

# Gastrointestinal angiodysplasia and bleeding in von Willebrand disease

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## Summary

Von Willebrand disease (VWD), the most common genetic bleeding disorder, is characterised by a quantitative or qualitative defect of von Willebrand factor (VWF). Patients with VWD suffer from mucocutaneous bleeding, of severity usually proportional to the degree of VWF defect. In particular, gastrointestinal bleeding associated with angiodysplasia is often a severe symptom of difficult management.

This review focuses on the pathophysiology, diagnosis and treatment of VWD-associated gastrointestinal angiodysplasia and related bleeding.

## Keywords

von Willebrand disease, bleeding, gastrointestinal angiodysplasia, therapy

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## Introduction

Von Willebrand disease (VWD) is the most common inherited bleeding disorder, with a prevalence of approximately 1% according to population studies (1), caused by a deficiency or dysfunction of von Willebrand factor (VWF), a large multimeric plasma glycoprotein that plays a pivotal role in primary and secondary haemostasis by mediating platelet haemostatic function and stabilising blood coagulation factor VIII (FVIII) (2). Inherited VWD is phenotypically heterogeneous and is classified into three types. Type 1 and 3 reflect the partial or complete quantitative deficiency of VWF, while type 2 VWD reflects qualitative defects of this moiety. Type 1, transmitted as an autosomal dominant trait with incomplete penetrance, is the most common VWD type (approx. 60–70% of all VWD cases), characterised by mild to moderately severe reduction in plasma levels of VWF antigen (VWF:Ag) and ristocetin cofactor activity (VWF:RCo). Type 1 patients present with a spectrum of mucocutaneous bleeding symptoms, of severity usually paralleled by the degree of their VWF and FVIII deficiencies. Type 2A, inherited with an autosomal dominant pattern, is characterised by a low VWF:RCo to VWF:Ag ratio (<0.7), with lack of larger and intermediate size VWF multimers and impaired ristocetin-induced platelet agglutination (RIPA) in platelet-rich plasma. The laboratory hallmark of type 2B VWD is heightened RIPA, usually accompanied by mild to moderate thrombocytopenia, mildly reduced or normal FVIII and VWF:Ag, reduced VWF:RCo and absence of large multimers in plasma. In type 2M VWD the VWF multimeric distribution is normal, but platelet-dependent VWF activities are reduced. Type 2N VWD is characterised by normal plasma levels of VWF:Ag and VWF:RCo and a

normal multimeric pattern, but FVIII is low owing to increased plasma clearance of this factor, which binds poorly to VWF as a consequence of specific qualitative abnormalities of this moiety. Type 2N VWD therefore resembles mild haemophilia A, but the inheritance pattern is autosomal recessive. Type 3 VWD, inherited as an autosomal recessive trait, is characterised by undetectable levels of VWF in plasma (and platelets) and very low plasma levels (1–5 U/dl) of FVIII. Patients with type 3 VWD have a moderately severe bleeding tendency, characterised not only by excessive mucocutaneous bleeding but also by joint and muscle bleeding, as in moderately severe haemophilia (3).

The goal of treatment in VWD is to stop or prevent bleeding by correcting the primary haemostasis defect and the intrinsic coagulation defect due to FVIII deficiency secondary to the primary VWF deficiency (3, 4). Correction of both deficiencies can be achieved by administering the synthetic peptide desmopressin (deamino-8-D-arginine vasopressin; DDAVP) or, in unresponsive patients, plasma-derived VWF/FVIII or VWF concentrates devoid of FVIII (4–7). Antifibrinolytic amino acids, such as tranexamic acid and epsilon aminocaproic acid, platelet concentrates and combined estrogen-progestogen drugs may be co-administered as adjuvants (8).

