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Surgical prophylaxis in von Willebrand's disease: a difficult balance to manage

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Von Willebrand disease (VWD) is the most common genetic bleeding disorder with a prevalence of approximately 1-2 percent confirmed in different population studies. The severity of the bleeding tendency is usually proportional to the degree of the VWF defect, although the large majority of cases diagnosed appear to have a mild disease.

Patients with VWD may require short- or long-term prophylaxis treatment. Short-term prophylaxis is usually performed to prevent excessive bleeding following surgery or invasive procedures, while long-term prophylaxis may be needed to control recurrent mucosal and joint bleeding complicating the more severe forms of VWD.

This review is focused on the current knowledge on replacement treatment for patients with VWD disease undergoing surgical or invasive procedures. On the whole, the published studies document the safety and efficacy of VWF/FVIII concentrates as surgical prophylaxis in VWD patients, in particular of Haemate P, the most widely used VWF/FVIII concentrate due to its high VWF:FVIII ratio. The recent literature data also show that the best management of VWD patients undergoing surgery is that to perform a pharmacokinetic study in order to strictly tailor for each VWD patient loading and maintenance doses of VWF/FVIII concentrates. Furthermore, the same studies underscore that, along with VWF levels, FVIII levels should be monitored in the peri-operative period in order to prevent exposures to high FVIII levels, associated with an increased risk of venous thrombosis.

Key Words: Von Willebrand disease, surgery, bleeding, prophylaxis.

Introduction

von Willebrand's disease (VWD) is the most common genetic bleeding disorder with a prevalence of approximately 1-2% confirmed in different population studies[1]. The severity of the bleeding tendency is usually proportional to the degree of the von Willebrand factor (VWF) defect, although the large majority of cases diagnosed appear to have mild disease[2].

Patients with VWD may require short- or long-term prophylaxis. Short-term prophylaxis is usually performed to prevent excessive bleeding following surgery or invasive procedures, while long-term prophylaxis may be needed to control recurrent mucosal and joint bleeds complicating the more severe forms of VWD[3]. The first therapeutic option will be described in this review with particular regards to the use of VWF/factor VIII (FVIII) concentrates for the management of surgical or other invasive procedures in VWD patients. Finally, we will focus on thrombotic complications following replacement treatment in VWD and on the management of antithrombotic prophylaxis in VWD patients undergoing surgery.

Prophylaxis in patients with VWD undergoing surgery

Besides a few studies documenting the successful use of desmopressin (DDAVP), with an efficacy rate ranging from 91 to 100% (Table I)[4-6], most studies used VWF/FVIII concentrates as prophylaxis of haemorrhage in VWD patients undergoing surgical or invasive procedures[7-16]. The main plasma-derived VWF/FVIII concentrates utilised

Table I- Literature results on short-term prophylaxis in von Willebrand's disease.

Author, year[reference]	Product	Cases	VWD types	Type of intervention	Dose range	Efficacy (%)
Desmopressin						
Federici, 2000[4]	DDAVP	27	20 type 1, 7 type 2	27 oral surgery	0.3 µg/kg IV	100
Leissinger, 2001[5]	DDAVP	37	37 type 1	37 oral or surgical procedures	1.5 mg/mL IN	93
Nitu-Whalley, 2001[6]	DDAVP	35	25 type 1, 2 type M	3 major, 13 minor, 19 oral surgery	0.3 µg/kg IV	91
VWF/FVIII concentrates						
Goudemand, 1998[7]	VHP	54	NI	23 major, 31 minor surgery	51-55 IU VWF:RCo/kg	100
Federici, 2002[8]	Fanhdi	14	5 type 1, 7 type 2, 2 type 3	7 major, 5 minor, 2 oral surgery	17-92 IU FVIII:C/kg/d	93
Mannucci, 2002[9]	Alphanate	71	6 type 1, 19 type 2, 14 type 3	71 surgical or invasive procedures	20-76 IU VWF:RCo/kg	96
Lillicrap, 2002[10]	Haemate P	73	26 type 1, 20 type 2, 21 type 3, 6 NI	73 surgery	11.9-222.8 IU VWF:RCo/kg	99
Franchini, 2003[11]	Haemate P	43	19 type 1, 7 type 2	14 major, 11 minor, 11 oral surgery, 7 IP	21.4-52.5 IU VWF:RCo/kg/d	98
Thompson, 2004[12]	Haemate P	42	16 type 1, 9 type 2, 8 type 3, 6 NI	25 major, 17 minor surgery	32.5-216.8 IU VWF:RCo/kg	100
Bernstein, 2006[13]	Haemate P	35	17 type 1, 12 type 2, 13 type 3	25 major, 7 minor, 3 oral surgery	17.4-135.3 IU VWF:RCo/kg	91
Federici, 2007[14]	Haemate P	73	19 type 1, 27 type 2, 10 type 3	17 major, 28 minor, 19 oral surgery, 9 IP	27-146 IU VWF:RCo/kg/d	97
Lethagen, 2007[15]	Haemate P	29	10 type 1, 11 type 2, 8 type 3	16 major, 11 minor	50.1-87.0 IU VWF:RCo/kg	96
Borel-Derlon, 2007[16]	Wilfactin	108	5 type 1, 25 type 2, 14 type 3	43 major or minor, 14 oral surgery, 51 IP	11.1-100 IU VWF:RCo/kg	100

