

Von Willebrand Disease (VWD) 100 years after its first description: the research of Italian investigators for a better management of VWD patients

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Editor's note: this manuscript is dedicated to the memory of Armando D'Angelo.

ABSTRACT

Since the first description of the von Willebrand disease (VWD) families by Erik von Willebrand in 1926, VWD has been considered an inherited bleeding disorder completely different from hemophilia, already known for many years. The pivotal role of the adhesive glycoprotein von Willebrand factor in the early phases of hemostasis has been progressively unraveled in numerous publications. Still, actual progress in the clinical management of patients with VWD has always lagged that achieved in patients with hemophilia. After the pioneering studies of the first 50 years (1926-1975), the pathophysiology and diagnostics of patients with VWD became better distinguished from those with hemophilia. However, only in the last 50 years (1976-2025) have the basic and clinical aspects of VWD been clearly defined, with the scientific contributions of Italian investigators. Thanks to their research in collaboration with colleagues from Europe and the US, management of VWD patients improved significantly. In this review article, the most important milestones achieved in the diagnosis and treatment of VWD will be presented. Despite major efforts by experts, who recently (2021) summarized their recommendations in the International Guidelines on VWD diagnosis and therapy, there are still many unmet needs in this disease management. Indeed, the recommendations of the International Guidelines must be translated into current national practice by using a simplified diagnostic approach, as proposed recently by the joint AICE (Italian Association of Hemophilia Centers) and SISST (Italian Society for the Study of Hemostasis and Thrombosis) Italian Guidelines and by organizing structured clinical observation not only of severe VWD but especially of the more frequent mild-to-moderate types.

Key words: von Willebrand factor, von Willebrand disease, international guidelines on diagnosis and therapy, von Willebrand factor concentrates, secondary long-term prophylaxis, novel therapies.

Introduction

The 100th anniversary of the first description of families with von Willebrand disease (VWD) offers hematologists and experts of inherited bleeding disorders a good opportunity to point out the status of VWD management five years after the publication of the International Guidelines for diagnosis and therapy.^{1,2} Among the numerous review articles published to celebrate this

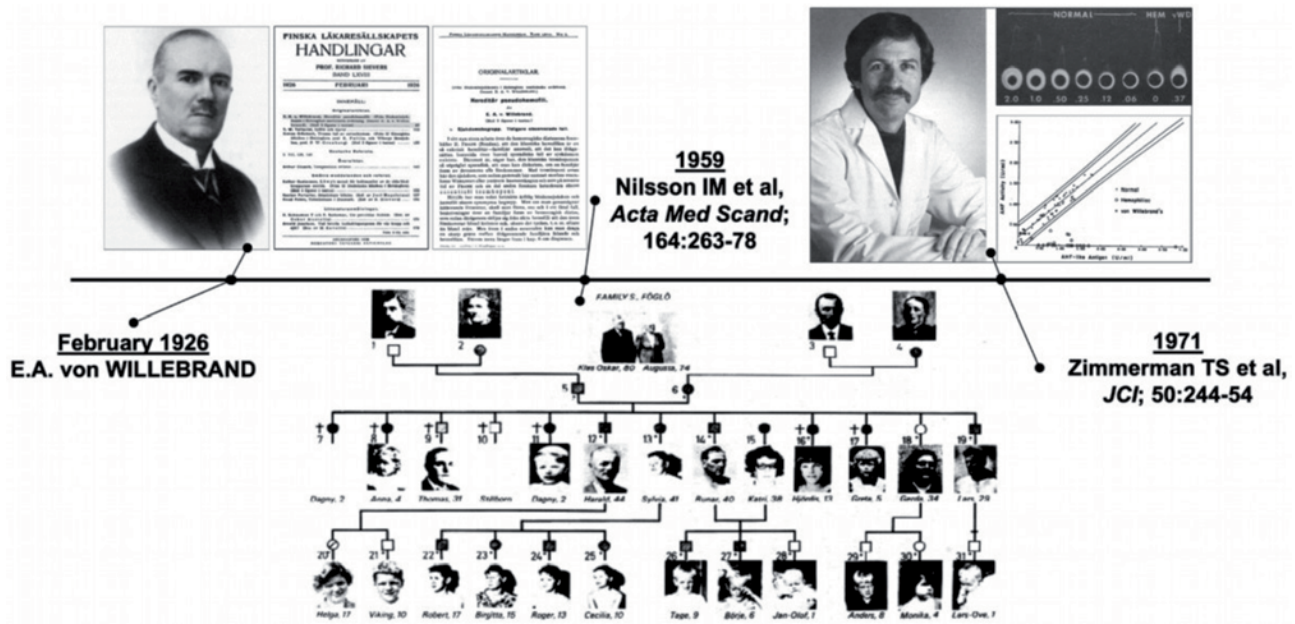


Figure 1. History of von Willebrand disease (VWD) starts in 1926. From top left, the picture of Erik Adolf von Willebrand with the front pages of his manuscript published in Finnish language in February 1926. The pedigree of the first family with VWD described in that original publication by Erik von Willebrand and discussed by Inga Maria Nilsson in her manuscript published in 1959. On the top right, the picture of Theodore Samuel Zimmerman with the two figures from his manuscript published in 1971 where the results obtained by the Electro-Immuno-Assay (EIA) according to Laurell were shown in patients with VWD *versus* patients with hemophilia A (HA) and carrier of HA.

