

Guidelines for the Evaluation of Intravenous Desmopressin and von Willebrand Factor/Factor VIII Concentrate in the Treatment and Prophylaxis of Bleedings in von Willebrand Disease Types 1, 2, and 3

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ABSTRACT

The current standard for the diagnosis and management of patients with congenital von Willebrand disease (vWD) includes bleeding times (BTs), PFA-100 closure time (PFA-CT), factor (F) VIII:coagulant activity (C), vWF:antigen (Ag), vWF:ristocetin cofactor activity (RCo), a sensitive vWF:collagen-binding activity (CB), ristocetin-induced platelet aggregation (RIPA), analysis of vWF multimers in low- and high-resolution agarose gels, and the response to desmopressin. Guidelines and recommendations for prophylaxis and treatment of bleedings in vWD patients with vWF/FVIII concentrates should be derived from analysis of the content of these concentrates and from pharmacokinetic studies in different types of vWD patients with severe type 1, 2, or 3 vWD. The vWF/FVIII concentrates should be characterized by labeling with FVIII:C, vWF:RCo, vWF:CB, and vWF multimeric pattern, which will determine their predicted efficacy and safety in prospective management studies. Because the bleeding tendency is moderate in type 2 and severe in type 3 vWD, and because the FVIII:C levels are subnormal in type 2 and very low in type 3 vWD patients, new guidelines using vWF:RCo unit dosing for the prophylaxis and treatment of bleeding episodes are proposed. Such guidelines should be stratified for the severity of bleeding, the type of surgery (either minor or major), and also for the severity and type of vWD (i.e., either type 2 or 3 vWD).

KEYWORDS: Von Willebrand factor, von Willebrand disease, ristocetin cofactor activity, von Willebrand collagen-binding activity, bleeding time, desmopressin (DDAVP), von Willebrand factor concentrates

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Hereditary von Willebrand Disease and Acquired von Willebrand

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The current standard of von Willebrand factor (vWF) parameters that are used to differentiate type 1 from type 2 vWD include bleeding times (BTs), factor (F) VIII:coagulant activity (C), vWF:antigen (Ag), vWF:ristocetin cofactor activity assay (RCo), a sensitive vWF:collagen-binding assay (CB), ristocetin-induced platelet aggregation (RIPA), analysis of vWF multimers in low- and high-resolution agarose gels, and the response to desmopressin (DDAVP).¹⁻⁵ The BTs and RIPA are normal in asymptomatic carriers of a mutant vWF allele, in dominant type 1, and in recessive type 2N vWD, and this group has a normal response of vWF parameters to DDAVP.³⁻⁵ The response of FVIII:C is compromised in type 2N vWD. The BTs and RIPA are usually normal in type Vicenza and mild type 2A vWD, and these two vWD variants show a transiently good response of BT and vWF parameters followed by short in vivo half life times of vWF parameters. The BTs are markedly prolonged and RIPA is typically absent in recessive severe type 1, type 3, dominant type 2A, and recessive type 2C vWD. These subtypes are associated with low or absent platelet vWF, and no or poor response of vWF parameters to DDAVP. Dominant type 2B vWD is characterized by prolonged BTs, increased RIPA, normal platelet vWF, and a poor response of BT and functional vWF to DDAVP. Dominant type 2A and 2U are characterized by prolonged BTs, decreased RIPA, low vWF platelet, very low vWF:RCo values compared with vWF:Ag, and a poor response of functional vWF to DDAVP. Platelet-binding dysfunction type 2M vWD is marked by the presence of all vWF multimers in a low-resolution agarose gel, normal or slightly prolonged BT, decreased RIPA, a poor response of vWF:RCo, and a good response of FVIII and vWF:CB to DDAVP. The characteristics of platelet-binding dysfunction type 2M vWD therefore lie somewhere in between dominant type 1 and 2U.³⁻⁵

The existing recommendations for prophylaxis and treatment of bleedings in type 2 vWD patients with vWF/FVIII concentrates are derived mainly from pharmacokinetic studies in type 3 vWD patients.⁵ vWF/FVIII concentrates should be characterized by labeling with FVIII:C, vWF:RCo, vWF:CB activities, and vWF multimeric pattern to determine their safety and efficacy in prospective management studies. Because the bleeding tendency is moderate in type 2 and severe in type 3 vWD, and the FVIII:C levels are near normal in type 2 and very low in type 3 vWD patients, proper recommendations of vWF/FVIII concentrates using vWF:RCo unit dosing for the prophylaxis and treatment of bleeding episodes are proposed and should be stratified for the severity of bleeding, the type of surgery (i.e., either minor or major), and for the severity and type of vWD (i.e., either type 2 or 3 vWD).⁵

This review analyzes the literature in search for established guidelines for the evaluation and monitoring

of intravenous DDAVP and vWF/FVIII concentrates in the treatment and prophylaxis of bleedings in patients with type 1, 2, or 3 vWD.