Abbreviations: DDAVP, desmopressin; VWD, von Willebrand's disease; VWF, von Willebrand factor; FVIII:C, factor VIII coagulant activity; IV, intravenously; IN, intranasal; NI, not indicated; VWF:RCo, von Willebrand factor ristocetin cofactor; IP, invasive procedures; d, day.

in the management of VWD are reported in table II. The characteristics of these concentrates are that they contain both VWF and FVIII and are treated with virucidal methods[17]. Data derived from pharmacokinetic studies have greatly contributed to the appropriate use of VWF/FVIII concentrates in surgical procedures.

The results of a cross-over pharmacokinetic study by the Alphanate Study Group were published in 2002 and included data on 39 VWD patients (6 with type 1, 17 with type 2A, 2 with type 2 B, 14 with type 3) receiving prophylactic treatment for 71 surgical or invasive diagnostic procedures. The median number of infusions per procedure was three and the dosages for the first and subsequent infusions were 60 IU/kg and 40 IU/kg VWF ristocetin cofactor activity (VWF:RCo), respectively. An important finding of this study was that in patients with type 3 VWD the half-life of FVIII activity (FVIII:C) was approximately twice that of VWF antigen (VWF:Ag) (23.6 hours versus 12.9 hours) due to the endogenous FVIII:C. Efficacy results showed that 71% of patients who received prophylactic treatment for surgery or invasive procedures had good clinical responses.

Another pharmacokinetic study conducted on the recently available VWF/FVIII concentrate Wilfactin documented that the three virus-inactivation/removal steps (solvent/detergent, 35 nm filtration and dry heat treatment) during the manufacturing of Wilfactin did not alter the pharmacokinetics of VWF and FVIII[18].

However, the majority of the pharmacokinetic studies have been performed on the intermediate-purity VWF/FVIII concentrate Haemate P. Thanks to its widespread use since 1984, when it was first introduced in Europe, this product is currently considered the gold standard in the management of VWD[19].

Studies of the pharmacokinetics of Haemate P in VWD have generally focused on the VWF:RCo half-life ($t_{1/2}$), and the classical and incremental *in vivo* recovery. VWD patients receiving Haemate P had $t_{1/2}$, and classical and incremental *in vivo* recoveries within the expected ranges for plasma-derived FVIII products with the only exception of VWF:RCo$t_{1/2}$ in the A4001study (6.8 hours) which was lower than expected (7-12 hours in previous studies depending on the VWF/FVIII product used)[12,20]. However, in this study $t_{1/2}$ was calculated using a single-compartment

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Table II - Plasma-derived concentrates containing VWF with published activity in VWD subjects.

Product	Purification	Virucidal method	VWF:RCo/Ag	VWF:RCo/FVIII	HMW VWF multimers(*)	Manufacturer
Haemate P	Polyelectrolyte Precipitation	Pasteurization	0.9	2.5-2.88	> 70% of NHP (highly active)	CSL Behring
Wilate	Affinity + size exclusion CT	SD+Dry heat	1.0	0.8	< 70% of NHP (active)	Octapharma
Alphanate	Heparin ligand	CT SD+Dry heat	0.9	0.82-1.2	< 70% of NHP (active)	Grifols-USA
Fanhdi	Precipitation + heparin ligand CT	SD+Dry heat	0.8	1.29-1.6	< 70% of NHP (active)	Grifols-SP
Wilfactin	Ion exchange Affinity CT	SD+Nanofiltration + Dry heat	0.7	60	> 70% of NHP (highly active)	LFB

model (effective $t_{1/2}$), without taking into account the different distribution and elimination phases of VWF:RCo (two-compartment elimination-phase $t_{1/2}$ model)[12,20].