anniversary, we have decided to discuss how basic and clinical research on von Willebrand factor (VWF) has improved VWD patients management, as extensively discussed in the last edition of the VWD textbook.³ Italian investigators were indeed instrumental in promoting clinical observations of VWD patients, often in collaboration with European and US Colleagues. Therefore, their publications will be discussed in this review, particularly those that formed the background for the International Guidelines evidence-based recommendations.^{1,2} Recently, the Italian Association of Hemophilia Centers (AICE) and the Italian Society of Hemostasis and Thrombosis (SISST) prepared

more practical recommendations for the treatment of VWD in Italy, also based on the results of a survey on current clinical practice. The Italian guidelines (ITAGL) were published in 2024 as an official guidance from the Italian Istituto Superiore di Sanità.^{4,5} In this review article, we describe the most important clinical milestones in the management of PWVWD compared with those for patients with hemophilia (PWH) over the last 50 years (1976-2025). By discussing the recommendations proposed by both International and Italian Guidelines, we will also focus on several still unmet needs. We will suggest how they could be met and translated into current practice by organizing structured clinical observations of more appropriate treatments in large VWD cohorts, especially those with the most frequent mild-to-moderate types, which are still misdiagnosed and underestimated.

History: the pioneering work of the first 50 years (1926-1975)

The major achievements of the first 50 years were described in detail in a previous review article celebrating the 80th anniversary.⁶ The original contributions of those years are summarized in Figure 1, which assembles the three figures published separately in that article. Thirty years after the original publication by Erik von Willebrand,⁷ Inga Marie Nilsson and co-workers revisited the Åland Islands and studied 15 patients from the original family. They confirmed that these patients had the same

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clinical and laboratory features as those observed in other Swedish patients, indicating that this novel disease was present in another Scandinavian country.⁸ Four years later, abnormal platelet adhesiveness was found in VWD patients.⁹ During the 1960s, knowledge about hemophilia improved significantly thanks to Frank Schnabel, President of the Canadian Association of Hemophilia, who had the mission and vision to organize the World Federation of Hemophilia (WFH) in 1963, aiming to promote hemophilia care worldwide. In a few years, in many countries, hemophilia patients and experts, following the example of President Schnabel, organized their National Association of Hemophilia and became Members of WFH. In Europe, many countries joined the WFH with their National Associations. In 1968, the first Italian Association of Hemophilia was founded in Milano by Umberto Randi, with the medical advice of Nicola Dioguardi and his young associate, Pier Mannucci. In that year, the first Italian Hemophilia Center was created at Milan Policlinico Hospital, supported by the Angelo Bianchi Bonomi Hemophilia Foundation starting from two years later.¹⁰ In February 1970, a small group of Italian Investigators (Coccheri, Crolle, de Nicola, Dettori, Neri Serneri, Ottaviani) at the University of Bologna signed the founding document of the Siset and organized its first Congress in Parma.

Until 1971, VWD was still poorly recognized because only in that year was it confirmed that the deficiency of a new factor, called VWF and distinct from FVIII, was responsible for the disease.¹¹ In their publication, Zimmerman *et al.* described an antiserum obtained from lab animals immunized with human

plasma-derived FVIII preparations that identified a novel protein using-immunochemical techniques. This protein, then called FVIII-related antigen (later designated VWF antigen), was present in normal individuals and in those with hemophilia A (HA) but was absent in those with VWD (Figure 1). This novel assay was also useful to distinguish hemophilia A carriers from patients with VWD. In the same year, 1971, Howard *et al.* observed that the antibiotic ristocetin triggered platelet agglutination in platelet-rich plasma (PRP) from normal individuals but not in PRP from VWD patients. Such a ristocetin effect could be linked to VWF antigen (VWF:Ag) and so, quantitative assays for VWF ristocetin cofactor (VWF:RCO) activity were developed.¹² From 1971 to 1975, many US and European investigators not only performed these novel assays, but also could use them to demonstrate *in vitro* that human endothelial cells were one of the sites of VWF synthesis.¹³⁻²¹ During those years, the role of carbohydrate side chains from human and bovine VWF was also studied in platelet aggregation assays by two Italian PhD students at the University of Leuven, Maria Benedetta Donati and Giovanni de Gaetano.¹⁶ The first basic and clinical data on Italian VWD patients were published by Pier Mannuccio Mannucci, Francesco Pareti and Zaverio Ruggeri.²²⁻²⁵ Other Italian investigators began to produce clinical and laboratory data on VWD, including those published by Dini and coworkers in 1974 on 13 VWD families in the province of Vicenza.²⁶ Thanks to collaboration with the European Hemophilia Centers and the Members of Scientific Societies and Associations, Italian investigators began promoting basic and clinical research on VWD from 1971 to 1975.