RECOMMENDED STUDY DESIGN TO EVALUATE IN VIVO RESPONSES TO DDAVP IN vWD

The protocol for the DDAVP challenge test can be performed in the outpatient setting after full informed consent and careful counseling of the patient with congenital vWD by the responsible nurse and doctor. DDAVP is dissolved in sterile saline to a total volume of 50 mL and infused over a 30-minute period at a dose of 0.3 µg/kg. We recommend measurement of BT, PFA-100 (Platelet Function Analyser; Dade-Behring, Marburg, Germany) closure times (CTs); FVIII:C; and all vWF parameters before ($t=0$) and immediately after (within 15 minutes) DDAVP, and after 1, 2, 4, 6, 12, and 24 hours postinfusion of DDAVP on the basis of which the biological half-life times of the vWF parameters can be calculated (Table 1).⁵

In general, Ivy BTs are recorded as normal (1 to < 4 minutes), prolonged (4 to 15 minutes), and markedly prolonged (> 15 minutes). Simplate BTs are usually recorded as normal (< 9 minutes), prolonged (9 to 20 minutes), and markedly prolonged (> 20 minutes). The PFA-100 CT is sensitive to mild vWF deficiency and this group of individuals usually has normal BT. BT and PFA-100 are not specific enough to differentiate between controls, mild type vWF deficiency, or mild acquired or congenital platelet function defects.

The vWF:RCo and vWF:CB assays are complementary to assess the functional intactness or defects in vWF in types 1 and 2 vWD, respectively.⁶⁻⁹ There is also very good evidence that the vWF:CB assay using equine collagen type 1 or a type I/III (95%/5%) mixture are much more sensitive than the vWF:CB assay using type III collagen,^{9,10} and for the measurement of the hemostatic, more potent high vWF multimers present in the vWF/FVIII concentrate Haemate P (ZLB Behring, Marburg, Germany).⁷⁻⁹

A low-resolution gel (0.6 to 1.2% agarose) has been used to differentiate between the presence of large vWF multimers in type 1 versus the loss of large vWF multimers in type 2 vWD, and the presence of supranormal multimers in type Vicenza,^{1,2} but has limited power to detect the different banding patterns in various type 2 vWD patients.¹⁰ High-quality medium-resolution gels (1.4 to 2.0% agarose) followed by quantitative evaluation by densitometry are warranted to show the presence or absence of all sizes of multimers (including supranormal), together with the triplet structure of individual multimers as the current method for proper laboratory phenotyping and classification of type 1⁴ and the specific variants of type 2 vWD patients.¹⁰

Table 1 Protocol 1: DDAVP Challenge Test Proposed by the Goodheart Institute, Rotterdam³⁻⁵

Blood Sample	Before DDAVP	Within 15 min after DDAVP	After DDAVP (h)						
			1	2	4	6	12	24	
Ivy BT	+	–	+	or	+	–	+	+?	+?
PFA-100	+	+	+		+	+	+	+	+
RIPA	+	+	+		+	+	+	+	+
FVIII:C	+	+	+		+	+	+	+	+
vWF:Ag	+	+	+		+	+	+	+	+
vWF:RCo	+	+	+		+	+	+	+	+
vWF:CB	+	+	+		+	+	+	+	+
vWF:MM	+	+	+		+	+	+	+	+

The DDAVP challenge test has to be started in the morning between 800 and 900 h and should be performed by a skilled nurse after informed consent of the patient by the responsible physician. (Blood sampling at 12 h is optional.)

DDAVP, desmopressin; BT, bleeding time; PFA, platelet function analyser; RIPA, ristocetin-induced platelet aggregation; FVIII, factor VIII; C, coagulant activity; vWF, von Willebrand factor; Ag, antigen; RCo, ristocetin cofactor activity; CB, collagen-binding activity; MM, multimer.

THE RESPONSE OF BT, FVIII:C, AND vWF PARAMETERS TO DDAVP IN TYPE 1 vWD

Carriers of type 3 vWF null allele or missense mutation usually have no or a mild bleeding tendency, with no or mild vWF deficiency of both vWF:Ag and vWF:RCo in the range between 0.20 and 0.90 U/mL. The response to DDAVP is completely normal.³ Mild type 1 vWF deficiency in the range of 0.30 to 0.45 U/mL vWF:RCo and vWF:Ag (adjusted for blood group O) or to 0.60 (not adjusted for blood group O) is usually associated with normal BT, no or a mild bleeding tendency, and a completely normal response to DDAVP, with increase of FVIII:C and vWF parameters from below to above 1.0 U/mL or even to values ~2.0 U/mL.^{3,5}

The biological responses to DDAVP in a very heterogeneous group of 26 patients with type 1 vWD patients reported by Federici et al¹¹ are difficult to interpret. The details of individual responses are lacking, but at least three main categories can be identified easily in this group of patients.¹¹ First, seven of eight patients with vWF:RCo/Ag ratios below 0.6 showed a poor response to vWF:RCo and a much better response of FVIII:C to DDAVP, consistent with a type 2A-like vWD.³⁻⁵ Second, a group of at least 12 patients with so-called type 1 vWD was characterized by prolonged to markedly prolonged BT, undetectable or very low (<0.05 or <0.10 U/mL) vWF:RCo, and measurable FVIII:C levels. This is consistent with dominant 2A-like vWD with poor response to DDAVP.³⁻⁵ Third, a group of eight type 1 vWD patients had mean values of vWF:RCo of ~0.50 U/mL, showed a partial or good response to DDAVP, followed by normal biological half-life time for FVIII:C and vWF:RCo, consistent with a laboratory phenotype 1 vWD.¹⁻⁵

