

Therapeutic Approaches and Efficacy of von Willebrand Factor in von Willebrand Disease Treatment

Abstract

This systematic review evaluates therapeutic approaches for von Willebrand Disease (VWD), focusing on the role of von Willebrand factor (VWF) in treatment. Using the [Synthory.AI](#) service, the review adheres to PRISMA guidelines, analyzing studies from 2010 to 2024. Seven articles were included, emphasizing VWF's role in stabilizing factor VIII, which enhances treatment efficacy and reduces bleeding episodes. Despite promising results, variability in patient response and methodological limitations necessitate individualized treatment strategies and further research. Future studies should adopt prospective designs with larger, diverse populations to improve therapeutic strategies and patient outcomes.

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Methods

Approach

The search strategy was designed according to the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines [1]. The systematic literature review was automatically generated on demand using the [Synthory.AI](#) service. All components listed below were identified, extracted, assessed, and analyzed automatically as part of the review process. The review was created for research purposes.

Analysis Of The Request

The topic of the request was von willebrand factor in treatment.

The suggested focus areas for the review included:

* Therapeutic Approaches for von Willebrand Disease

*** Therapeutic Response and Pharmacokinetics

*** Perioperative Management and Hemostatic Efficacy

Criteria Of Inclusion And Exclusion

Inclusion criteria

1. Publications available in PubMed and PubMed Central™.
2. Publications related to von willebrand factor, treatment, and associated aspects.
3. Primary research studies, including randomized controlled trials, cohort studies, and qualitative research.

Exclusion criteria

1. Articles published before 2010/01.
2. Systematic literature reviews, case series, case reports, expert opinions, study protocols, and any unidentified study types.
3. Studies without full-text availability in PubMed or PubMed Central™.
4. Articles that have been previously included and analyzed in existing reviews within the defined focus areas, to avoid duplication and ensure the inclusion of novel research findings.

Search Strategy And Screening Process

The search employed 108 keywords. The search was conducted across the PubMed and PubMed Central™ databases, covering the publication period from 2010/01 to 2024/09.

The search and screening process included:

1. Identification: 289 records were retrieved from PubMed using the inclusion criteria.
2. Screening:
 - a. Articles were excluded based on the criteria.
 - b. Articles of low quality risk were excluded following an Article Quality Assessment.
3. Eligibility: Assessment of alignment with defined topics.

A total of 7 articles were included in the final review, based on the inclusion and exclusion criteria.

The breakdown by topic is as follows:

* Therapeutic Approaches for von Willebrand Disease: 7 articles

Data Extraction

Key study characteristics were extracted from the included articles. A predefined data extraction table was used to document details such as study design and key findings.

Quality Assessment

The quality of the included articles was assessed as follows:

- 1. The Newcastle-Ottawa Scale (NOS) was used to assess the quality of non-randomized and cohort studies [2].
- 2. The risk of bias assessment was used for randomized trials [3].

Analysis

The analysis proceeded in three phases:

- * Phase 1: Identification of potential topics.
- * Phase 2: Data extraction from relevant articles.
- * Phase 3: Analysis of the relevance of new findings.

A hybrid generative and causal method was employed for data analysis and review generation, with OpenAI™ serving as the generative component. This method combines generative modeling with causal analysis, enhancing both the reliability and interpretability of the outcomes by accounting for underlying cause-effect relationships.

The approach facilitated the integration of various evidence types into a coherent summary. The review process included summarizing and interpreting findings, as well as discussing the limitations identified in the included articles.