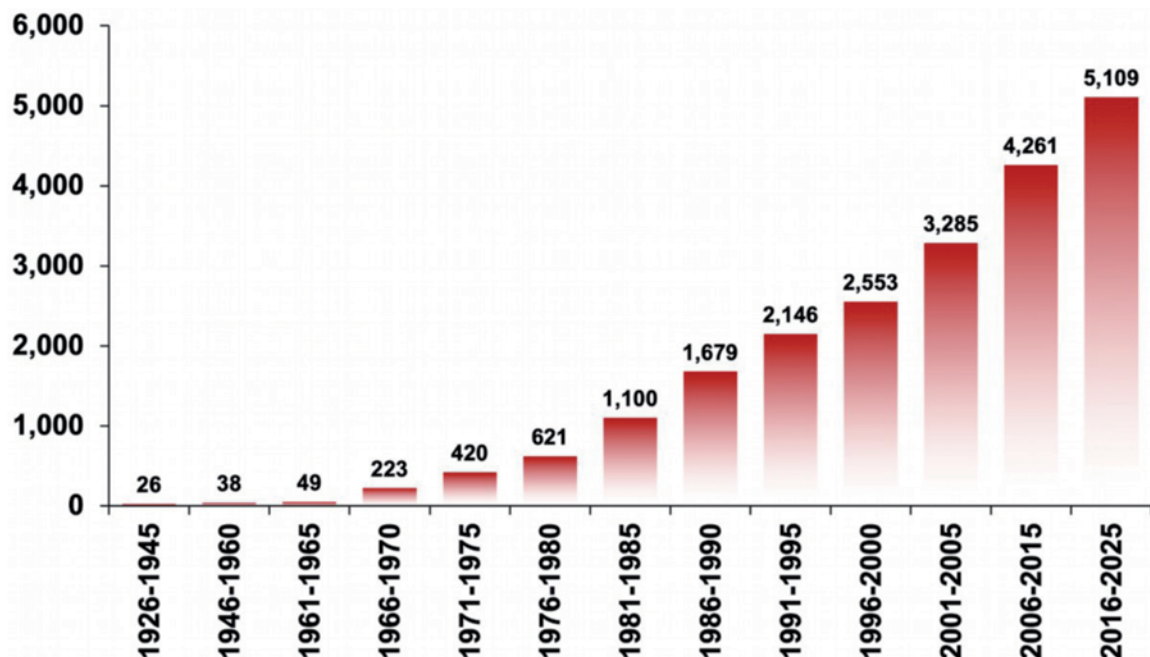


Figure 2. Number of publications retrieved in PubMed according to the simplest keywords VWF and/or VWD from 1926 to 2025. Note that these publications have increased progressively every five years since 1966 and continued to increase by one thousand in the remaining two decades, namely 2006-2015 and 2016-2025.

Milestones about management of patients with von Willebrand disease *versus* patients with hemophilia (1976-2025)

During the last 50 years, the knowledge about VWD management, together with the role of VWF in hemostasis, progressively increased decade after decade, as shown by the number of scientific publications retrieved from PubMed according to the simplest key words VWD and VWF (Figure 2). The original contributions, including those of Italian investigators, are selected from the beginning of 1976 through the end of 2025,²⁷⁻¹⁴⁴ and grouped by decade. Indeed, from the 420 reports found at the end of 1975, publications referring to VWD and/or VWF increased to 1,100 by 1985, 2,146 by 1995, 3,285 by 2005, 4,261 by 2015, and 5,109 by 2025.

Despite the accumulating information about VWD/VWF, progress in patients management has always lagged that of hemophilia. The milestones in VWD patient management are compared with those for hemophilia in Figure 3 during the first decade (1976-1985), along with related publications on VWD.²⁷⁻⁴² While hemophilia patients started to be home-treated with lyophilized FVIII/FIX concentrates, VWD patients were still treated in hospital by cryoprecipitate. On the other hand, in 1976, the pathogenesis of VWD was further clarified by the important role of the bleeding time as a test for VWD diagnosis and by the demonstration that megakaryocytes were another site of VWF synthesis.²⁸ In 1977, two important clinical studies were published: the first complete report on desmopressin (DDAVP) as a novel pharmacological approach for mild hemophilia and VWD, and the first Italian Registry of 100 VWD cases.^{29,30} Three years

later, new electrophoretic methods (cross-immunoelectrophoresis, followed by the novel agarose gel electrophoresis) were very useful in demonstrating that VWF was composed of a series of homologous oligomers originating from a basic subunit, with the largest multimers reaching molecular weights as high as 20.000 kilo-Daltons. In 1980, Ruggeri and Zimmerman published their seminal observation of abnormal VWF multimeric structure in two novel types of VWD (IIA and IIB),³¹ with the identification of the first cases of VWD2B characterized by heightened interactions with homologous platelets.³² Since then, many laboratories have used the technique developed by Ruggeri and Zimmerman to identify additional VWD variants characterized by loss of high-molecular-weight multimers (HMWM) and an abnormal inner structure of VWF. During the early 1980s, the hemophilia communities were dramatically involved in the tragedy of AIDS and most patients were infected by plasma-derived concentrates. Treatment of hemophilia was immediately modified with the advent of virus-inactivated plasma-derived factors. The structure and function of VWF in VWD was further investigated and correlated to treatment of VWD.³³⁻³⁶ The complex biosynthesis of VWF by endothelial cells and megakaryocytes provided more insights into the possible cellular events leading to abnormal VWF synthesis and organization.^{37,38} In 1985, data about cloning of FVIII and FIX genes became available with promising perspectives to develop recombinant products for hemophilia care. In the same year, the VWF gene was also characterized by four independent groups,³⁹⁻⁴² establishing the molecular basis for a better understanding of VWD.