THE RESPONSE OF BT, FVIII:C, AND vWF PARAMETERS TO DDAVP IN TYPE 2 vWD

A minority of type 2A have mild vWD characterized by near normal to slightly prolonged values for BT, normal

FVIII:C and vWF:Ag, low vWF:RCo and vWF:CB levels, a normal RIPA, and complete correction of BT and functional vWF parameters to normal for only a few hours, followed by short half-life times for vWF:RCo and vWF:CB.^{4,5,12,13} This mild type 2A vWD has a transiently complete response to DDAVP that may be good enough for the treatment and prophylaxis of minor bleedings.^{3-5,11} Most type 2A vWD patients have pronounced or very low vWF:RCo, prolonged (markedly) BT, PFA-100 CT longer than 250 seconds, and show only a transient minor or a poor response to DDAVP with no correction of the BT despite some increase of vWF:RCo. Therefore, these patients are candidates for vWF/FVIII concentrate substitution for the treatment and prophylaxis of bleeding symptoms.^{4,5,12}

The response to DDAVP in type 2B vWD is normal for FVIII:C and vWF:Ag, transiently good and reaching normal values for vWF:RCo, and subnormal for vWF:CB, without correction of BT and no reappearance of large vWF multimers. Therefore, these patients are candidates for vWF/FVIII concentrate substitution for the prophylaxis and treatment of bleeding episodes.^{4,5}

Autosomal recessive type 2C vWD, and autosomal recessive type 1 vWD are characterized by variable FVIII:C levels, very low vWF:RCo, decreased or absent RIPA, and a very poor response to DDAVP.¹⁴⁻¹⁶

Federici et al¹¹ evaluated the biological responses in 20 patients with type 2M vWD. Gene mutations were not known in six patients, but were known in 14 of 20 patients: R1315C was evident in three patients, R1374C was evident in nine patients, and R1384H was evident in two patients. These three mutations are reported in the literature to be linked with types 2M or 2 unclassifiable (U) vWD.⁴ The response to DDAVP was rather good for FVIII:C, was not evaluated for vWF:Ag and vWF:CB, and was poor for vWF:RCo in 18 of the 20 so-called type 2M/U vWD. In the cohort of 20 patients with type 2M vWD, seven had borderline to slightly prolonged BTs, 10 had prolonged BTs, and three had

markedly prolonged BTs (≥ 30 minutes). The prolonged BTs were normal at 2 hours post-DDAVP in 13 of 20 patients with type 2M vWD.¹¹

Type 2N vWD is characterized by normal BT, normal PFA-100 CT, and normal or equally decreased vWF:Ag and vWF:RCo (simulating recessive type 1 vWD^{15,16}). However, FVIII:C is much lower (simulating mild hemophilia¹⁶⁻¹⁸) when compared with vWF:Ag due to a FVIII binding defect in the D-domain of the vWF protein.¹⁸ The severity of type 2N vWD depends on the degree of FVIII binding defect in the vWF protein of the various missense mutations in the D-domain of the vWF protein. Type 2N vWD patients homozygous or double heterozygous for a missense mutation (e.g., R854Q, C1060R) in the D-domain respond better to DDAVP than those with double heterozygosity for such missense mutation and null allele.^{5,18,19} Mild type 2N vWD patients have normal values for vWF parameters, decreased FVIII:C levels, and a good DDAVP response, but shortened half-life time of FVIII:C.^{5,11,18,19} Pronounced type 2N vWD patients have decreased values of vWF, low values of FVIII:C, and a rather poor response to DDAVP for FVIII:C, but a rather good response for vWF.^{5,11,18,19}

The laboratory phenotype and response to DDAVP in vWD type 2E are less well defined and are variable.^{4,5,10} Type 2E vWD is usually autosomal dominant, but may be recessive, and accounts for about one third of patients with type 2A in a large cohort of vWD patients.^{4,10}

RECOMMENDED STUDY DESIGN TO EVALUATE THE EFFECTS vWF/FVIII CONCENTRATES IN vWD

The *in vivo* responses of vWF parameters to vWF/FVIII concentrates have to be evaluated according to protocol proposed by the Scientific Standardization Committee of the International Society on Thrombosis and Haemostasis for studies on *ex vivo* biological effects of virus-inactivated concentrates in vWD patients.^{20,21} Each vWD patient, who needs the recommended infusion of vWF/FVIII concentrate using both FVIII:C and vWF:RCo dosing in units per kilogram body weight for the treatment of spontaneous bleeding or bleeding prophylaxis during surgery, has to be evaluated prospectively after the first loading dose during daytime, evening, night, and on the weekend by the responsible hematologist in the hospital (Table 2). Each dose of vWF/FVIII concentrate has to be administered by intravenous infusion over a period of 15 to 30 minutes. Blood samples after the first loading dose have to be taken for FVIII:C and vWF parameters before infusion and at 1 hour (not earlier), and 3, 6, 12, and 24 hours after infusion, together with assessment of BT or PFA-CT based on the decision of the responsible physician. If two

Table 2: Protocol 2: Pharmacokinetic Study of vWF/FVIII Concentrate in Type 2 vWD^{5,20}

Blood Sample	Before	After Substitution of vWF/FVIII Concentrate (h)				
		1	3	6	12	24*
Ivy BT	+	+	+	+	+	+
PFA-100	+	+	+	+	+	+
RIPA	+	+	+	+	+	+
FVIII:C	+	+	+	+	+	+
vWF:Ag	+	+	+	+	+	+
vWF:RCo	+	+	+	+	+	+
vWF:CB	+	+	+	+	+	+
vWF:MM	+	+	+	+	+	+

*Blood sampling at 24 h is optional but recommended for pharmacokinetic studies.

