe clinical phenotype that she died from exsanguination at the age of 14 years at the time of her fourth menstrual period. Hjordis was referred to Erik von Willebrand's clinic and had to go to Deaconess Hospital in Helsinki repeatedly during as many as 9 years because of severe bleeding episodes in multiple sites and mucosal tracts. Her frequent pilgrimages by boat from Föglö to Helsinki bear witness to the limited therapeutic facilities available at the time, practically only vitamins and whole blood transfusion. On the other hand, Figure 4 in the article by Berntorp and Lassila shows the impressive battery of laboratory tests that Erik von Willebrand employed to diagnose in Hjordis a defect of platelet function with vascular abnormalities. Thus, Professor von Willebrand had fully understood, even at that early time, the importance of laboratory expertise and knowledge for the proficient investigation of bleeding disorders.

Haberichter and O'Donnell outline the relationship between the complex structure of the VWF glycoprotein and its multiple functions in primary and secondary hemostasis. Although it is now clear that VWF circulates in plasma tightly bound in molecular excess to coagulation factor VIII, their identity as distinct proteins was initially uncertain and firmly established only in the 1970s. Since then, an array of reports greatly enhanced knowledge on VWF structure and function. In their article, Haberichter and O'Donnell highlight

the biochemical and molecular bases of the functions of VWF in primary hemostasis as well as in blood coagulation as a chaperone stabilizing factor VIII. They also describe that the domain structure of VWF was recently assigned by electronic microscopy to specific nodules. On the basis of data that accumulated, particularly in the last decade, on multiple ligands binding to VWF, Haberichter and O'Donnell also focus on non-hemostatic functions of VWF with biological implications for angiogenesis, inflammation, bone health and carcinogenesis, and potential clinical translations to be fully elucidated.

The pioneering findings by Ted Zimmerman that VWD was distinguishable from hemophilia A by means of immunochemical tests,[9] and by Harvey Weiss, who used the antibiotic ristocetin following Barry Firkin to quantitate the platelet function activity of VWF in plasma,[10,11] paved the way to a more accurate diagnosis of VWD, which can nevertheless remain a conundrum not only for general hematologists but also for hemostasis experts. Tosetto and Eikenboom address this diagnostic complexity.[3] As the understanding of diverse VWD phenotypes has evolved, there has been an increasing development of specific assays to ensure a more accurate diagnosis, with focus on the multiple tests currently available to measure the platelet-related functional activity of VWF beside the time-honored ristocetin cofactor assay. Unlike many other coagulation disorders, VWD requires a comprehensive panel of phenotypic investigations, some widely available but most confined only to specialized laboratories. Their article also details the broad clinical spectrum of VWD, spanning from mild skin and mucocutaneous tract symptoms to soft tissue and postoperative bleeding, hemarthrosis and severe gastrointestinal hemorrhages. Given the subjective nature and inter-individual variability of clinical presentations, bleeding assessment tools and related scores have been employed to introduce more objectivity into the clinical evaluation of the bleeding history. These tools are a step forward, because they help to distinguish between physiological and pathological bleeding and improve diagnostic confidence in borderline cases. However, they do have limitations such as the age-dependence of the bleeding scores, which hamper their use in children and premenstrual girls who have not yet accumulated a history of spontaneous and provoked bleeding symptoms needed to build the scores. Importantly, Tosetto and Eikenboom advocate the integration of clinical and laboratory data by means of a Bayesian approach that uses pre-test probability as a basis for diagnosis. They also show that identical laboratory findings may have different implications in such contexts as age and family history, underscoring the need for a personalized diagnostic approach. The laboratory diagnosis of VWD is presented in three tiers: screening tests, first-level diagnostic tests and second-level subtyping, with the value of each of them described. Final statements affirm the enduring value of the current VWD classification, emphasize the usefulness of a more accurate evaluation of the bleeding risk, and call for a cautious revision of the diagnostic framework but only when backed by clear clinical benefits.