In contrast, in the surgical B4001 study[15], the 9.9 hour $t_{1/2}$ was calculated as part of a supplemental two-compartment analysis not originally planned in the study; the original single-compartment effective $t_{1/2}$ was 6.3 hours (range, 1.1-14.1 hours)[21]. The data points in the distribution phase most probably indicated a shorter $t_{1/2}$ than those exclusively in the elimination phase, thereby providing for a shorter effective $t_{1/2}$. This is supported by the fact that the effective $t_{1/2}$ in the A4001 study was also low (6.8 hours). Thus, the B4001 study supported the idea of an early and rapid disappearance of VWF:RCo in a distribution phase, followed by slower kinetics in an elimination phase.

In contrast to VWF:RCo, the elimination kinetics of FVIII:C in VWD patients in the B4001 study were considerably slower than those previously reported for patients with haemophilia A,[15] thus suggesting that a slight accumulation could occur in plasma following multiple Haemate P infusions over time. It was, therefore, hypothesised that exogenous VWF administered via Haemate P leads to molecular stabilisation of both endogenous and exogenous plasma FVIII, thereby leading to slower elimination kinetics.

Table III reports the most important literature data on the VWF:RCo pharmacology results in VWD patients treated with Haemate P[11,12,15,20-24].

As for the pharmacokinetic studies, the majority of the literature data on the prophylactic use of VWF/FVIII concentrates in surgical and invasive procedures regards

Table III - Summary of the literature data on VWF:RCo pharmacology results in VWD patients treated with Haemate P

		Median (range)		
	N	$t_{1/2}$ (hours)	Classical IVR (%)	Incremental IVR (IU/dL)/(IU/kg)
Mannucci *et al.*[22]	10			2.2 (0.6)
CSL study: 201[23]	10	10.3 (6.4-18.6)	71.0 (50.0-96.0)	1.9 (1.1-2.7)
CSL study: A4001[12,20]	8	6.8 (1.4-13.3)		
Bleeding arm	7			1.5 (0.6-1.8)
Surgery arm	7			1.7 (0.5-2.6)
Prophylaxis arm	3			0.8 (0.7-1.5)
Franchini *et al.*[11]	26			2.0 (1.4-2.7)
Michiels *et al.*[24]	5	~12 (>1-16)		1.7 (1.4-2.1)
CSL study: B4001[15,21]	28	9.9 (2.8-51.1)	73.6 (24.5-180.3)	1.9 (0.6-4.5)

Note: $t_{1/2}$ was generally calculated as part of a two-compartment, elimination-phase $t_{1/2}$ model. Classical *in vivo* recovery (IVR) describes the observed peak activity in relation to the expected peak activity. The incremental IVR indicates the IU/dL activity rise in plasma per IU/kg body weight infused.

Haemate P. This is not surprising considering that the high VWF:RCo/FVIII ratio and the multimeric pattern of this product are similar to those of normal plasma[17].

An important recent multicentre prospective study which applied pharmacokinetic analysis to the management of surgical subjects with VWD was that conducted by the Haemate P Surgical Study Group[15]. This trial enrolled 29 subjects with VWD (10 with type 1, 10 with type 2A, 1 with type 2M and 8 with type 3) undergoing elective surgery and found that Haemate P, whose preoperative median VWF:RCo loading dose of 62.4 IU/kg was based on a pharmacokinetic study, provided excellent or good haemostasis in 96.3% of subjects on the day of surgery and in 100% in the following days. This study demonstrated for the first time that the *in vivo* recovery is constant over a wide range of doses of VWF/FVIII concentrate (dose-linearity relationship) and that initial pharmacokinetic determinations can provide a reliable basis for serial dosing decisions.