Inclusion criteria: All type 2 and 3 and severe type 1 vWD patients, who do not respond or poorly respond to DDAVP and who are to be treated for bleeding or prophylaxis of bleeding during elective surgery, are candidates for the pharmacokinetic study of vWF/FVIII concentrate after the first loading dose using vWF:RCo dosing per kilogram body weight.

Each lot of vWF/FVIII concentrate should be evaluated for the content of FVIII:C, vWF parameters, and vWF multimers.

FVIII, factor VIII; BT, bleeding time; PFA, Platelet Function Analyser; RIPA, ristocetin-induced platelet aggregation; C, coagulant activity; vWF, von Willebrand factor; Ag, antigen; RCo, ristocetin cofactor activity; CB, collagen-binding activity; MM, multimer.

or more vWF/FVIII infusions are needed during one period of treatment, subsequent blood samples should be taken before and 1 hour after infusion.

IN VIVO EFFECTS OF vWF/FVIII CONCENTRATES IN TYPE 3 vWD

Mannucci et al²¹ compared the effect of four virus-inactivated vWF/FVIII concentrates (Haemate P, Factor 8Y [LFB, Lille, France] [BPL, London, United Kingdom], high-purity vWF, and Alpha 250 [Alpha Therapeutics, Los Angeles, CA]) in 10 type 3 vWD patients. All concentrates were equally effective in attaining normal and sustained vWF:RCo plasma levels between 0.60 and 2.00 U/mL at 1 hour postinfusion in the 10 patients and > 0.50 U/mL at 6 hours postinfusion in the majority of the 10 patients. The pasteurized vWF/FVIII concentrate, Haemate P, completely or partially corrected the Simplate BT in eight of 10 patients, the dry-heated solvent detergent (SD) vWF/FVIII concentrates Factor 8Y and Alpha 250 in five patients, and the high-purity vWF concentrate did not correct the BT. The BTs were slightly to partially corrected at 6 hours postinfusion in six of 10 patients treated with Haemate P and three of 10 patients treated with the other vWF/FVIII concentrates.

Fukui et al²² treated two patients with Haemate P at doses of 52 and 65 IU vWF:RCo/kg, which corrected the BT, FVIII:C, and vWF:RCo to normal, with the appearance of all vWF multimers for several hours after infusion. Lethagen et al²³ evaluated the pharmacokinetic

and hemostatic effect of four different vWF/FVIII concentrates (Haemate P, Profilate [Grifols, Barcelona, Spain], Facteur Willebrand [LFB, Lille, France], and FVIII very high purity vWF [FVIII-VHP-vWF; LFB, Lille, France]) in five patients with type 3 vWD. vWF/FVIII concentrates were given as one loading dose of 30 to 63 IU FVIII:C/kg body weight, and Facteur Willebrand and FVIII-VHP-vWF were given at dosages of 71 to 110 IU vWF:RCo/kg body weight. Given that the ratio of vWF/FVIII:RCo is ~ 2.2 for Haemate P, the dosage of Haemate P given in vWF:RCo ranged from 66 to 130 IU vWF:RCo/kg body weight. Both Duke and Simplate II bleeding times exceeded 1200 seconds in all type 3 patients before infusion of vWF/FVIII concentrate. The correction and shortening of bleeding times in five type 3 vWD patients lasted longer after Haemate P (24 to 36 hours) than after FVIII-VHP-vWF (4 to 24 hours) or Facteur Willebrand (8 to 24 hours).²³ The shortening of bleeding times after Profilate was of shorter duration, except when the dosage was large (60 IU FVIII:C/kg body weight). The multimeric vWF pattern in vitro was almost normal in Haemate P, FVIII-VHP-vWF, and Facteur Willebrand, whereas Profilate lacked the largest vWF multimers.²³ Almost all vWF multimers appeared in vivo after substitution of Haemate P, FVIII-VHP-vWF, and Facteur Willebrand were still detectable after 4 hours, but after 12 hours the largest multimers had disappeared. After Profilate, the large multimers were lacking in vivo. The plasma levels of FVIII:C increased after all four concentrates and remained high for long periods.

