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Von Willebrand disease and von Willebrand factor: an old story, a new perspective

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Chapter 8

Summary and general discussion

SUMMARY OF MAIN RESULTS

The present thesis aimed to evaluate the role of VWF in haemostasis, and focused on both functions of this complex protein: preventing bleeding and increasing the risk of thrombosis. Specifically, we aimed 1) to assess the evolution of VWF levels with age in healthy individuals and in a large population of patients affected by VWD, 2) to assess the clinical impact of VWD in older people and the treatment with desmopressin of AVWS characterized by increased VWF clearance, and 3) to assess the role of global coagulation assays in assessing the risk of a first and recurrent VTE.

Chapter 2. In this chapter, we showed the increase of VWF with age in healthy individuals enrolled in the MEGA study. VWF levels in plasma are determined by genetic factors, (among which blood group is an important variable), and by acquired factors, such as obesity, inflammation, cancer, pregnancy, arterial hypertension, and reduced kidney function. These acquired factors could be mediators of the age effect on VWF levels. We analyzed VWF levels in 2923 individuals, after exclusion of individuals with active cancer and pregnant women. We showed a linear increase of VWF after the age of 40 years. The increase of VWF with age was partially mediated by acquired risk factors (comorbidities, obesity, hormone use, renal function and C reactive protein). We also showed that the increase of VWF with age is steeper in individuals with blood group non-O than in individuals with blood group-O. This difference was annulled after adjustment for acquired risk factors.

Chapter 3. In this chapter, we analyzed the increase of VWF and FVIII with age in a large cohort of patients affected by type 1 or type 2 VWD or who had low levels of VWF, followed up at the A. Bianchi Bonomi Hemophilia and Thrombosis Center (Milan, Italy). Patients with type 3 and severe type 1 VWD were excluded since they have VWF levels <10 IU/dL and an increase of VWF with age would not be clinically relevant. Repeated measurements obtained between 1970 and 2018, were analyzed by linear mixed-effect models, in which the fixed effect of age was modeled using restricted cubic splines. A random intercept and slope for age were used to account for the repeated measurements per individuals. We performed an unadjusted analysis, followed by an analysis adjusted for age at first measurement, sex, blood group (O or non-O), presence of comorbidities (high blood pressure, diabetes, cancer), and test type (VWF:Ag and activity). A differential increase of VWF and FVIII was found for different ages and types of VWD. More specifically, the increase of VWF and FVIII

became linear after the age of 40 years. In patients affected by type 2 VWD, we showed an increase of FVIII, whereas an increase of both VWF activity and FVIII were shown in patients with type 1 VWD and low levels of VWF.

Chapter 4. Gastro-intestinal bleeding is a rare but potentially severe symptom of VWD in the older patients. The presence of arteriovenous malformations is often described when endoscopic examinations are performed, in particular using second and third level endoscopic examinations, such as video-capsule endoscopy or double balloon endoscopy. Patients with congenital type 3, 2A, and 2B VWD are those most frequently affected by this symptom, possibly due to the loss of VWF high-molecular-weight multimers. Gastro-intestinal bleeding is also frequently described in patients affected by acquired von Willebrand syndrome. Endoscopic examination of the gastro-intestinal tract is necessary to exclude ulcers and polyps or cancer as causes of bleeding and facilitates local treatment. Iron supplementation must be prescribed to avoid chronic iron deficiency. In congenital VWD. Prophylaxis with VWF/FVIII concentrates is generally started after gastro-intestinal bleeding events, but this therapy is not always successful. Rescue therapies (high-dose statins, octreotide, thalidomide, lenalidomide, and tamoxifen) have been described in several case reports and series. The choice between the various rescue therapies can be based on the presence of comorbidities and patient characteristics. However, surgery may be necessary in emergency situations, or when medical treatment fails to stop the bleeding.

Chapter 5. In this chapter, we evaluated the response to desmopressin (DDAVP) in patients with acquired VWF deficiency (Acquired von Willebrand syndrome, AVWS). This is a rare disorder, although possibly underdiagnosed, with several pathogenetic mechanisms, based on the underlying disease. The main pathogenetic mechanisms are increased VWF clearance (as described in monoclonal gammopathies and lymphoproliferative disorders) and decreased production of VWF. The treatment of bleeding events with VWF concentrate is not efficacious in case of AVWS due to increased clearance of VWF. In these patients, DDAVP that releases endogenous VWF from endothelial cells is an alternative.

In this case series of 18 patients, we evaluated the early and late response to DDAVP (1 and 4 hours after DDAVP administration). In the subgroup of 11 patients with monoclonal gammopathies, a complete or partial response to DDAVP after 1 hour was obtained in the majority of patients, but the response was sustained after 4 hours only

in a minority of them (38%). Nevertheless, DDAVP was used in the majority of patients to prevent bleeding in minor surgeries or to treat minor bleeding events.