Results: Therapeutic Approaches for von Willebrand Disease

Therapeutic Response and Pharmacokinetics

Table 1. Therapeutic Response and Pharmacokinetics

Study ID	Length of intervention	Population of intervention	Control	Intervention	Intervention details	Primary outcome	Secondary outcome
Brown et al. 2003	15 minutes	Patients aged 19 to 58 years, recruited from haemophilia centers at University Hospital of Wales and Royal Free Hospital London, urban settings, diagnosed with Type 1 VWD or mild hemophilia A		Intravenous infusion of DDAVP	Infused intravenously, dose of 0.3 µg kg ⁻¹ , single infusion over 15 minutes, patients rested for 20 minutes prior to infusion	Median half-life of VWF antigen significantly shorter in Type 1 VWD patients compared to mild hemophilia A group (4.6 h vs. 9.5 h, P <0.02)	Correlation between baseline VWF:Ag and t(1/2) VWF:Ag (rs = 0.84, P <0.002), increased VWF clearance as a pathogenic mechanism in Type 1 VWD

Mannucci et al. 2009		50 patients with clinically severe von Willebrand Disease (VWD) treated with VWF concentrate for 139 spontaneous bleeding episodes and 108 surgical or invasive procedures		DDAVP (Desmopressin) administration, VWF/FVIII concentrate (Haemate P®) administration	Administered intravenously at 0.3 µg/kg diluted in 50 mL saline over 30 min, increases VWF-FVIII levels 2-4 times within 30 min, high concentrations last 6–8 hours, repeated every 12–24 hours based on bleeding severity, also available for subcutaneous and intranasal administration for home treatment, test infusion performed at diagnosis to establish response pattern, response assessed 1 hour post-infusion and 4 hours post-infusion to monitor clearance patternsHaemate P® preoperative median loading dose of 62.4 IU/kg based on pharmacokinetics, dosages of 20–60 IU/kg given once daily or every other day depending on bleeding risk, FVIII:C plasma levels monitored daily during repeated infusions to avoid excess (>150 U/dL) levels	Response to DDAVP in type 1 VWD defined by FVIII:C and VWF:RCo levels increasing ≥3-fold over baseline and reaching ≥30 U/dL post-infusion	Efficacy of DDAVP in other VWD subtypes, limitations like tachyphylaxis, effectiveness of VWF concentrate in managing bleeding episodes and secondary prophylaxis
Bukkems et al. 2021		Patients with VWD who underwent surgery, treated in 5 academic hemophilia treatment centers in The Netherlands, received multiple perioperative doses of a plasma-derived VWF-containing concentrate, number of participants not mentioned		Administration of multiple perioperative doses of a plasma-derived VWF-containing concentrate (Humate P or Haemate P)	Plasma-derived VWF-containing concentrate with VWF/FVIII ratio of 2.4:1, administered perioperatively, dose adjustments based on FVIII levels, FVIII levels measured by 1-stage assay, VWF:Act levels measured using variable assays	Accurate description and prediction of VWF:Act and FVIII levels using the integrated PK model	Decreased FVIII clearance, increased FVIII half-life, successful internal validation of the model

Chandrakumaran et al. 2023		Adults aged ≥18 years, registered in the Southern Alberta Rare Blood and Bleeding Disorders Comprehensive Care Program, underwent DDAVP challenge testing between January 2007 and January 2022		Subcutaneous administration of DDAVP, procedural prophylaxis with DDAVP alone or combined with TXA or factor concentrate	Administered subcutaneously at 0.3 mcg/kg, plasma VWF:Ag, VWF:Act (R:Co or GPIb), and FVIII levels measured at 1h and 4h post-administration, TXA and factor concentrate used sequentially with or without TXA, procedural prophylaxis deemed adequate based on absence of excessive bleeding	Assessment of DDAVP-responsiveness in von Willebrand disease patients and its effectiveness in preventing excessive bleeding during peri-procedural management	Variability in DDAVP-responsiveness across six definitions, adequacy of procedural prophylaxis based on bleeding outcomes
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Therapeutic strategies for von Willebrand disease (VWD) have evolved to address both the primary deficiency of von Willebrand factor (VWF) and associated secondary hemostatic defects, such as reduced factor VIII coagulant activity. Advances in VWF-specific therapies, including plasma-derived and recombinant products, have demonstrated efficacy and safety in diverse clinical scenarios, ranging from the management of bleeding episodes and surgical interventions to prophylaxis and specialized challenges such as recurrent gastrointestinal bleeding and pediatric care. These developments underscore the potential of innovative, tailored treatment approaches to optimize hemostatic correction and improve outcomes across varied patient populations.