Goudemand et al²⁴ evaluated the pharmacokinetic response of one loading dose of FVIII-VHP-vWF (63 IU/kg vWF:RCo and 4 IU/kg FVIII:C) in one patient with type 3 vWD and documented the following typical kinetic differences among FVIII:C, vWF:RCo, and other vWF parameters: maximum levels of vWF:RCo and vWF:Ag were observed 1 hour after infusion, whereas maximum levels of FVIII:C were attained from 6 to 12 hours after the first infusion. The biological half-life times of FVIII:C, vWF:Ag, and vWF:RCo were 74, 21, and 18 hours, respectively. The markedly prolonged Duke BTs were normalized for at least 4 hours. In subsequent pharmacokinetic studies in type 3 vWD patients infused with purified vWF product (LFB, Lille, France) devoid of FVIII, 10 infusion studies at doses of 50 or 100 IU vWF:RCo/kg body weight revealed that FVIII:C was found to synthesize (bind to the infused vWF) at 0.6 U/dL/h and decay with a half-life of 16 hours, and that the infused vWF:Ag and vWF:RCo decayed with a half-life of 12 hours.^{25,26} Purified vWF did not correct the BTs at 50 IU vWF:RCo/kg, whereas four of five patients had normalization of the BTs lasting for 4 hours at 100 IU/kg.^{25,26} Purified vWF has been studied in type 2 vWD and for the most part produced similar results.²⁴

The vWF/FVIII concentrate, Immunate (Baxter, Vienna, Austria), lacks the large vWF multimers and the vWF:RCo/FVIII:C ratio is ~ 0.5 .^{27,28} This information will predict a normal recovery of FVIII:C and a poor recovery of vWF:RCo after a regular loading dose. Auerswald et al²⁷ reported on a patient with type 3 vWD and showed that a loading dose of Immunate of 83 IU FVIII:C/kg body weight indeed resulted in predicted high values for FVIII:C and vWF:Ag of 1.5 U/mL (2% recovery per infused IU FVIII:C/kg), whereas vWF:RCo increased from < 0.10 to 0.60 U/mL (0.75% recovery per infused IU FVIII:C/kg).

Mannucci et al²⁹ performed a pharmacokinetic study on Alphanate SD and Alphanate SD heat treated (SD/HT; Alpha Therapeutics) in 11 type 3 vWD patients. Alphanate lacks the highest molecular weight (MW) vWF multimers. The in vivo recoveries per transfused IU FVIII:C/kg body weight were an increase in FVIII:C of 2.1% for Alphanate SD and 2.9% for Alphanate SD/HT (Table 3). The ratio of FVIII:C to vWF:RCo in Alphanate was 0.6. Therefore, the calculated in vivo recoveries per transfused IU FVIII:C/kg body weight were an increase in vWF:RCo of 1.3% for Alphanate SD and 1.8% for Alphanate SD/HT. The calculated in vivo recoveries per transfused IU vWF:RCo/kg in this cross-over pharmacokinetic study in 11 type 3 vWD patients were an increase in vWF:RCo of 2.1% for Alphanate SD, and 2.9% for Alphanate SD/HT, and an increase of FVIII:C of 3.4% for Alphanate SD and 4.5% for Alphanate SD/HT (Table 3).²⁹ The biological half-life times of transfused Alphanate SD and Alphanate SD/HT were shortened (7.1 and 6.5 hours) for vWF:RCo, normal (12.4 and 12.9 hours) for vWF:Ag, and prolonged (26 and 23 hours) for FVIII:C, respectively (Table 3).²⁹

The French study compared two purified vWF concentrates Wilfactin (LFB) and Facteur Willebrand in eight type 3 vWD patients and found no differences (Table 4).³¹ The BTs were fully or partially transiently corrected for a few to several hours in 86% of the patients. The measured properties of the two high-purity vWF concentrates Wilfactin versus Facteur Willebrand, as well as the calculated incremental recoveries of vWF:RCo (2.1 versus 2.0%) and vWF:Ag (1.8 versus 1.9%), and the half-life times of vWF:RCo (12.4 versus 13.7 hours) and vWF:Ag (15.9 versus 17.1 hours, respectively), did not differ and were very similar to previous reports.^{24-26,33,34}

THE USE OF vWF/FVIII CONCENTRATES IN TYPE 2 vWD

Prospective comparative studies of various vWF/FVIII concentrate replacement therapies for type 2 and type 3 vWD patients have not been conducted. vWF/FVIII replacement therapy largely has been empirical, not

Table 3 Comparative Analysis of the Calculated in Vivo Recoveries of FVIII:C and vWF:RCo, and Their Biological Half-Life Times after a Loading Dose of vWF/FVIII Concentrate for Bleeding Prophylaxis in vWD Patients

vWF/FVIII Concentrate	Author				
	Ver Elst ²⁸ Immunate	Michiels ³⁰ Haemate-P	Mannucci ²⁹ Alphanate SD	SD/HT	ISTH 2006 ^{36,37} Wilate
Number of patients	7	5	13		21
vWD type	2A/B	2A/B	3		2/3
Mean loading dose given					
IU FVIII/kg body weight	54	40	60		50
Product information					
Ratio vWF:RCo to FVIII:C	0.5	2.2	0.625	0.625	0.82
Ratio FVIII:C to vWF:RCo	2	0.45	1.6	1.6	1.2
Ratio vWF:RCo/vWF:Ag	NT	0.84	NT		NT
Ratio vWF:CB/vWF:Ag	NT	0.97	NT		NT
Incremental recovery					
As per unit FVIII:C					
FVIII:C	2.1%	3.2%	2.1%	2.9%	2.0%
vWF:RCo	NT	3.9%*	1.3%†	1.8%†	1.6%
vWF:CB (type 1 collagen)	0.65%	2.8%	NT	NT	NT
As per unit vWF:RCo					
FVIII:C	4.2%	1.3%	3.4%	4.6%	2.4%
vWF:RCo	NT	1.7%*	2.5%†	2.9%†	1.9%
vWF:CB	0.35%	1.25%	NT	NT	NT
Biological half-life times					
t _{1/2} vWF:RCo (h)	14	> 12	6.5	7.1	> 12
t _{1/2} vWF:Ag (h)					17.5

*Measured 15 minutes after end of vWF/FVIII infusion.