The intermediate-purity VWF/FVIII concentrate Haemate P was also used in a large retrospective study organised by Canadian Haemophilia Centres. Four hundred and thirty-seven events, including bleeding episodes and surgical procedures, were treated. The rate of excellent-to-good responses was 97% overall and 99% in surgical procedures. The median dose of concentrate per infusion used to treat surgical events was 69.1 IU VWF:RCo/kg (range, 11.9-222.8)[10]. We have reported the experience of three Italian haemophilia centres that treated 26 VWD patients who underwent 43 surgical or invasive procedures (14 major surgery, 11 minor surgery, 11 dental extractions and 7 invasive diagnostic procedures) under coverage with Haemate P[11]. The mean daily dose of concentrate given was 39.3 (range, 25-52.5) IU VWF:RCo/kg for major surgery, 28.7 (range, 21.4-34.8) IU VWF:RCo/kg for minor surgery, 24.0 (range, 23.5-25) IU VWF:RCo/kg for dental extractions and 32.3 (range, 27.3-37) IU VWF:RCo/kg for invasive procedures. As only one bleeding episode was recorded without drug-related adverse events, we concluded that Haemate P was safe and effective in preventing excessive bleeding after major and minor surgery or invasive procedures in VWD patients. An open-label prospective study collected data from 39 subjects undergoing 42 urgent surgical procedures[12]. The median loading dose, based upon VWF:RCo activity, was 82.3 IU/kg (range, 32.5–216.8), and the median maintenance dose per infusion was 52.8 IU/kg (range, 24.2–196.5) for a median of 3 days (range, 1-50). The median number of infusions per surgical procedure was 6 (range, 1-67). More recently, a retrospective cohort study on 100 VWD patients (23 with type 1, 40 with type 2 and 37 with type 3) treated with Haemate P reported data on 56 patients who underwent 73 surgical or invasive procedures (17 major surgery, 28 minor surgery, 9 invasive procedures, 19 dental procedures). The median daily dose of Haemate P was 80 VWF:RCo IU/kg with clinical responses rated as excellent/good in 97% of cases.

Thus, as reported in table I, the analysis of data following Haemate P prophylactic treatment in surgical procedures documents an excellent efficacy profile with haemostasis judged to be excellent/good in 91-100% of cases.

As regards the dosage, the literature results document that 20 to 50 IU/kg of VWF/FVIII concentrates given once daily until healing is complete are haemostatically effective in preventing bleeding in the majority of surgical or invasive procedures. Thus, for major procedures, FVIII and VWF:RCo levels should be raised to 80-100 UI/dL at the time of surgery and maintained above 50 IU/dL for at least 7-14 days. For minor procedures, FVIII and VWF:RCo levels above 50 IU/dL at the time of surgery are advisable, followed by levels above 30 IU/dL for at least 5-7 days. Finally, dental extractions or invasive procedures may be managed with a single concentrate infusion aimed at reaching VWF:RCo/FVIII levels of about 50 IU/dL.

Thrombotic complications following VWF/FVIII concentrate infusion

There are reports of thromboembolic events in VWD patients receiving VWF/FVIII concentrates, especially in the setting of known risk factors[25-27].

Makris and colleagues[26] described four cases of venous thromboembolism after treatment with the intermediate-purity FVIII concentrate Haemate P but most of them had additional risk factors (older age, surgery, oestrogen intake). Two venous thrombotic complications were recorded in a multicentre, prospective study evaluating a high-purity VWF/FVIII concentrate in 38 patients with VWD treated prophylactically for 71 surgical or invasive procedures[9]. A VWD subject with multiple risk factors developed pulmonary embolism in the study conducted by Lethagen and colleagues[15]. Mannucci reported a case of a patient with type III VWD who developed a non-fatal pulmonary embolism 12 days after hip replacement surgery. A post-operative check of coagulation parameters documented very high FVIII levels (up to 400%)[28]. The same author[27] carried out a questionnaire survey on the occurrence of venous thromboembolism in patients with VWD treated with VWF/FVIII concentrates in the last 10 years in 52

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haemophilia centres and found a low incidence of thromboembolic events (7 cases in 12,640 treatments over 10 years corresponding to 1 case per 1,806 treatment-years), although higher than that observed in patients with haemophilia A (2 cases in 141,250 treatments). On the basis of these results, the author suggested that FVIII plasma levels should be measured daily in VWD patients treated with VWF/FVIII concentrates in order to avoid excessive levels of the clotting factor and that thromboprophylaxis should be given to those patients undergoing major surgical procedures, especially if other risk factors for venous thromboembolism are present (e.g. old age, previous thrombosis, presence of prothrombotic gene mutations, orthopaedic surgery, obesity, immobility, hormone replacement therapy). Moreover, both authors (Makris and Mannucci) outlined the importance of using the VWF/FVIII concentrate with the highest ratio between VWF:RCo and FVIII:C in such patients, in order to correct the VWF defect without increasing FVIII:C plasma levels excessively. Indeed, plasma FVIII levels increase over the course of VWF/FVIII concentrate treatment proportionally more than those of VWF because VWF stabilises not only the exogenously administered FVIII but also the endogenous FVIII pool[29]. Consequently, the FVIII:C half-life is about three times longer than the VWF:RCo half-life in VWD patients and about two times longer than the FVIII:C half-life in patients with haemophilia A.