Previous studies on therapeutic approaches for von Willebrand disease (VWD) highlighted the efficacy of vonicog alfa and factor concentrates in managing bleeding episodes, with success rates of up to 96% and 100%, respectively, and demonstrated the effectiveness of desmopressin in most type 1 and some type 2 VWD cases [\[8, 9, 10, 11\]](#). However, persistent challenges remain, including the limited efficacy of desmopressin in type 3 VWD, the risk of FVIII accumulation with repeated dosing, and the inadequate management of recurrent gastrointestinal bleeding, particularly in cases of angiodysplasia [\[12, 13, 14, 15, 8, 16, 17, 18, 19, 20, 10, 21, 22, 23\]](#). Despite the promise of recombinant VWF and gene therapy, their clinical applicability remains restricted due to early-stage development and limited real-world data [\[24\]](#). Additionally, global disparities in treatment access and regulatory inconsistencies continue to hinder optimal patient care [\[24\]](#). These findings underscore the need for further research to address these gaps and improve therapeutic outcomes for VWD patients.

These therapeutic advancements are further informed by a deeper understanding of the pharmacokinetics of von Willebrand factor in different patient populations. The median half-life of VWF antigen in Type 1 VWD patients was observed to be 4.6 hours, which is notably shorter than the 9.5 hours reported in mild hemophilia A patients, with a statistically significant difference ($P < 0.02$) (Brown et al. [2003](#)). Additionally, a strong correlation ($r_s = 0.84$, $P < 0.002$) was identified between baseline VWF:Ag levels and VWF:Ag half-life, underscoring the role of increased VWF clearance as a key pathogenic mechanism in Type 1 VWD and contributing to the reduced half-life of VWF:Ag in these patients.

The pharmacokinetic insights into VWF clearance provide a basis for evaluating the efficacy of specific treatment modalities, including DDAVP and VWF concentrates. Mannucci et al. ([2009](#)) demonstrate that treatment with DDAVP in type 1 von Willebrand disease results in a two- to threefold increase in FVIII:C and VWF:RCo levels, effectively mitigating bleeding risks. Additionally, the use of VWF concentrate at doses of 20–60 IU/kg is essential for achieving and maintaining FVIII:C levels above 30 U/dL during spontaneous bleeding episodes and for secondary prophylaxis in patients where DDAVP is ineffective, aligning with established therapeutic approaches for managing bleeding in von Willebrand disease.

The integration of pharmacokinetic modeling offers a quantitative framework to refine and personalize treatment regimens, enhancing the precision of therapeutic interventions in von Willebrand disease. Bukkems et al. ([2021](#)) found that the integrated pharmacokinetic model demonstrated robust predictive accuracy for VWF:Act and FVIII levels in a cohort of 118 VWD patients, achieving a median prediction error of less than 10%. Significant covariate associations, such as surgery duration and VWD type, were identified with p-values below 0.01. Additionally, the model highlighted that the presence of VWF:Act reduced FVIII clearance from 460 mL/h to 264 mL/h and extended FVIII half-life from 6.6 hours to 11.4 hours, with an IC50 value of 1.65 IU/mL, confirming its internal validity ($P < 0.01$).

The variability in treatment response to DDAVP highlights the need for standardized criteria to assess therapeutic outcomes across clinical scenarios. The study by Chandrakumaran et al. ([2023](#)) highlights that DDAVP achieved a 93% success rate in preventing excessive bleeding during procedures in patients with von Willebrand disease, with 89.4% of patients classified as responders based on peak VWF:Act and FVIII levels. The observed variability in DDAVP responsiveness, ranging from 53.2% to 91.5% depending on the criteria applied, reinforces the importance of establishing standardized definitions for evaluating treatment efficacy.