The complexity of the diagnosis of VWD is also discussed by Giancarlo Castaman and Augusto Federici in the frame of an epidemiological approach. To begin with, they emphasize the high prevalence of the disease, amounting to approximately 1% (14 of 1,218 children 11-14 years old) according to an epidemiological investigation led by Rodeghiero in collaboration with Castaman in two different areas, 70 km apart, of the Vicenza province: one near the mountains in the north and the other in the southern plains.[12] This review series offers the opportunity to reveal the reasons that prompted the first and largest epidemiological investigation on VWD. In Italian folklore, the northern part of the Vicenza province, at variance from the southern part, was inhabited by descendants of Cimbri, an ancient population from Nordic countries, including the Jutland peninsula, southern Sweden and the Åland archipelago. The Cimbri retreated and settled in the Vicenza area to find shelter after the Roman victory over them in the first century BC, and still today a few Cimbrian words are used in the local dialect. Thus, it would have been fascinating to find a higher prevalence of VWD in the northern part of the province, supporting a founder effect by Cimbri, in keeping with the discovery by Erik von Willebrand in the Aland archipelago and the higher prevalence of VWD in the Nordic regions once inhabited by Cimbri tribes. To the disappointment of those who believed in the Cimbri myth, the prevalence of VWD was similarly high in the two areas of Vicenza, in keeping with the current evidence of a homogenous worldwide distribution of VWD. Some years later the same children and families were re-investigated and it was found that only one of the 14 children with a previous diagnosis of VWD had subsequently required a clinical visit for bleeding.[13] Most probably the children classified as having VWD in the epidemiological survey would be now classified as having low VWF. Castaman and Federici appropriately suggest a cautious approach to classifying subjects with plasma levels between 30 to 50% as having low VWF, also considering a tendency toward normalization of levels with aging and their mild or very mild bleeding manifestations. They agree with Tosetto and Eikenboom that more emphasis should be put on the personal and family history of bleeding as assessed through bleeding scores rather than by means of extensive laboratory investigations. Castaman and Federici enhance the translational impact of their article by highlighting topics such as the identification of mild or borderline and yet clinically relevant cases of VWD, as well as the issue of limited awareness of this frequent disease among non-specialized clinicians.

The huge gene size and complex biology of VWF offer ample scope for gene variants impairing the biosynthesis, secretion and multiple functions of this protein, resulting in different types of VWD. The importance of understanding

the genetic basis of VWD and related diagnostic applications is outlined by Omid Seidizadeh and David Lillicrap, who emphasize the major advances in molecular genetics coinciding with the centennial of the first description of VWD and the 40th anniversary of the cloning of the *VWF* gene, i.e., one of the many discoveries of genes encoding coagulation factors in the mid-1980s. The authors provide an overview of the *VWF* gene and its pseudogene, tracing the history of the discovery of *VWF* and development of genetic testing, which help to support a diagnosis of VWD when phenotypic results are unavailable or inconclusive and to distinguish subtypes (e.g., type 2N *vs*. mild hemophilia A, or type 2B *vs*. platelet-type). Genetic investigations can also guide family counseling, and identify causative variants that inform appropriate management and deepen the understanding of disease mechanisms. While VWD genetics have improved considerably, a subset of patients still lack identifiable *VWF* variants, i.e., approximately less than 10% of type 2 and type 3 cases but up to 35% of type 1/low VWF cases. The article also discusses genotype–phenotype correlations alongside the limitations of genetic testing and concludes with a forward-looking perspective on the future of *VWF* molecular diagnostics, highlighting the advances in whole-exome and whole-genome sequencing that promise to offer not only a more comprehensive identification of coding and non-coding variants, but also a deeper analysis of the multiple genes influencing VWF plasma levels.

The penultimate article of the review series, jointly written by Caterina Casari, Frank Leebeek and Flora Peyvandi, to begin with tackles such time-honored therapeutic weapons as plasma-derived products that replace both factor VIII and VWF as well as desmopressin (DDAVP), which acts by transiently releasing these moieties from endogenous stores into plasma. The authors also discuss the developing therapeutic role of recombinant VWF and end by dealing with multiple potential new drugs with varied mechanisms of action still in the infancy of clinical development.

After the pioneering experiences with plasma fraction I-O and cryoprecipitate,[14,15] replacement therapy of VWD was first based on plasma-derived products originally developed for hemophilia A. They are still the most used products worldwide, particularly after their viral safety was consistently assured in the last few years of the 1980s. On the basis of mainly retrospective case series, all these products are effective for the prevention and treatment of bleeding but the lack of head-to-head comparative studies makes it difficult to choose one over the others.

The rationale for their therapeutic use is that in most cases of VWD both VWF and factor VIII are deficient. It is unclear to what extent each deficiency contributes to the bleeding tendency, although it is known that factor VIII deficiency is the main determinant of soft tissue and postoperative bleeding, while that of VWF is the main determinant of mucosal tract bleeds.[16] With this preamble, a potential key to the choice is the ratio of VWF to factor VIII in the different products: those richer in VWF may be preferred for mucosal bleeds, those richer in factor VIII for joint, soft tissue and postoperative bleeds.