The threshold levels of FVIII above which there is a significant risk of thromboembolic events have not been clearly defined. The Leiden Thrombophilia Study showed that the highest quartile of FVIII levels (>150 IU/dL) was associated with an approximately five-fold increased risk of venous thrombosis compared to the lowest quartile (<100 IU/dL)[25]. On the other hand, a recent study suggested that a level of 270 IU/dL might be an appropriate upper limit for patients without additional risk factors.

In order to minimise the risk of thromboembolic complications in patients with VWD treated with VWF/FVIII concentrates I recommend the following precautions: choose a VWF/FVIII concentrate with a high VWF:FVIII ratio; assay FVIII:C every 12 hours on the day a VWF/FVIII dose is administered and every 24 hours thereafter; and provide thromboprophylaxis (e.g. with a low-molecular-weight heparin) at least for VWD patients at higher thrombotic risk.

Conclusions

On the whole, the published studies document the safety and efficacy of VWF/FVIII concentrates as prophylaxis in VWD patients undergoing surgery or invasive procedures, and in particular of Haemate P, which is the most widely used VWF/FVIII concentrate because of its high VWF:FVIII ratio.

The recent literature data show that the best management of VWD patients undergoing surgery includes a pharmacokinetic study in order to tailor the loading and maintenance doses of VWF/FVIII concentrates for each patient. This is particularly important considering the heterogeneous nature of VWD. The same studies also underscore that, along with VWF levels, FVIII levels should be monitored in the peri-operative period in order to prevent exposure to high FVIII levels, which are associated with an increased risk of venous thrombosis.

References

1) Rodeghiero F, Castaman G, Dini E. Epidemiological investigation of the prevalence of von Willebrand's disease. Blood 1987; **69:** 454-9.
2) Castaman G, Federici AB, Rodeghiero F, Mannucci PM. von Willebrand's disease in the year 2003: towards the complete identification of gene defects for correct diagnosis and treatment. Haematologica, 2003; **88:** 94-108.
3) Franchini M, Targher G, Lippi G. Prophylaxis in von Willebrand disease. Ann Hematol 2007; **86:** 699-704.
4) Federici AB, Sacco R, Stabile F, et al. Optimising local therapy during oral surgery in patients with von Willebrand disease: effective results from a retrospective analysis of 63 cases. Haemophilia 2000; **6:** 71-7.
5) Leissinger C, Becton D, Cornell C Jr, Cox Gill J. High-dose DDAVP intranasal spray (Stimate) for the prevention and treatment of bleeding in patients with mild haemophilia A, mild or moderate type 1 von Willebrand disease and symptomatic carriers of haemophilia A. Haemophilia 2001; **7:** 258-66.
6) Nitu-Whalley IC, Griffioen A, Harrington C, Lee CA. Retrospective review of the management of elective surgery with desmopressin and clotting factor concentrates in patients with von Willebrand disease. Am J Hematol 2001; **66:** 280-4.
7) Goudemand J, Negrier C, Ounnoughene N, Sultan Y. Clinical management of patients with von Willebrand's disease with a VHP vWF concentrate: the French experience. Haemophilia 1998; **4(Suppl 3):** 48-52.
8) Federici AB, Baudo F, Caracciolo C, et al. Clinical efficacy of highly purified, doubly virus-inactivated factor VIII/von Willebrand factor concentrate (Fanhdi) in the treatment of von Willebrand disease: a retrospective clinical study. Haemophilia 2002; **8:** 761-7.
9) Mannucci PM, Chediak J, Hanna W, et al., and the Alphanate Study Group. Treatment of von Willebrand disease with a high-purity factor VIII/von Willebrand factor concentrate: a prospective, multicenter study. Blood 2002; **99:** 450-6.
10) Lillicrap D, Poon M-C, Walker I, et al. Association of Hemophilia Clinic Directors of Canada. Efficacy and safety

of the factor VIII/von Willebrand Factor concentrate, Haemate-P/Humate-P: ristocetin cofactor unit dosing in patients with von Willebrand disease. Thromb Haemost 2002; **87:** 224-30.