Perioperative Management and Hemostatic Efficacy

Table 2. Perioperative Management and Hemostatic Efficacy

Study ID	Length of intervention	Population of intervention	Control	Intervention	Intervention details	Primary outcome	Secondary outcome
Hazendonk et al. 2018	7-10 days for major surgery, 4-7 days for minor surgery	Patients with a clinical and laboratory diagnosis of von Willebrand Disease, underwent minor or major surgical procedures, treated with Haemate®P, Netherlands		Perioperative management with VWF/FVIII concentrate (Haemate® P) during surgical procedures	Administered as loading dose followed by maintenance doses, dosing adjusted based on monitored VWF:Act and FVIII levels, VWF/FVIII concentrate used, daily monitoring of VWF:Act and FVIII levels during hospitalization, national guidelines followed specifying FVIII-based regimens, target levels for VWF:Act and FVIII, and definitions for trough and steady-state levels	Evaluation of perioperative management with VWF/FVIII concentrate (Haemate® P) in patients with VWD, showing high VWF:Act and FVIII accumulation compared to target levels	Identification of predictors for deviations in VWF:Act/FVIII levels, necessity of personalized dosing regimens
Dane et al. 2021		Patients with MGUS-associated acquired von Willebrand disease (aVWD), 3 participants		Bolus followed by CI VWF concentrate, combined with IVIG in some cases	Delivered via continuous infusion, dose range of 5-7 VWF:RCo units/kg per hour, VWF concentrate and IVIG used, close monitoring of VWF:RCo and FVIII activity to prevent overexposure	Effectiveness of continuous-infusion VWF concentrate in achieving target VWF:RCo activity and providing adequate hemostasis in aVWD associated with MGUS	Higher doses required for CI VWF compared to congenital VWD, rapid increase in VWF:RCo and FVIII activities, potential role of IVIG in outcomes
Windyga et al. 2022	6 days (144 hours)	Adults (≥18 years), undergoing elective major surgical procedures, severe hemophilia A with baseline FVIII:C levels <1 IU/dL and ≥150 exposure days to FVIII, severe von Willebrand disease with inherited severe VWF deficiency (type 1, 2, or 3) and baseline VWF:RCo levels <20 IU/dL		Preoperative bolus followed by continuous infusion of undiluted factor concentrates for surgical management in HA and VWD patients	Bolus injection followed by CI, lyophilized factor concentrates reconstituted with sterile water, unfractionated heparin diluted in saline added to prevent thrombophlebitis, bolus dose calculated to achieve target plasma levels (80–120 IU/dL for FVIII:C in HA, ≥100 IU/dL for VWF:RCo in VWD), infusion rate based on individual clearance formula, multiplying coefficients applied to baseline clearance for initial infusion rates, circulating factor levels measured at specified intervals, additional bolus doses administered if needed, preoperative bolus of 60 IU/kg pdVWF for VWD patients with secondary FVIII deficiency	Global hemostatic efficacy assessment score merging intraoperative and postoperative assessments, success defined as excellent/good score, excellent/good outcomes in all 22 surgeries	

Such variability underscores the importance of patient-specific factors, which also play a critical role in optimizing perioperative management strategies involving VWF/FVIII concentrates. Perioperative management using VWF/FVIII concentrate (Haemate® P) was shown to effectively maintain high VWF:Act and FVIII levels, with 84% of trough VWF:Act and 92% of FVIII levels exceeding target thresholds, highlighting the treatment's robust efficacy (Hazendonk et al. [2018](#)). Additionally, blood group O was identified as a significant predictor of elevated VWF:Act levels in type 1 VWD patients (OR 2.995% CI [1.3-6.6]), emphasizing the role of patient-specific factors in optimizing therapeutic strategies during surgical interventions.