The milestones of VWD patient management compared with that of hemophilia patients during the second decade (1986-1995) are reported in Figure 3, along with related publications.⁴³⁻⁴⁸ VWD

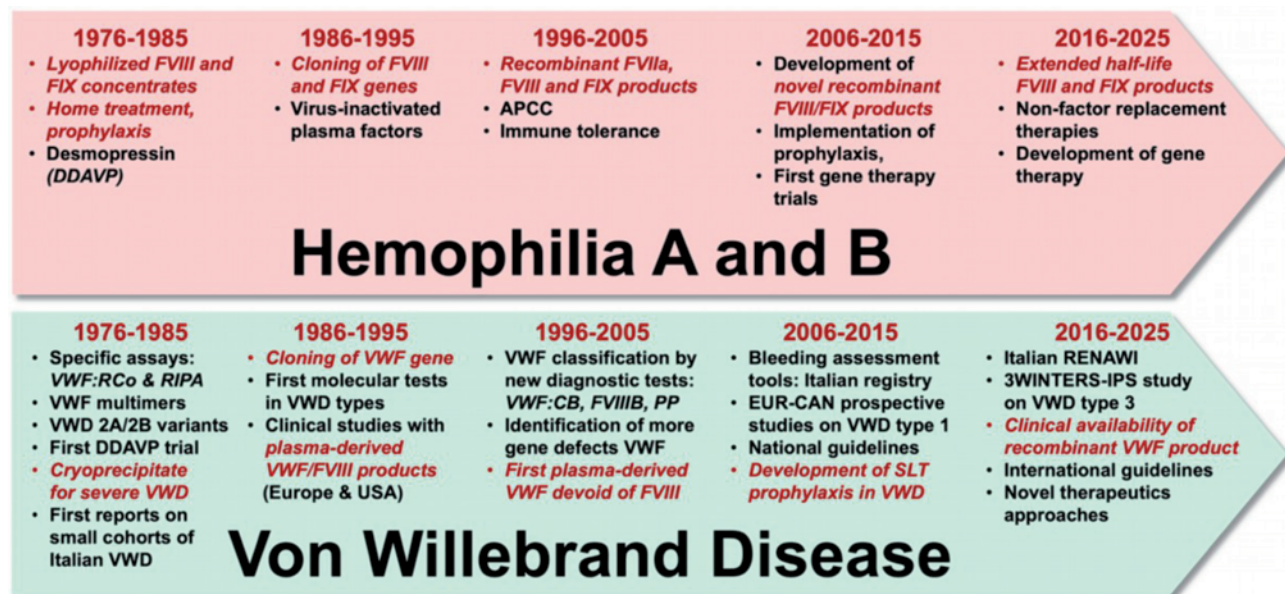


Figure 3. Milestones on management of patients with hemophilia *versus* those of patients with von Willebrand Disease (VWD) during the last 50 years (1976-2025). The most significant milestones for patients with hemophilia and VWD are shown in red for comparison of milestones achieved.

VWF, von Willebrand factor; VWF:RCo, VWF ristocetin cofactor; RIPA, ristocetin-induced platelet aggregation; SLT, secondary long-term.

were preserved from HIV infections because of their infrequent exposure to large-pool lyophilized concentrates. In 1986, Rodeghiero *et al.* published a large epidemiological study, showing for the first time the high frequency of VWF defects in the general population.⁴³ More information was available about the role of carbohydrates on VWF structure and function and on the binding of different VWF forms to platelet receptors.^{44,45} As concerns management, patients with VWD not responding to DDAVP started to be treated with viral-inactivated intermediate-purity FVIII concentrates, previously used in hemophilia, because some of them contained significant amounts of active VWF. In 1989, one of these virus-inactivated plasma-derived FVIII/VWF concentrates (*pd-FVIII/VWFC*) was shown to be effective in European VWD, and in 1992, a specific protocol on the *ex vivo* biological effects of virus-inactivated *pd-FVIII/VWFC* in PWVWD was developed.^{46,47} From 1992 to 1995, while patients with VWD started to be exposed to *pd-FVIII/VWFC*, those with hemophilia were enrolled in the first clinical trials with recombinant FVIII and FIX products. Indeed, in the early 1990s, clinical research focused mainly on novel therapies for hemophilia, while less attention was paid to innovative treatments for VWD. This is confirmed by the fact that one of those recombinant products obtained from CHO cells could synthesize the entire FVIII/VWF complex *in vitro* and therefore could be useful for treating both hemophilia and VWD patients. Incredibly, to satisfy the rule of *purus is better* requested by the *US Food and Drug Administration (FDA)*, the VWF moiety was removed from recombinant FVIII (*r-FVIII*) for hemophilia therapy. So, VWD could have been treated with recombinant VWF (*r-VWF*) since early 1990s, instead of waiting more than 20 additional years to use their *r-VWF*. In 1994, a revised classification of VWD was available reporting novel information about the disease.⁴⁸

The milestones in VWD patient management during the third decade (1996–2005) are compared with those for hemophilia in Figure 3, along with related publications.^{49–71} The major milestone in the pathophysiology of VWF was its characterization not only in VWD but also in microvascular thrombosis, when VWF was shown to be the substrate of the ADAMTS-13 protease.^{49,50} It was clear for the first time that increased amounts of VWF-HMWM, due to reduced activity of this cleaving protease, were the cause of Thrombotic Thrombocytopenic Purpura (TTP).^{49,50} The important role of VWF in shear-dependent hemostatic phenomena was also demonstrated.⁵¹ While patients with hemophilia could benefit from recombinant FVIII/FIX also in primary prophylaxis, in 1996 the results of a pharmacokinetic study with a novel plasma-derived VWF concentrate (*pd-VWFC*) almost devoid of FVIII were published.⁵² This was the first attempt to design a more specific therapeutic approach for VWD because the authors demonstrated that even very low endogenous FVIII levels (<15 U/dL), such as those found in type 3 VWD, could be normalized 6 hours after administration of *pd-VWFC* devoid of FVIII. Following the recommendations of the UK von Willebrand Working Party,⁵³ many clinical studies were conducted in both inherited and acquired VWF defects from 1996 to 2005,^{54–74} that addressed acquired von Willebrand Syndrome therapies,⁵⁴ bleeding problems in women,^{55,56} tests for VWD diagnosis such as PFA-100,⁵⁷ as well as VWF collagen binding activity,⁵⁸ and health-status as well as health-related Quality of Life (QoL) of VWD patients.⁶⁷ These data were in-

troduced in the first Italian recommendations for the diagnosis and therapy of VWD, indicated as Italian Guidelines on behalf of AICE.⁶² Thanks to the discovery of new VWF gene defects, novel VWD variants could be identified such as VWD type 2N,⁶⁰ together with the results of the international registry on acquired von Willebrand Syndrome.⁵⁹ However, while hemophilia patients were already submitted to primary prophylaxis using recombinant products, severe VWD just started the first approaches of secondary long-term prophylaxis.^{69–71}