## Mechanism of VWD-associated angiodysplasia

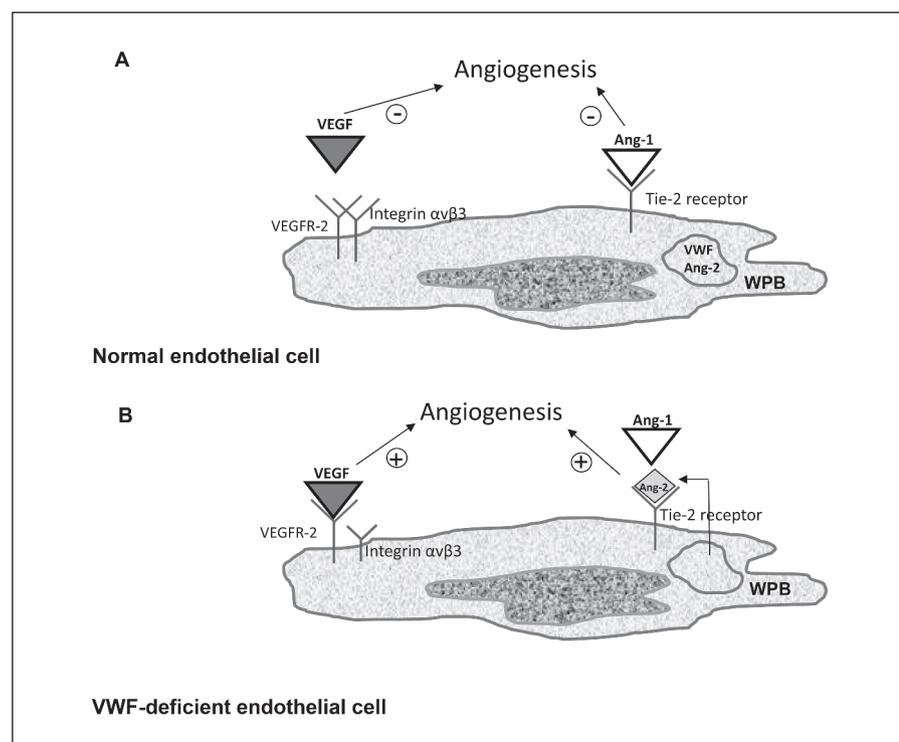
Patients with VWD may suffer from recurrent overt or occult bleeding in the gastrointestinal tract associated with angiodysplasia, a rare but challenging complication. In the last few years a

number of investigators have demonstrated that the function of VWF is not limited to platelet activation and aggregation but that this moiety, through interactions with several ligands involved in cellular signalling processes, is directly modulates various (patho)-physiological processes beyond haemostasis (9). The clinical observation that qualitative or quantitative defects of VWF are associated with vascular malformations, especially in the gastrointestinal tract, led to the hypothesis that VWF plays a regulatory role in angiogenesis, and recent research has elucidated the molecular mechanisms underlying this association (10, 11). Starke et al. (12) were the first to demonstrate that lack of VWF in the Weibel-Palade bodies of endothelial cells promotes angiogenesis, as documented *in vitro* by markedly increased endothelial cell proliferation in the absence of VWF and increased neovascularisation in VWF-deficient mice. The molecular basis of this mechanism involves a VWF-dependent negative modulation of vascular endothelial growth factor receptor-2 (VEGFR-2)-dependent angiogenesis via multiple intra- and extra-cellular pathways involving  $\alpha v\beta 3$  and angiopoietin-2, both of which are ligands for VWF (►Figure 1) (12). Other VWF-associated pro-angiogenic regulators, such as connective tissue growth factors (CTGF), insulin-like growth factor binding protein-7 (IGFBP7) and galectin-1 and -3 may be involved in this process (13-15). In agreement with these experimental data on the mechanisms of VWF-mediated regulation of angiogenesis are the findings that in patients with VWD there is an increased number of circulating endothelial cells and high levels of cytokines involved in angiogenesis (16). Considering globally these findings, it can be hypothesised that in VWD the VWF defect or dysfunction in the Weibel Palade bodies is responsible for enhanced endothelial cell proliferation leading to

the development of angiogenesis and the vascular malformations typical of angiodyplasia (17, 18).