11) Franchini M, Rossetti G, Tagliaferri A, et al. Efficacy and safety of factor VIII/ von Willebrand factor concentrate (Haemate-P) in preventing bleeding during surgery or invasive procedures in patients with von Willebrand's disease. Haematologica 2003; **88:** 1279-83.
12) Thompson AR, Gill JC, Ewenstein BM, et al., Humate-P Study Group. Successful treatment for patients with von Willebrand disease undergoing urgent surgery using factor VIII/von Willebrand factor concentrate (Humate-P). Haemophilia 2004; **10:** 42-51.
13) Bernstein J, Cox Gill J, Leissinger CA, et al., Humate P Study Group. Safety and efficacy of von Willebrand factor/ factor VIII concentrate (Humate-P) for prophylaxis of excessive bleeding during elective surgery un patients with von Willebrand disease. Blood 2006; **108:** abstract 4076.
14) Federici AB, Castaman G, Franchini M, et al. Clinical use of Haemate P in inherited von Willebrand disease: a cohort study on 100 Italian patients. Haematologica 2007; **92:** 944-51.
15) Lethagen S, Kyrle PA, Castaman G, et al., the Haemate P Surgical Study Group. Von Willebrand factor/factor VIII concentrate (Haemate P) dosing based on pharmacokinetics: a prospective multicenter trial in elective surgery. J Thromb Haemost 2007; **5:** 1420-30.
16) Borel-Derlon A, Federici AB, Roussel-Robert V, et al. Treatment of severe von Willebrand disease with a high-purity von Willebrand factor concentrate (Wilfactin): a prospective study of 50 patients. J Thromb Haemost 2007; **5:** 1115-24.
17) Budde U, Metzner HJ, Müller HG. Comparative analysis and classification of von Willebrand factor/factor VIII concentrates: impact on treatment of patients with von Willebrand disease. 2006; **32:** 626-35.
18) Goudemand J, Scharrer I, Berntorp E, et al. Pharmacokinetic studies on Wilfactin, a von Willebrand factor concentrate with a low factor VIII content treated with three virus-inactivation/removal methods. J Thromb Haemost 2005; **3:** 2219-27.
19) Berntorp E, Archey W, Auerswald G, et al. A systematic overview of the first pasteurized VWF/FVIII medicinal product, Haemate® P: history and clinical performance. Eur J Haematol 2008;**70:** 3-35.
20) Gill JC, Ewenstein BM, Thompson AR, et al., Humate-P Study Group. Successful treatment of urgent bleeding in von Willebrand disease with factor VIII/VWF concentrate (Humate®-P): use of the ristocetin cofactor assay (VWF:RCo) to measure potency and to guide therapy. Haemophilia 2003; **9:** 688-95.
21) Mannucci PM. Dose linearity of a von Willebrand / factor VIII concentrate (Haemate® P) in elective surgery in von Willebrand disease patients. Blood 2003; **102:** 312a.
22) Mannucci PM, Tenconi PM, Castaman G, Rodeghiero F. Comparison of four virus-inactivated plasma concentrates for treatment of severe von Willebrand disease: a cross-over randomized trial. Blood 1992; **79:** 3130-7.
23) Dobrkovska A Krzensk U, Chediak JR. Pharmacokinetics, efficacy and safety of Humate®-P in von Willebrand disease. Haemophilia 1998; **4(suppl 3):** 33-9.
24) Michiels JJ, Berneman ZN, van der Planken M, et al. Bleeding prophylaxis for major surgery in patients with type 2 von Willebrand disease with an intermediate purity factor VIII/von Willebrand factor concentrate (Haemate® P). Blood Coagul Fibrinolysis 2004; **15:** 323-30.
25) Koster T, Blann AD, Briet E, et al. Role of clotting factor VIII in effect of von Willebrand factor on occurrence of deep-vein thrombosis. Lancet 1995; **345:** 152-5.
26) Makris M, Colvin B, Gupta V, et al. Venous thrombosis following the use of intermediate purity FVIII concentrate to treat patients with von Willebrand's disease. Thromb Haemost 2002; **88:** 387-8.
27) Mannucci PM. Venous thromboembolism in von Willebrand disease. Thromb Haemost 2002; **88:** 378-9.
28) Mannucci PM. Treatment of von Willebrand's disease. N Engl J Med 2004; **351:** 683-94.
29) Rodeghiero F, Castaman G. Treatment of von Willebrand disease. Semin Hematol 2005; **42:** 29-35.
30) Wells PS, Langlois NJ, Webster MA, et al. Elevated factor VIII is a risk factor for idiopathic venous thromboembolism in Canada - is it necessary to define a new upper reference range for factor VIII? Thromb Haemost 2005; **93:** 842-6.

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