The milestones about VWD patient management during the fourth decade (2006–2015) are compared with those of hemophilia in Figure 3, with related publications.^{72–104} The fourth decade started with the official document of the ISTH Scientific and Standardization Committee (SSC) on VWF about the update on pathophysiology and classification of VWD,⁷² followed by the first *in vitro* attempt to develop gene therapy of VWD,⁷³ the preliminary results of the VWD prophylaxis network,⁷⁴ and the validation of a standardized questionnaire to assess bleeding symptoms in a large cohort of European patients proposed by Tosetto *et al.*, later indicated as Bleeding Assessment Tool (BAT).⁷⁵ Patients with VWD could benefit from the results of two clinical studies organized in Canada and in Europe on behalf of the ISTH-SSC on VWF.^{76,77} In both studies, the new criteria for clinical and molecular diagnosis of type 1 VWD were applied, including the detailed questionnaire BAT.⁷⁵ More reports about novel lab tests for diagnosis,⁸² and the treatment with different *pd-VWFC* were published in specific VWD cohorts,^{78–81,86,91,93} with correlations with molecular defects observed in different VWD types, especially in type 2 VWD variants.^{86,96} Furthermore, the correlations between molecular defects and response to desmopressin in type 1 and the changes during pregnancy according to specific mutations were also demonstrated.^{85,92} Between 2013 and 2015 clinical data about the recombinant VWF concentrate (*r-VWFC*) were published.^{98,103} The availability of this interesting clinical data set formed the basis for the preparation in this decade of many national recommendations as those proposed by US and EU expert groups,^{83,101} and also the results of prospective observations, such as those collected on behalf of AICE (RENAWI-2) became available,^{95,102} together with those from Prophylaxis Network.¹⁰⁴

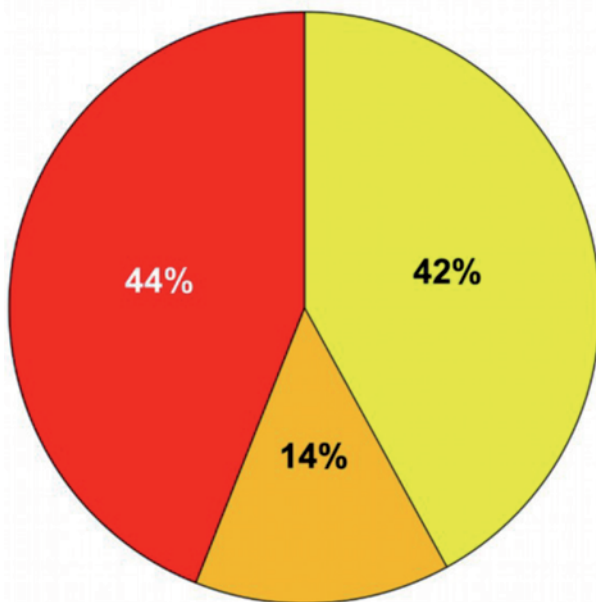
The most relevant milestones in VWD patient management during the fifth decade (2016–2025) are compared with those of hemophilia in Figure 3, with related publications.^{102–144} During the last decade, the previously established concepts about VWD management could be extended worldwide, thanks to specific activities of Scientific Societies such as American Society of Hematology (ASH), International Society of Thrombosis and Haemostasis (ISTH) and World Federation of Hemophilia (WFH). Indeed, many clinical studies for the standardization of laboratory assays and of therapeutic regimens were organized by the SC on hemostasis of ASH, the ISTH-SSC on VWF and the SC on VWD of WFH. Projects on how to improve awareness of patients with VWD were organized worldwide to promote patient identification, especially in medium- and low-income countries.¹²⁹ The efforts of experts in VWD management culminated in the evidence-based recommendations published in International Guidelines.^{1,2} However, the gap between the management of hemophilia and that of VWD remains clear today. While hemophilia can now be treated with extended half-life FVIII and FIX products and by non-factor replacement therapy in primary prophylaxis, VWD was treated for the first time with a *r-VWF* with very recent

approval in secondary long-term prophylaxis. Most importantly, gene therapy has been introduced in clinical practice for hemophilia A and hemophilia B while previous attempts for VWD gene therapy could not be confirmed and proposed in clinical trials. The lack of innovative therapeutic approaches still found in VWD, compared with those developed and in use for hemophilia, could be easily explained by data from the Italian Registry on inherited bleeding disorders, published in 2018 by the Italian Istituto Superiore di Sanità (ISS).¹⁰⁹ To compare distribution of hemophilia

A classified by FVIII levels as mild (5-30 U/dL), moderate (1-5 U/dL) and severe (<1 U/dL) with that of VWD, progressively lower levels of both VWF and FVIII activities were applied to VWD1, VWD2 and VWD3 shown in that report,¹⁰⁹ according to the levels used to calculate bleeding incidence rate in Italian VWD:¹⁰² mild (VWF:RCo=30-50 U/dL; FVIII:C=40-70), moderate (VWF:RCo=10-30 U/dL; FVIII:C=20-40), severe (VWF:RCo=<10 U/dL; FVIII:C=<20 U/dL). Based on levels, moderate-severe cases represent the large majority (58%) of he-