†Measured 1 hour after end of vWF/FVIII infusion.

FVIII, factor VIII; C, coagulant activity; vWF, von Willebrand factor; RCo, ristocetin cofactor activity; vWD, von Willebrand disease; ISTH, International Society on Thrombosis and Haemostasis; SD, solvent detergent; SD/HT, solvent detergent heat treated; Ag, antigen; CB, collagen-binding activity; NT, not tested.

tailored to different types of vWD patients, and based primarily on FVIII:C for dosing recommendations. The recommendations to treat congenital vWD type 2 patients with vWF/FVIII concentrates are derived from pharmacokinetic studies in type 3 vWD patients. We compared the pharmacokinetic and hemostatic effects of

two vWF/FVIII concentrates, Haemate P and Immunate, for the treatment of patients with type 2 vWD in three recent studies (Table 3).^{28–30} The calculated in vivo recoveries of Immunate per transfused unit of FVIII:C were 2.1% for FVIII:C and 0.65% for vWF:CB in seven type 2 vWD patients in the study by Ver Elst et al.²⁸

Table 4 The French Study Directly Comparing Wilfactin and Facteur Willebrand LFB in Eight Patients with von Willebrand Disease (vWD) Type 3³¹

Parameter	Wilfactin	Facteur Willebrand
Number of patients	8	8
Product information		
vWF:RCo (IU/mL)	103 (90–110)	56–60
vWF:Ag (IU/mL)	108 (107–125)	56–74
vWF:RCo/vWF:Ag ratio	0.95	0.98
FVIII:C (IU/mL)	2.1–3.1	0.1–1.2
vWF/FVIII:RCo ratio	< 0.04	< 0.02
In vivo vWF:RCo recovery (%)	89 ± 3	84 ± 12
Incremental recovery per unit vWF:RCo	2.1%	2.0%
Half-life times vWF:RCo (h)	12.4	13.7
In vivo vWF:Ag recovery (%)	76 ± 12	78 ± 3
Incremental recovery per unit vWF:Ag	1.8%	1.9%
Half-life time vWF:Ag (h)	15.9	17.1

vWF, von Willebrand factor; RCo, ristocetin cofactor activity; Ag, antigen; FVIII, factor VIII; C, coagulant activity; CB, collagen-binding activity.

Mean in vivo recoveries of Haemate P per transfused IU FVIII:C/kg body weight were 3.2% for FVIII:C, 3.9% for vWF:RCo, and 2.8% for vWF:CB, indicating a clear superiority of Haemate P over Immunate.³⁰ Dosing Immunate and Haemate P in IU vWF:RCo/kg to reach an equal 1.7% in vivo increase of vWF:RCo will induce an increase in FVIII:C of more than 4.2% for Immunate and only 1.3% for Haemate P (Table 3). These in vivo data are directly related to their in vitro characteristics of the absence of high and intermediate MW vWF multimers in Immunate and the presence of all vWF including the large vWF multimers in Haemate P, and with the ratio of vWF:RCo to FVIII:C of 0.5 for Immunate and 2.2 for Haemate P.^{27,28}

The comparative analysis of data in Table 3 demonstrate that treatment of vWD patients with Alphanate or Immunate using FVIII:C dosing will lead to undertreatment with regard to vWF:RCo. Treatment with the two using vWF:RCo dosing in units per kilogram body weight will result in overtreatment with regard to FVIII:C.³² When comparing the shortened half-life times for vWF:RCo of 6.5 to 7.1 hours after transfusion of Alphanate versus ~12 hours for Haemate P, it becomes clear to clinicians that sufficient hemostatic levels of vWF:RCo persist with Haemate P for a much longer time.²⁹ For repeated doses (e.g., major surgery in vWD), clearance becomes even more important, leading to a significantly lower amount of overall Haemate P needed when compared with Alphanate.²⁹ Given that the average ratio of FVIII:C to vWF:RCo is 0.45 for Haemate P, 1.6 for Alphanate SD and SD/HT, and 2 for Immunate, the treatment of vWD patients with the recommended dose

of 60 IU vWF:RCo/kg to reach normal values for vWF:RCo of ~1.0 to 1.2 U/mL will result in much higher and very high levels of FVIII:C > 2.0 U/mL up to 3.0 to 4.0 U/mL for Alphanate and Immunate.²⁸⁻³⁰ Such high FVIII:C levels for more than 1 week after treatment with vWF/FVIII concentrate for major surgery in vWD patients is, according to Mannucci,³² a plausible explanation to contribute to the already existing increased risk of postoperative venous thrombosis.