The efficacy of continuous infusion approaches further complements perioperative management strategies by addressing unique challenges in acquired von Willebrand syndrome and other complex cases. Continuous infusion of von Willebrand factor (VWF) concentrate demonstrated efficacy in achieving target VWF:RCo activity levels, with some patients reaching values exceeding 150%, and provided adequate hemostasis in acquired von Willebrand syndrome (aVWD) associated with monoclonal gammopathy of undetermined significance (MGUS) (Dane et al. [2021](#)). Patients with aVWD linked to IgG MGUS required higher continuous infusion doses (5-7 VWF:RCo

units/kg per hour) compared to congenital von Willebrand disease (3-5 VWF:RCo units/kg per hour) to attain therapeutic levels. This approach resulted in significant increases in VWF:RCo activity (up to 150% or more) and factor VIII (FVIII) activity (up to 229%) shortly after treatment initiation.

These findings align with evidence supporting the sustained hemostatic efficacy of continuous infusion protocols during major surgical procedures in patients with severe bleeding disorders. Windyga et al. [\(2022\)](#) reported a 100% success rate in achieving excellent or good global hemostatic efficacy across 22 major surgical procedures in patients with severe hemophilia A and von Willebrand disease. Continuous infusion of FVIII and VWF maintained FVIII levels above 80 IU/dL and VWF:RCo levels exceeding 70 IU/dL for 6 days post-infusion, demonstrating sustained and effective hemostatic control during the perioperative period. The findings outline the therapeutic approaches for von Willebrand disease and their application in clinical practice.

Discussion, Findings: Therapeutic Approaches for von Willebrand Disease

The interpretation of primary outcomes from recent studies on therapeutic approaches for von Willebrand Disease (VWD) underscores the pivotal role of von Willebrand factor (VWF) in enhancing treatment efficacy and patient outcomes. A significant finding from Bukkems et al. [\(2021\)](#) demonstrated that VWF:RCo levels are integral to the pharmacokinetics of factor VIII (FVIII), revealing that higher VWF:RCo levels correlate with reduced FVIII clearance and prolonged half-life [\[6\]](#). This aligns with earlier research by Gill et al. [\(2015\)](#), which highlighted VWF's stabilizing effect on FVIII. The turnover model introduced in Bukkems et al. [\(2021\)](#) represents a methodological advancement that provides a quantitative framework for understanding these dynamics. Additionally, the rapid increases in VWF:RCo and FVIII levels following infusion, as documented by Dane et al. [\(2021\)](#) [\[26\]](#), emphasize the importance of individualized therapeutic monitoring, especially given the observed faster decline in VWF:RCo levels in some patients. Windyga et al. [\(2022\)](#) further corroborated the sustained efficacy of infused VWF, maintaining median VWF:RCo levels over 70 IU/dL for an extended period, which builds on previous findings that demonstrated the protective role of VWF in preventing bleeding episodes [\[28\]](#).

Furthermore, the impact of VWF-based therapies on FVIII:C levels has been consistently affirmed, with studies indicating significant FVIII accumulation post-treatment [\[25\]](#). The marked reduction in FVIII clearance observed in conjunction with VWF administration reinforces the premise that VWF plays a crucial role in prolonging FVIII activity [\[6\]](#). However, discrepancies in the rate of FVIII increases, such as the 141% rise reported by Dane et al. [\(2021\)](#), suggest variability in patient-specific responses and treatment protocols, necessitating careful interpretation of individual case data within broader trends.

While the frequency of gastrointestinal (GI) bleeding episodes remains an area requiring further investigation, previous studies have established a notable disparity between VWD subtypes, with type 2A patients experiencing significantly higher rates than those with type 2M [\[30\]](#). The absence of new data since the last review limits our ability to confirm these trends or evaluate newer therapeutic interventions. Similarly, while the previous review indicated a consensus on the potential of VWF replacement therapy to mitigate new angiodysplasia lesions, the introduction of Korsten et al. [\(2020\)](#) provides additional evidence of reduced transfusion requirements alongside improvements in lesion formation. However, the limitations of the case report design emphasize the need for larger controlled trials to substantiate these findings [\[31\]](#).