Desmopressin was first used in the late 1970s when exogenous replacement products were in limited supply and carried a high risk of transmission of bloodborne infections. Desmopressin is the treatment of choice in the most frequent type 1 VWD, but there is currently a shortage or limited availability of the more concentrated formulations for intranasal and subcutaneous use,[17] preferred by pediatricians because of their more patient-friendly use.

It is a monument of ingenuity that a huge protein such as VWF was produced industrially by recombinant DNA technology. It is being ever more used in the USA, but less so in Europe, for prophylaxis as well as for the episodic treatment of bleeds and in the perioperative period. It is the only replacement product with an intact VWF multimeric structure and even ultralarge multimers are present in the formulation for intravenous use. It has not been demonstrated that this unique biochemical feature offers clinical advantages, considering also that, following infusion, highly active ultralarge multimers are quickly cleared by endogenous ADAMTS13 proteolysis. The efficacy of recombinant VWF for the prevention and treatment of bleeding and to handle surgical operations in adults, has been clearly demonstrated, but evidence of its advantages over plasma-derived products suffers from lack of head-to-head comparative studies.

In the last part of the article the authors emphasize that after limited progress in first 30-40 years, the last decade has witnessed an impressive proliferation of potentially new treatments, some only evaluated in the context of animal models but a few in the early phases of clinical development. Their mechanisms of action are different from those of traditional replacement products: some heighten thrombin formation, others extend the plasma half-life of endogenous VWF, yet others increase the platelet-related activity of VWF or rebalance hyperfibrinolysis.[18] They are all designed for the prevention rather than the episodic treatment of bleeds and are conveniently administered subcutaneously. Prophylaxis is not as frequently or strongly recommended by therapeutic guidelines in VWD as it is in hemophilia, because bleeding episodes are generally less prevalent in most cases, as shown by an average yearly number of four or five bleeds in patients treated episodically, compared to 30-40 or more in the corresponding hemophilia cases. The varied mechanisms of action of these products offer the possibility of a personalized approach to prophylaxis depending on the type and mechanism of the prevalent bleeds. For instance, products enhancing procoagulant potential may be useful for joint and soft tissue bleeds, those that enhance and extend the platelet activity of VWF may be preferred for mucosal tract bleeds, those rebalancing local hyperfibrinolysis for the control of heavy menstrual bleeding.[18]

We elected to devote the last article of the review series to

girls and women with VWD: with the purpose of once more paying tribute to Hjordis Sundblom, but also of highlighting that bleeding at menstruation and childbirth is the most cogent lifelong hurdle for an acceptable quality of life in women living with VWD. We involved Margaret Ragni, who recently tackled the controversial management of menorrhagia in the frame of one of the few randomized clinical trials in VWD,[19] and the gynecologist Rezan Abdul-Kadir, who contributed extensively with her clinical research not only to VWD but also to the broad spectrum of bleeding disorders in women. Their article points out once more the still existing underdiagnosis and undertreatment of VWD in women and also advocates action for the low rate of diagnostic yield and treatment of iron deficiency, particularly in women from deprived and vulnerable minorities. They recommend employing ferritin values, rather than hemoglobin and red cell blood counts, for an early diagnosis of iron deficiency and propose a diagnostic threshold of 50 ng/mL. They also suggest greater use of intravenous formulations to manage iron deficiency, thus avoiding oral products that often contain inadequate amounts of elemental iron beside being of difficult gastrointestinal tolerance. Finally, after noting once again the weakness of evidence regarding choice of the currently available weapons for heavy menstrual bleeding, they conclude their article on "iron ladies" emphasizing that the forthcoming new medications addressed by Casari, Leebeek and Peyvandi are tackling but not solving this still unsettled issue.

Concluding this review series celebrating Erik von Willebrand a century after his discovery, we are impressed to realize that he was able to differentiate Hjordis' ailment from classic hemophilia and Glanzmann thrombasthenia in spite of the limited array of laboratory tests available. The disease first described by him is still fascinating and challenges many clinicians and scientists. Notwithstanding a lot of progress in management and the normal life expectancy of the affected cases, many of them suffer from an impaired quality of life. In VWD continuous prophylaxis is not a must as in hemophilia, but it is advocated and efficacious in frequent and severe bleeders: children with repeated episodes of epistaxis and cases with type 3 VWD, joint bleeding and arthropathy. In addition, the most cogent unsolved clinical problem is the poor control of menstrual and gastrointestinal bleeding. The latter and the underlying angiodysplasia are expected to increase with the aging of the cases most frequently affected (type 3, types 2A and 2B and acquired von Willebrand syndrome, not dealt with in this review series). Nevertheless, the main problem to be tackled as soon as possible is to assure more awareness of the disease in low- and middle-income countries, its accurate diagnosis and more adequate treatment.

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Contributions

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