## Diagnosis

Angiodysplastic lesions are characterised by a thin-walled, fragile vascular network with a disrupted architecture, increased permeability and susceptibility to rupture. Gastrointestinal angiodysplasia leading to recurrent bleeding is a well-known clinical complication of VWD, first described in 1976 (19). Since then, many reports have linked this vascular malformation with both inherited and acquired VWD (11, 20). Angiodysplasia occurs most commonly in middle-age or elderly patients in the cecum and ascending colon, but throughout the whole colon, small intestine and stomach (20). Affected patients may need to be hospitalised for long periods of time and often require several weeks of treatment leading to high costs and poor quality of life. In a seminal international survey conducted in 4,503 VWD patients, angiodysplasia was reported only in patients lacking high-molecular-weight (HMW) multimers, i.e. those with type 2 (2%) and type 3 (4.5%) VWD (21). The almost exclusive association of angiodysplasia with VWD types characterised by the lack of HMW VWF multimers in plasma was confirmed in subsequent studies (22, 23). In addition, a number of investigators have reported cases of angiodysplasia in patients with acquired VWD, especially when this syndrome is associated with aortic stenosis or lymphoproliferative disorders, including monoclonal gammopathy of uncertain significance (MGUS), multiple myeloma and chronic lymphocytic leukaemia (24, 25). The loss of



**Figure 1: Mechanisms of angiogenesis regulation by von Willebrand factor (VWF).** In normal quiescent endothelial cells (A), angiopoietin-2 (Ang-2) is stored in Weibel Palade bodies (WPB) with VWF and several other moieties. Angiopoietin-1 (Ang-1) can thus interact with its receptor Tie-2 promoting endothelial cell stability and quiescence. In parallel, the integrin  $\alpha v\beta 3$  antagonises the binding of vascular endothelial growth factor (VEGF) to its receptor (VEGFR-2). Both mechanisms result in the inhibition of angiogenesis. As VWF is essential for WPB formation, a decrease or dysfunction of VWF (B) causes a defective packaging of these proteins, resulting in the release of Ang-2, which can in turn bind to the Tie-2 receptor and antagonise the effects of Ang-1. In parallel, the VWF defect also causes a decrease of integrin  $\alpha v\beta 3$  via Ang-2, with subsequent interaction of VEGF with its receptor (VEGFR-2). Ang-2 acts synergistically with VEGF to promote angiogenesis. VWF, von Willebrand factor; VEGF, vascular endothelial growth factor; VEGFR-2, vascular endothelial growth factor-2; Ang, angiopoietin; WPB, Weibel Palade bodies.

HMW multimers, due to elevated shear stress through the stenotic aortic valve or to their sequestration onto malignant cells or abnormal immunoglobulins has been implicated in the pathogenesis of these acquired cases (11).

Although several diagnostic methods, including traditional and videocapsule endoscopy, helical computed tomography and angiography are available, the identification of angiodysplasia can be difficult and a number of affected patients may remain undiagnosed so that vascular abnormalities are revealed only at autopsy (17). Thus, in VWD patients, especially those with types 2 and 3, presenting clinically with laboratory (i.e. otherwise unexplained iron deficiency) or clinical symptoms of gastrointestinal bleeding, it is crucial to investigate accurately and repeatedly the whole gastrointestinal tract.

## Treatment

### Acute bleeding

The treatment of gastrointestinal bleeding in patients with VWD and angiodysplasia is challenging due to frequent recurrence and severity of haemorrhagic episodes, that usually develop and increases in severity with aging. Various therapeutic options, including surgery, endoscopic procedures (thermo-, electro- and photo-coagulation) and angiographic arteriography with embolisation have been proposed (17, 26). However, these interventions are not consistently effective. They provide better results when applied to locally affected areas of limited extension, because angiodysplastic lesions are usually multiple and diffuse in the gastrointestinal tract and tend to recur after surgical or invasive procedures (17). Thus, replacement therapy with plasma-derived VWF/FVIII concentrates, given at dosages ranging between 40 and 60 U/kg once daily until bleeding stops, is the mainstay of the episodic treatment of acute gastrointestinal bleeding in VWD (11). Even though this approach is usually clinically efficacious, it appears somewhat less efficacious than in other bleeding sites. For instance, in a study evaluating prospectively the clinical effectiveness of a VWF/FVIII concentrate in VWD, the mean daily dose and number of treatment days required to control gastrointestinal bleeding were higher than those required for bleeding in other sites (mean daily dose: 44 U/Kg vs 29 U/kg; treatment duration: 4.2 vs 1.9 day) (27). Early infusion of VWF/FVIII concentrates seems to improve the chance of success of replacement therapy (28). The importance of correcting the underlying anaemia by means of red cell blood transfusions and/or intravenous iron must be also emphasised, because a low haematocrit further reduces platelet-subendothelial interactions, impairs primary haemostasis and may exacerbate bleeding (29, 30). While antifibrinolytic agents and desmopressin (DDAVP) are usually of little help to control acute bleeding in cases refractory to standard replacement therapy (31), the bypassing agent recombinant activated factor VII (rFVIIa) was employed, although experience in this clinical setting is very limited (32). Also platelet concentrates were effective in some patients who continued to bleed excessively from the gastrointestinal tract despite replacement with VWF/FVIII concentrates (33).