HA (n = 4,109)			VWD (n = 3,245)	
FVIII:C	5-30 U/dL	Mild	VWF:RCo FVIII:C	30-50 U/dL 40-70 U/dL
FVIII:C	1-5 U/dL	Moderate	VWF:RCo FVIII:C	10-30 U/dL 20-40 U/dL
FVIII:C	< 1 U/dL	Severe	VWF:RCo FVIII:C	< 10 U/dL < 20 U/dL

HA distribution (n = 4,109)



VWD distribution (n = 3,245)

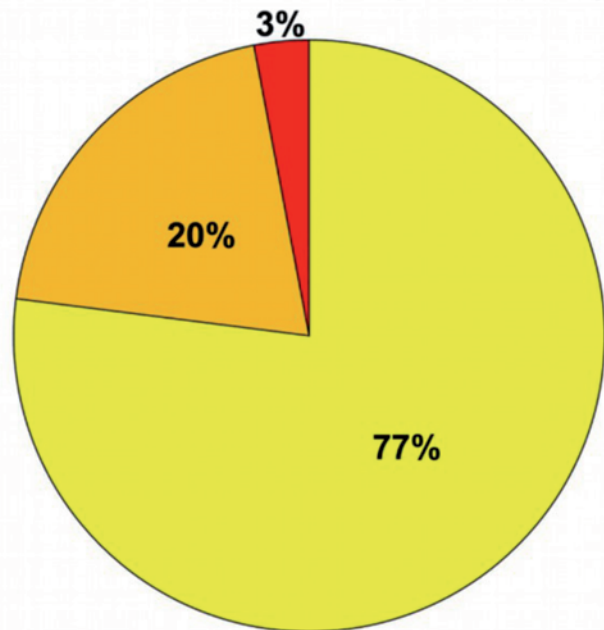


Figure 4. Distribution of mild-moderate-severe Italian patients with hemophilia A (HA) *versus* patients with Von Willebrand disease (VWD). To compare the 3 different categories of mild, moderate, severe HA with the 3 different VWD1, VWD2, VWD3 types shown in the original table of Italian Inherited Bleeding Disorders published in 2018 by the Italian Istituto Superiore Sanità,¹⁰⁹ we have classified VWD1, VWD2 and VWD3 patients by progressively lower levels of both VWF and FVIII activities. The range of VWF and FVIII activities were derived from those used to calculate bleeding incidence rate in Italian VWD patients:¹⁰² mild (VWF:RCo=30-50 U/dL; FVIII:C=40-70), moderate (VWF:RCo=10-30 U/dL; FVIII:C=20-40), severe (VWF:RCo=<10 U/dL; FVIII:C=<20 U/dL). Distribution of mild (*shown in yellow*), moderate (*shown in orange*) and severe (*shown in red*) cases of patients with HA and VWD. Note the different percent distribution of mild cases in HA (42%) *versus* those in VWD (77%), as shown in the lower panel of the figure.

mophilia A while only 23% of VWD are characterized by severe-moderate types (Figure 4). Probably, because of relatively large number of patients with severe bleeding phenotypes since their childhood and more information from clinical studies of Quality of Life (QoL), hemophilia A have been offered more therapeutic options since 2000 while innovative therapies have been proposed in VWD only recently.¹⁴⁴

From national versus international guidelines to address unmet needs in von Willebrand disease management

The recommendations list for VWD management, called National Guidelines, is quite long, especially because more editions of each National Guideline have been published. One of the first was published in 1997 by the UK Working Party.⁵³ In Italy, Guidelines were published five years later, on behalf of AICE.⁶² Another comprehensive report was published in 2008 by US experts who tried to prepare evidence-based National Guidelines.⁸³ Certainly, these were useful to improve VWD management, but they should be considered principle of care generated by opinion of experts, as those published by Castaman *et al.* on behalf of European Investigators.¹⁰¹ Therefore, for a correct definition of Guidelines for VWD management, we must consider only those published in 2021 as International Guidelines,^{1,2} because the authors used current methodological and statistical criteria into the extensive analyses of published clinical trials to determine the levels of recommendation. Since most clinical studies on VWD were only retrospective, with a very limited number of prospective trials, mostly non-randomized, levels of recommendations reported in the International Guidelines were not very strong when clinical questions were analyzed. Another important message derived from International Guidelines was the list of specific definitions for future research in VWD management.¹¹⁷ The authors described the meaning of the following clinical definitions: desmopressin (DDAVP) response, prophylaxis in VWD *versus* that of hemophilia, major *versus* minor bleeding episodes, major *versus* minor surgery, heavy menstrual bleeding, primary and secondary postpartum hemorrhage.¹¹⁷ They also identified several unmet needs about VWD management to be fulfilled. Among those about VWD diagnosis, the first unmet need is certainly the lack of VWD awareness, especially in bleeding women. VWD underdiagnosis is certainly caused by the current insufficient collaboration between hematologists and other medical specialists, such as anesthesiologists, general practitioners, oral surgeons, obstetricians-gynecologists, otolaryngologists, pediatricians. But certainly, the