The European study compared Wilfactin and human FVIII concentrate (Haemate P or Innobrand [LFB]) in 17 patients with vWD (two type 1, nine type 2A/B, and six type 3; Table 5).³¹ The administration of Wilfactin or vWF/FVIII concentrate resulted in a transient shortening of Ivy or Simplate BTs in 71 and 82% of the patients, respectively.³¹ The shortening of BTs was maximal between 1 to 3 hours postinfusion, and was lost after 24 hours.³¹ The measured vWF content of the products Wilfactin versus Haemate P/Innobrand as well as the calculated incremental recoveries of vWF:RCo (1.9 versus 1.9%) and vWF:Ag (2.2 versus 2.2%), and the half-life times of vWF:RCo (11.7 versus 12.8 hours) and vWF:Ag (14.8 versus 17.8 hours, respectively) were bioequivalent in terms of efficacy. This confirms that the pharmacokinetic profile of vWF does not depend on the amount of FVIII. This is true for the comparison of Wilfactin and Haemate P, which contain the large MW vWF multimers, as reflected by the normal vWF:RCo/vWF:Ag ratios (Table 5).

As can be predicted from previous studies,^{24-26, 30,33-35} the pattern of FVIII:C kinetics typically was very different after the infusion of a vWF/FVIII

Table 5 The European Study Comparing Wilfactin and Haemate-P/Innobrand in Patients with Type 1, Type 2, and Type 3 vWD³¹

Parameter	Wilfactin	Hemate-P	Innobrand
Number of patients	17	17	
Type 1	2	2	
Type 2A, 2B	9	9	
Type 3	6	6	
Product information			
vWF:RCo (IU/mL)	96 (90-110)	98	60
vWF:Ag (IU/mL)	112 (95-130)	102	63
vWF:RCo/vWF:Ag ratio	0.99	0.96	0.95
vWF:CB/vWF:Ag ratio	NT	NT	
FVIII:C (IU/mL)	0.9-9.2	33	34
vWF/FVIII:RCo ratio	< 0.09	0.34	0.40
In vivo vWF:RCo recovery (%)	78 ± 22	77 ± 18	
Incremental recovery per unit vWF:RCo	1.9%	1.9%	
Half life times vWF:RCo (h)	11.7	12.8	
In vivo vWF:Ag recovery (%)	89 ± 22	87 ± 18	
Incremental recovery per unit vWF:Ag	2.2%	2.2%	
Half life time vWF:Ag, (h)	14.8	17.8	

vWF, von Willebrand factor; RCo, ristocetin cofactor activity; Ag, antigen; FVIII, factor VIII; C, coagulant activity; CB, collagen-binding activity; NT, not tested.

concentrate (Haemate P or Innobrand) compared with a purified vWF concentrate (Wilfactin). The human vWF/FVIII concentrates Haemate P (FVIII:C/vWF:RCo ratio 0.34) and Innobrand (FVIII:C/vWF:RCo ratio 0.40) were followed by the predicted incremental recoveries, resulting in a two times higher concentration of vWF parameters compared with FVIII:C immediately after the loading dose (Fig. 1). In contrast, after infusion of Wilfactin that contains a very small amount of FVIII:C (FVIII:C/vWF:RCo ratio < 0.04), the maximal FVIII:C levels were progressively attained between 12 to 24 hours postinfusion, reaching subnormal to low normal levels (Fig. 1). This delayed increase is due to the progressive stabilization of endogenous FVIII by its binding to the infused purified vWF concentrate. Depending on the pretreatment FVIII:C levels, types 2A and 2B vWD had significantly higher FVIII:C levels during the first 12 hours after infusion of Wilfactin compared with type 3 vWD. This will predict equal efficacy and safety in the prophylaxis and treatment of bleeding in type 2 vWD with subnormal or low normal FVIII:C levels. In both studies the half-life of endogenous FVIII was almost identical (15.8 hours in the French study and 15.1 hours in the European study). Comparing the FVIII:C levels after infusion of Wilfactin (endogenous FVIII:C) and Haemate P or Innobrand (exogenous and endogenous FVIII:C), the decay curves of FVIII:C were not parallel until 72 hours postinfusion (Fig. 1). This has important implications for the treat-

ment of acute bleeding episodes. It may also have an impact on the efficacy of long-term prophylaxis of joint bleeds in type 3 vWD because the much higher levels of FVIII:C for 2 to 3 days after each infusion with Haemate P or Innobrand as compared with Wilfactin surely will have consequences with regard to dosing of each of the products.

The vWF/FVIII concentrate Wilate (Octapharm AG, Lachen, Switzerland) showed the absence of large MW vWF multimers compared with controls, and in vivo recoveries were comparable to those of Alphanate (Table 3).^{36,37} The ratio of vWF:RCo/FVIII:C in Wilate is 0.82 as compared with a vWF:RCo/FVIII:C ratio of 2.2 in Haemate P.³⁸ With this in mind, Haemate P will limit the thrombotic risk that may occur due to increased FVIII:C following repeated infusion as compared with Wilate and Alphanate.³² Given that the vWF:CB assay using equine collagen type 1 or a mixture of type I/III (95%/5%) is much more sensitive than the vWF:CB assay using type III collagen^{9,10} for the measurement of the hemostatically more potent high MW vWF multimers, the product information on Wilate, which used the insensitive vWF:CB (type III collagen) assay, provides the false impression of functional integrity of vWF:Ag. Additional product characterization of Wilate in direct comparison with Haemate P and Wilfactin is warranted.