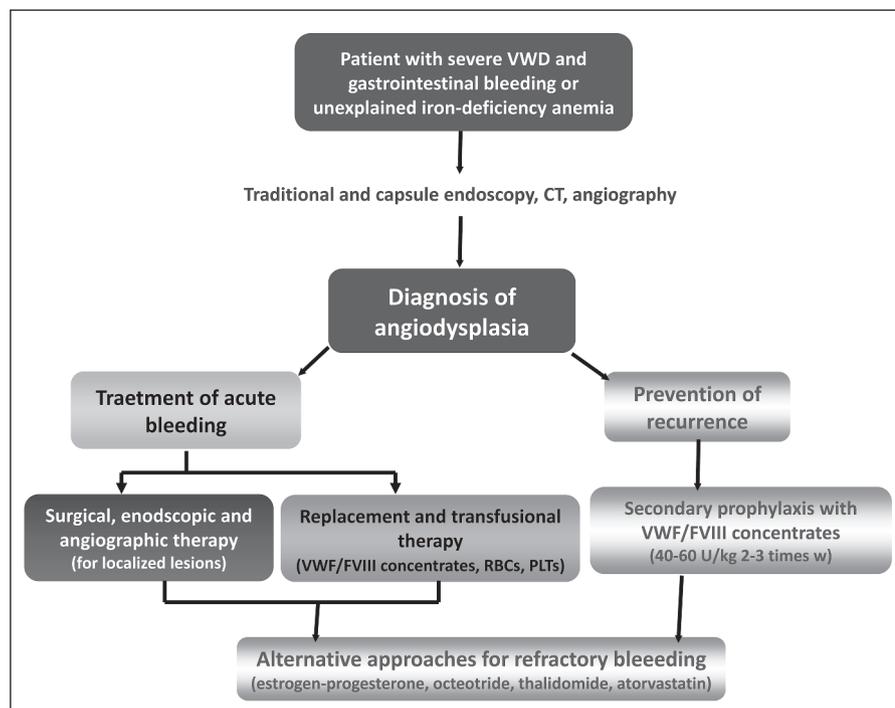
### Long-term management

Due to its marked tendency to recur, angiodysplasia-associated gastrointestinal bleeding is probably the best example of a clinical bleeding episode that can benefit from secondary prophylaxis in VWD (34-37). A number of studies have indeed documented that in patients with a history of recurrent gastrointestinal bleeds the optimal therapy may be regular prophylaxis with VWF/FVIII concentrates, usually given at dosages ranging between 40 and 60 U/kg 2-3 times weekly, instead of treatment on demand on the occasion of bleeding episodes (11). In the frame of an Italian cohort study of 452 VWD patients including 11 kept on long-term prophylaxis, the majority of them (7/11) suffered from recurrent haemorrhage in the gastrointestinal tract. Among these seven patients regular prophylaxis stopped bleeding in four and reduced the need for red cell transfusions and hospitalisation in the remaining three (38). On the other hand, a multicentre study which retrospectively collected data on eight VWD patients on long-term secondary prophylaxis with a VWF-FVIII concentrate in order to prevent recurrent gastrointestinal bleeding (39), clinical responses were rated as excellent/good in all cases, with no significant adverse effect. The largest published experience is that of the von Willebrand Disease Prophylaxis Network (VWD PN), who retrospectively collected data on the indications and efficacy of secondary prophylaxis in 59 patients with clinically severe VWD and related bleeds (40). Recurrent gastrointestinal bleeding was, along with epistaxis, the most common reason to initiate prophylaxis with VWF/FVIII concentrates (23.6% of cases), with an average dosage of 60 U/kg three times weekly. Although the number of gastrointestinal bleeding episodes occurring during prophylaxis was significantly smaller than before, a favourable clinical outcome (expressed as % reduction in bleeding frequency) was lower for gastrointestinal bleeding (49%) than for joint bleeding (86%).