most relevant unmet need identified by the International Guideline members is the little availability of appropriate laboratory VWF assays to be added to the collection of bleeding assessment tools (BAT) in most laboratory departments devoted to the screening of inherited bleeding disorders. Among the unmet needs concerning VWD treatment are the exact benefits and limitations of DDAVP therapy, with or without tranexamic acid (TXA), in mild-moderate VWD patients during bleeding episodes and after minor or major surgery. The authors of the International Guidelines encourage the treaters of VWD to assess individually the biological response to DDAVP and to evaluate its efficacy and safety, with or without TXA, *versus* VWFC with or without FVIII:C especially in women during menorrhagia, pregnancies and deliveries. Moreover, a more appropriate use of *pd- or r-VWFC* during major surgery, with a clear definition of doses and lab monitoring of VWF and FVIII levels, was proposed to avoid excessive doses. Another unmet need about PWVWD management is the appropriate therapeutic regimens with VWFC to manage GI bleeds with the association of drugs interfering with pro- and anti-angiogenic activities. Finally, the definition of evidence-based criteria for medium- or long-term secondary prophylaxis in severe VWD, following the most recent classification of severe cases, was given.

From guidelines to current clinical practice in Italy

Previous experiences obtained from retrospective and prospective Italian VWD registries unfortunately pointed out that assays for VWF activities,^{95,102} as those proposed in the International Guidelines for diagnosis, were not present in several AICE Centers. To overcome this insufficient availability of VWF assays, a Working Group on VWD diagnosis (WG-VWDIAG) was organized by AICE in October 2022 to explore the current level of VWD assessment and to propose a simplified approach that might allow the correct identification and management of Italian patients with inherited and acquired defects of VWF. The current diagnostic landscape of Italian VWD was reported in detail in a recent publication.¹⁴¹ Members of the WG-VWDIAG were also invited to prepare a list of minimal requirements for the diagnosis of VWD types and to propose a simplified diagnostic approach to be applied in all the AICE Centers. Among recommendations to be transferred into the Italian Guidelines, members of WG-VWDIAG have approved the following statements: 1) The ISTH BAT must be always applied to all suspected cases for VWD. 2) The identification of VWD patients should be preferably performed using one of the recent automatic tests for PD-VWFact

Table 1. Minimal diagnostic requirements at Italian hemophilia centers for the diagnosis of von Willebrand disease types.

VWD general + VWD3	BAT, platelet count, PD-VWF: act and FVIII:C
VWD type 1 and 2	+ VWF:Ag with PD-VWF: act/Ag ratio > or < 0.7
VWD type 2A and 2M	+ VWF:CB with VWF:CB/Ag or multimers
VWD type 2B	+ RIPA or genotype or low platelet count post DDAVP
VWD type 1C	+ VWF:pp or three VWF activities post-DDAVP
VWD type 2N	+ VWF:FVIII:B or genotype or FVIII/VWF:Ag ratio post-DDAVP

VWD, von Willebrand disease; BAT, Bleeding Assessment Tool; PD-VWF, plasma-derived von Willebrand factor; FVIII:C, Coagulation factor VIII; VWF:Ag, von Willebrand factor antigen; AG, antigen; + VWF:CB, von Willebrand factor collagen-binding; DDAVP, desmopressin; VWF:pp von Willebrand Factor propeptide.

and not with the VWF:RCO assay. 3) VWF:Ag and FVIII:C tests must be also assessed at first level together with PD-VWFact. 4) VWF:CB assay must be applied as first-level test, especially in Centers where the VWF Multimeric Analyses (VWF:MA) are not available. 5) RIPA is an essential assay for the identification of VWD2B. A possible alternative for centers familiar with Flow Cytometry (FC) is the RIPA-FC assay, which requires smaller sample volumes.⁸² The minimal assessment tools for the diagnosis of VWD types are listed in Table 1, and the simplified diagnostic approach is shown in Figure 5. As far as Italian Guidelines for VWD treatment are concerned, these issues were discussed by a panel of AICE-SISET Members. The most important statements approved by the panel are the need for long-term prophylaxis in VWD characterized by frequent and severe bleeding episodes, defined as >5 requiring treatment with VWFC. Such a prophylaxis should include the administration of VWFC at least

once a week for at least 6 months. Another important recommendation was related to the use of DDAVP. DDAVP must be used in clinical practice in VWD characterized by VWF levels <30 IU/dL only following a previous trial showing an optimal biological response. This is defined as a 2-times increase of VWF and FVIII activities respect to basal levels, with values >50 IU/dL for at least 4 hours. As far as menorrhagia is concerned, the panelists suggested to use tranexamic acid or DDAVP in women with excessive menstrual bleeding and desire for pregnancy. Finally, the recommendations for management of VWD patients undergoing major surgery were related to the time of laboratory investigation and minimal levels of VWF and FVIII activities to be maintained. The panelists suggested maintaining both parameters to >50 U/dL for at least 3 days and adjusting any following administration of VWFC according to the detected daily levels of both activities and the type of surgery.