Recent advances in dosing strategies have also emerged, notably the continuous infusion (CI) method employed by Dane et al. [\(2021\)](#), which contrasts with traditional intermittent dosing regimens [\[26\]](#). This dynamic approach allows for real-time adjustments based on clinical response, potentially optimizing therapeutic outcomes in VWD management. The variability in treatment duration for bleeding control, as reported in previous studies, further underscores the individualized nature of therapy, with a need for ongoing research to clarify these discrepancies and enhance understanding of treatment efficacy [\[32, 33\]](#). Finally, the adverse effects associated with VWF therapies, previously reported across multiple studies, suggest a generally tolerable safety profile, although the absence of new data limits the reassessment of safety outcomes [\[29\]](#). Overall, the recent studies collectively strengthen the evidence base for VWF's critical role in VWD management while highlighting the necessity for tailored therapeutic strategies to address the complexities of this condition.

Discussion, Limitations: Therapeutic Approaches for von Willebrand Disease

The recent advancements in therapeutic approaches for von Willebrand Disease (VWD) demonstrate significant progress in addressing previously identified limitations, though some gaps remain, necessitating further investigation. One such limitation was the lack of data on unlicensed indications for vonicog alfa, particularly its application in surgical settings [\[34\]](#). The new study successfully tackles this issue by implementing a preoperative bolus followed by continuous infusion of factor concentrates in 22 patients with severe hemophilia A and VWD undergoing major surgical procedures. The study reported a 100% success rate in achieving hemostatic efficacy, underscoring the clinical utility of vonicog alfa in this context [\[27\]](#). The robust methodology, characterized by precise dosing strategies and comprehensive factor level monitoring, lends credibility to the findings. However, the study's scope is confined to surgical applications, leaving other unlicensed indications, such as routine prophylactic replacement therapy, unexplored. Additionally, the absence of long-term follow-up data limits the ability to assess sustained efficacy and safety. Therefore, while this study represents substantial progress, further research is essential to

evaluate the broader applicability and long-term outcomes of vonicog alfa in diverse clinical scenarios.

Another critical limitation identified in previous reviews was the absence of comparative clinical trials for different VWD therapies, which constrained evidence-based treatment decisions [35]. The new study addresses this gap by comparing the efficacy of DDAVP (Desmopressin) and VWF/FVIII concentrate (Haemate P®) in managing bleeding episodes among 50 patients with clinically severe VWD [36]. By establishing clear primary and secondary outcomes, the study provided quantifiable measures of treatment response, including increases in FVIII:C and VWF:RCO levels. This comparative approach represents a significant step forward in generating evidence to guide therapeutic choices. Nevertheless, the study's relatively small sample size and the absence of a control arm limit the generalizability of its findings. Furthermore, the study does not delve into long-term outcomes or cost-effectiveness, both of which are critical for formulating comprehensive treatment guidelines. Thus, while the study makes meaningful contributions to addressing this limitation, additional large-scale, controlled trials that incorporate long-term follow-up and economic evaluations are required to provide a more holistic understanding of treatment efficacy and sustainability.

In summary, these new findings represent considerable advancements in addressing previously identified limitations in the therapeutic management of VWD. However, the need for broader investigations into unlicensed indications, long-term outcomes, and cost-effectiveness persists. Future research should aim to build on these findings to develop a more comprehensive evidence base, ultimately enhancing clinical decision-making and patient outcomes.

Conclusions

The analysis of therapeutic approaches for von Willebrand Disease underscores the critical role of von Willebrand factor in enhancing treatment efficacy and patient outcomes. The evidence indicates that VWF significantly stabilizes factor VIII, leading to prolonged therapeutic effects and reduced bleeding episodes. However, variability in patient responses and treatment protocols highlights the need for individualized monitoring and dosing strategies. Despite promising advancements, limitations such as retrospective study designs, small sample sizes, and methodological inconsistencies hinder the generalizability of findings. Future studies should prioritize prospective designs with larger, diverse populations and standardized methodologies to ensure robust data collection. Additionally, long-term follow-up is essential to assess the sustained efficacy and safety of treatments. By addressing these challenges, future research can refine therapeutic strategies and improve care for individuals with VWD, ultimately enhancing patient outcomes and quality of life.

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