All in all, these data establish the usefulness of on demand replacement therapy to stop acute gastrointestinal bleeding, and of regular prophylaxis to reduce recurrences. However, the results suggest that the efficacy of replacement therapy is lower than that for bleeding in other sites (41). Interestingly, Federici et al. reported the usefulness of high-dose intravenous immunoglobulin regimen, administered every three weeks, as long-term therapy for chronic gastrointestinal bleeding in two cases of MGUS-associated acquired VWD (25).

### Other therapeutic approaches

A number of alternative therapeutic measures have been attempted in the last few years for the management of recurrent gastrointestinal bleeding in VWD (17). Oestrogens, progestogens and the somastatin analogue octreotide have been tried, but from the few available data (26, 31, 42, 43) it is not possible to obtain solid evidence on their effectiveness. More recently, the interest of investigators was focused on the use of drugs with angiostatic properties, such as thalidomide, based on its successful use in a severe hereditary haemorrhagic disorder such as hereditary haemorrhagic telangiectasia (HHT) (44). Thalidomide acts by both in-



**Figure 2: Diagnostic and therapeutic algorithm for the management of angiodysplasia-associated gastrointestinal bleeding in VWD patients.** VWF, von Willebrand factor; VWD, von Willebrand disease; FVIII, factor VIII, CT, computed tomography; w, weekly; RBCs, red blood cell concentrates; PLTs, platelet concentrates.

hibiting angiogenesis and promoting vessel maturation (44). A few case reports indicate that this drug, at a dose ranging between 50 and 100 mg daily, may be useful to control refractory gastrointestinal bleeding from angiodysplasia in VWD patients, improving the clinical picture and reducing the transfusion requirement (45, 46). A positive effect on refractory gastrointestinal bleeding in two patients with VWD has also been reported for atorvastatin, that has anti-angiogenic properties when administered at very large doses (up to 80 mg daily) (47, 48). However, these newer therapeutic approaches should be attempted only in cases that failed replacement therapy, unless their safety and effectiveness is firmly established by larger and controlled studies.

► Figure 2 reports a diagnostic and therapeutic algorithm suggested for the management of angiodysplasia-associated gastrointestinal bleeding in VWD patients.

## Conclusions

Gastrointestinal bleeding is likely to be the most challenging bleeding event in patients with VWD, particularly in types 2 and 3. The most frequent anatomical basis of this symptom is the presence of angiodysplasia in the gut. Even though bleeding can be usually stopped by replacement therapy, it is common experience that control of these episodes is not as effective as that of episodes in other sites. Continuous prophylaxis is the mainstay of treatment of bleeding associated with angiodysplasia. However, this approach implies considerable costs, the inconvenience of repeated intravenous injections and is not invariably capable to prevent bleeding recurrence. Failures may occur because all the currently available VWF/FVIII products lack the HMW VWF multimers, which may

be particularly important for the full haemostatic function of VWF in conditions of high shear stress such as those occurring in the tortuous blood vessels of the angiodysplasia lesions (49). Perhaps the newly available recombinant VWF may help to circumvent this problem, because at variance with other products it has an intact multimeric structure (50).

It was not understood for a long term why there was an association between congenital and acquired VWD and the development of angiodysplasia. Recent experimental studies have shown that VWF has potent angiostatic properties, so that its deficiency or dysfunction in VWD causes the heightened proliferation of abnormal vessels. According to these newer findings, the most plausible hypothesis is that VWD and its related VWF deficiency or defect directly contribute to the development of angiodysplasia, rather than making coincidental angiodysplasia more clinically overt through an indirect effect. This new knowledge has paved the way to the consideration of a number of anti-angiogenic drugs in order to stop this process, but evidence of their clinical usefulness is still scanty. It is hoped that new angiodysplastic lesions may be prevented by regular replacement therapy with VWF-containing products, but we have the clinical impression that new lesions continue to develop despite this approach. This impression is mechanistically consistent with our knowledge that replacement therapy replenishes the plasma VWF compartment, but not the cellular components including endothelial cells, which remain VWF-deficient thus maintaining the mechanism of heightened angiogenesis (51).

## Conflicts of interest

None declared.

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