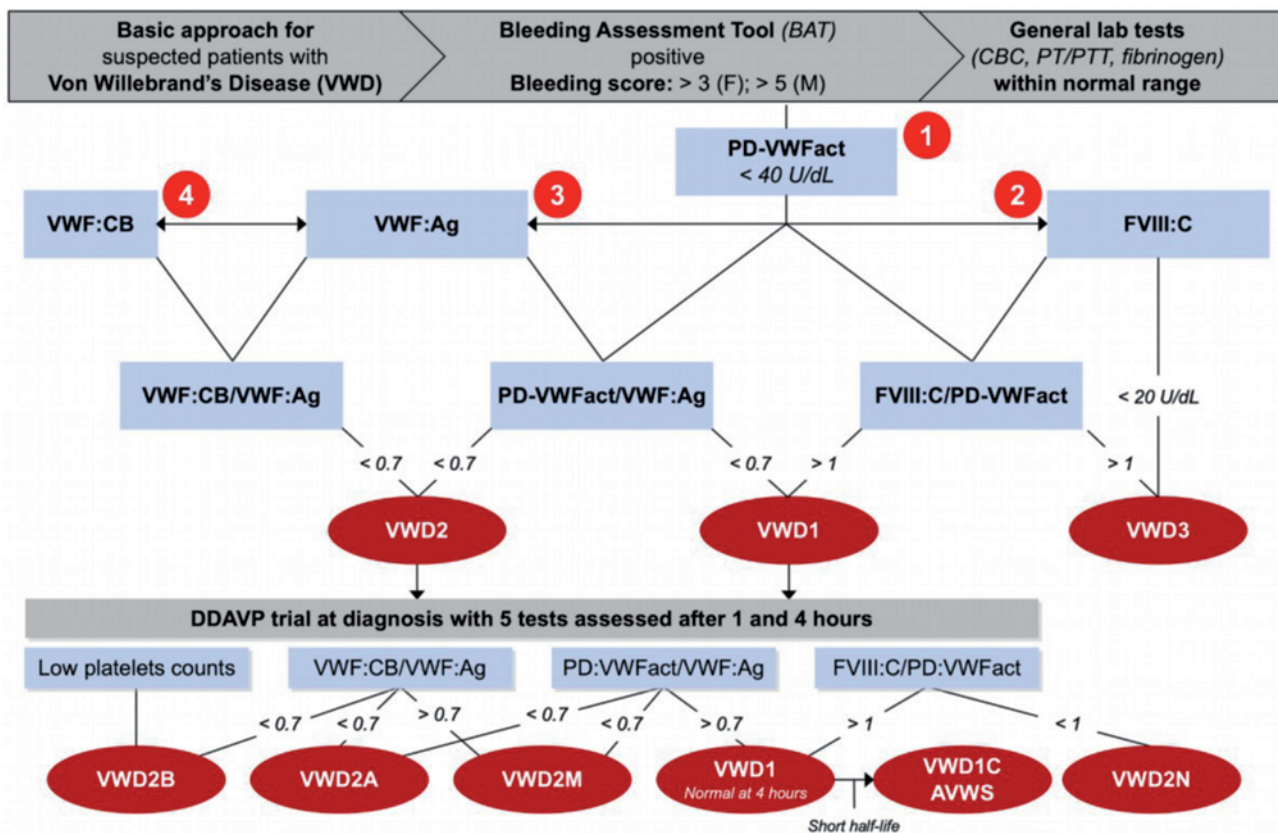


Figure 5. Flow-chart proposed for a more rapid diagnosis and classification of different VWD types, as partially modified from previous AICE publication.¹⁴¹ VWD3 can be diagnosed in case of undetectable PD-VWFact. FVIII:C is always reduced in VWD3 and in VWD2N: it can be partially reduced or normal in all the other VWD types. After bleeding history of suspected patients with VWD is collected by BAT and family history of bleeding investigated, a reduced level of VWF activity should be measured as first parameter (1) using one of the PD-VWFact tests together with FVIII:C (2), VWF:Ag (3) and VWF:CB (4). The use of DDAVP challenge test at the time of diagnosis with the assessment before and after DDAVP of platelet counts and of all four tests, with calculated PD-VWFact/Ag, VWF:CB/Ag and FVIII/VWF:Ag ratios, might allow the provisional identification of VWD types in most patients without performing additional tests. As examples, VWD2B can be identified without using RIPA (ristocetin-induced platelet aggregation), if platelet counts are reduced from baseline after DDAVP. Different PD-VWFact/Ag and VWF:CB/Ag ratios may suggest VWD2A or VWD2M types. Moreover, VWD patients with circulating short half-life VWF to be assessed by the increased VWF:PP/Ag ratio and the VWD2N cases with abnormal VWF:FVIIIIB can be identified by evaluating the behavior of the PD-VWFact/Ag, VWF:CB/Ag and FVIII/VWF:Ag ratios after 1 and 4 hours after DDAVP. Therefore, DDAVP trial can immediately identify clinical diagnosis of patients with different VWD types and cases who can be treated with DDAVP or VWF concentrates.

Current perspectives and future expectations

Despite great improvement of the knowledge on VWF pathophysiology during the last 50 years, clinical diagnosis and the identification of different VWD types are still unsatisfactory in many countries, including Italy. The likelihood of a correct diagnosis of VWD enhances when the clinical assessment of bleeding is associated with appropriate laboratory assays. The ASH-ISTH-NHF-WFH guidelines have highlighted many challenges in VWD diagnosis, mainly due to the limited availability of recommended tests to assess VWF-specific activities. The International Guidelines has recommended molecular diagnosis in some VWD types, but it is not mandatory in clinical practice for choosing appropriate treatments with DDAVP or VWFC. Major efforts are still required to promote simplified and less expensive diagnostic approaches. Prospective clinical studies, especially in mild-moderate VWD treated with DDAVP with or without TXA, or with pd-VWFC or r-VWFC, are warranted. Another important task for VWD experts is to validate in prospective clinical studies evidence-based criteria for including VWD patients since their childhood into secondary long-term prophylaxis by demonstrating its benefits *versus* on-demand therapy also for their Quality of Life. Finally, investigators must develop new drugs and/or therapeutic approaches specifically devoted to normalizing the vascular and/or platelet VWF defects (*bleeding time factors responsible for mucosal bleeds*) of patients with VWD.

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