We recently introduced adjusted recommendations for dosing of vWF/FVIII concentrates in IU

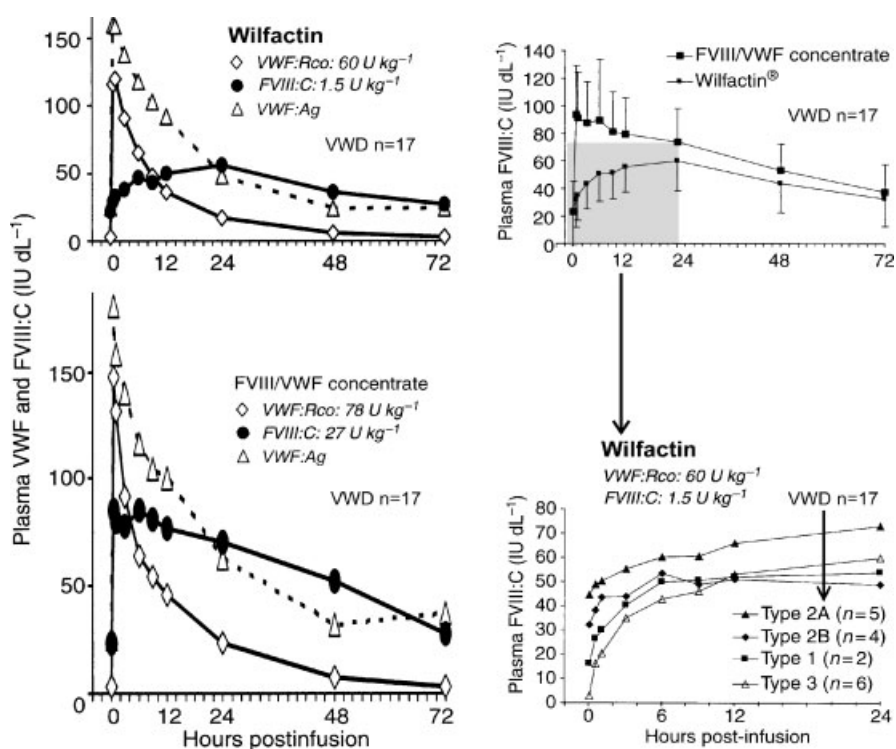


Figure 1 Direct comparison of the in vivo responses of von Willebrand factor (vWF):ristocetin cofactor activity (RCo), vWF:antigen (Ag), and factor (F) VIII:coagulant activity (C) after one loading dose of Wilfactin and vWF/FVIII concentrate (Haemate P or Innobrand) in 17 patients with von Willebrand disease (vWD) subdivided in type 1, type 2A, type 2B, and type 3 for the responses to FVIII:C.

Table 6 Proposed Guidelines Using vWF:RCo Dosing for Prophylaxis and Treatment of Bleeding during Surgery or Trauma in Patients with Type 2, Severe Type 1, and Type 3 von Willebrand Disease (vWD)

vWD Type	Initial Dose vWF:RCo (IU/kg)	Subsequent Infusions	Objective
Type 2A, 2B, 2C, 2D, 2U, Recessive 1, severe 2N vWD			
Type of surgery/bleeding			
Major surgery or trauma	60–80	40 IU/kg every 12 hours for a few days and 30 IU/kg/d for another 2–4 d; no tranexamic acid	Adjust to maintain vWF:RCo > 0.60 U/mL until wound healing is normal for 4–7 d
Severe bleeding			
Minor surgery or trauma	40–60	40 IU/kg once on day 1; add tranexamic acid	Normal vWF:RCo > 0.50 for 12 h and adequate vWF:RCo for 2 days
Dental extraction	40–60	No, add tranexamic acid	Adequate vWF:RCo > 12 h
Mucocutaneous bleeding	40–60	No, add tranexamic acid	Adequate vWF:RCo > 12 h
Type 3 vWD			
Major surgery or trauma	80–100	30–40 IU/kg every 12 h for 2–4 d and 30–40 IU/kg/d for another 3–6 d	Adjust to maintain FVIII:C and vWF:RCo > 0.60 U/mL until wound healing is completed (7–10 d)
Minor surgery or trauma or musculoskeleton bleeding	60	40–60 IU/kg once a day for 3 d	Maintain FVIII:C and vWF:RCo > 0.40 U/mL for one to a few days
Dental extraction	60	40 IU/kg once on day 1	Maintain FVIII:C and vWF:RCo > 0.30 f or 1 or 2 d
Prophylaxis joint bleeds	60	2 or 3 times a week	Maintain FVIII:C > 0.02 U/mL

vWF, von Willebrand factor; RCo, ristocetin cofactor activity.

vWF:RCo/kg body weight for the treatment and prophylaxis of bleeding in type 2 vWD, and extended it to recessive types 1 and 3 vWD (Table 6).^{4,5} vWF/FVIII concentrates should be characterized by labeling their content of FVIII:C, vWF:Ag, vWF:RCo, and vWF:CB activities using sensitive tests and the vWF multimeric pattern. Such proper characterization of vWF/FVIII concentrates will determine their predicted efficacy and safety in prospective management studies. The adjusted recommendations should be tailored for the severity of bleeding complications, for the type of surgery (minor or major), and for patients with types 2 and 3 vWD (Table 6). These recommendations have to be evaluated for safety and cost effectiveness in prospective management studies, and are to be amended where necessary to improve the management of vWD patients.

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