Chapter 6. In this chapter, we evaluated the association between the endogenous thrombin potential and a first event of VTE. The endogenous thrombin potential assay is a global hemostatic test, which is able to capture the interaction of procoagulant and anticoagulant proteins. We tested several conditions of the assay to evaluate which can better detect hypercoagulability. In particular, the assay was performed with the following three conditions: a low tissue factor trigger concentration, a high tissue factor trigger concentration, and a high tissue factor trigger concentration with addition of activated protein C. We showed an association between the risk of VTE and thrombin generation parameters under the different assay conditions, but the strength of the association (based on the relative risk estimation) was highest using a low procoagulant stimulus (low tissue factor trigger concentration or a high tissue factor trigger concentration with addition of activated protein C).

Chapter 7. In patients with a first event of venous thrombosis clinicians must decide when to stop anticoagulation while evaluating the risk of recurrent thrombosis and bleeding. In this setting, global haemostasis assays could help clinicians in evaluating both risks. In this chapter, we analysed the association between recurrent VTE and two global tests (D-Dimer and the endogenous thrombin generation potential) in the MEGA study. Analysis were performed in 1895 individuals with a first event of VTE, who were followed up for recurrent venous thrombosis. We showed three classes of risk of recurrent VTE, according to the levels of D-Dimer and thrombin generation: low risk for patients with low D-Dimer and low thrombin generation (incidence rate 1.20/100 patient years, 95% CI 0.75-1.62), intermediate risk for patients with either high D-Dimer and low thrombin generation (incidence rate 2.31/100 patient-years, 95% CI 1.97-2.66) or low D-Dimer and high thrombin generation (incidence rate 2.89/100 patient-years, 95% CI 0.06-5.73), and high risk for patients with high D-Dimer and high thrombin generation (incidence rate 4.70/100 patient-years, 95% CI 3.31-6.09). In the subgroup of patients with unprovoked VTE (n=539), the three levels of risk of recurrent VTE were confirmed. The combination of these two tests allows identification of patients with high risk of recurrent VTE who could benefit of long-term anticoagulation.

DISCUSSION

VWF levels in healthy individuals: the effect of ageing

VWF plasma levels (and consequently FVIII concentration) are the result of the equilibrium between VWF synthesis and its clearance. The normal range of VWF (antigen and activity) is wide in the healthy population (normal range, 50-150 IU/dL) and levels are correlated to ABO blood group. Studies in twins have reported that 66% of the total variation in plasma VWF:Ag levels is genetically determined. Moreover, 30% of this genetic influence on VWF levels is attributable to an effect of ABO blood group.¹

Levels of VWF are also strongly influenced by age, which itself is associated with several factors known to influence VWF levels, such as arterial hypertension, renal function impairment, obesity, and morbidities.

We have shown that the age-related increase of VWF is almost negligible until the age of 50 years and becomes linear after the age of 40 years. The increase is steeper in individuals with blood group non-O. Of all potential mediators of the association between age and VWF, reduced glomerular filtration together with elevated C-reactive protein, was the most important. Since VWF and FVIII are elevated in inflammation, the role of C-reactive protein was expected.²

C-reactive protein itself is the manifestation of several morbidities. High levels of C-reactive protein can be present in cancer, systemic autoimmune disorders, systemic infections, and cardio-vascular events. Elevated VWF and FVIII in reduced renal function are not likely to be due to decreased clearance by the kidney itself, because VWF and FVIII are cleared by the reticuloendothelial system of the liver and spleen. High levels of VWF and FVIII could be a manifestation of inflammation and vascular injury associated to decreased renal function, that is often the endpoint of diseases characterized by endothelial damage (such as diabetes mellitus, cardiovascular disease and atherosclerosis).

Since the increase of VWF with age is most evident after the age of 50 and the average age is increasing in the world, it would be interesting to evaluate VWF levels in individuals over the age of 70 years, which was the upper limit for age in the MEGA study. In a study on 25 healthy centenarians in Italy, the hypothesis of lower levels of procoagulant proteins in plasma (associated with decreased activation of coagulation and therefore decreased arterial and venous thrombotic events and decreased mortality) was not confirmed by the results. In contrast, results showed high levels of

factor VIII in the centenarians, compared with 2 groups of controls (between 18 and 50 years and between 51 and 70 years).

A population cohort study with repeated measurements of VWF (every 10 years) and information on blood group, concurrent diseases, and medications would be informative and could give us a more complete assessment of VWF increase with age. For this, one would need a population study, which is sufficiently large to allow a subgroup analysis of individuals with different blood groups.

The effect of ageing on VWF is clinically relevant for the evaluation of normal ranges of VWF in plasma, on which the diagnosis of VWD is based. Indeed, the diagnosis of type 1 VWD, characterized by moderate or mild quantitative VWF deficiency is actually the most challenging for clinicians due to three reasons: 1) individual variability of VWF levels due to inflammation, infection or physical exercise; 2) need of specific reference ranges for blood group and different ages; 3) variability of the test (in particular several tests are now available to measure VWF activity, based on various principles). Genetic testing is not helpful in this situation, since the VWF gene is highly polymorphic and no specific mutations are associated to type 1 VWD. This is also important, because recently clinicians are focusing on bleeding disorders of unknown cause which diagnosis is based on the exclusion of VWD.

VWF levels in patients affected by VWD: the effect of ageing

The increase of VWF with age was also described in patients affected by VWD type 1 and low levels of VWF. This increase and the different normal range of VWF according to blood group (O versus non-O) makes the diagnosis of VWD type 1 the most difficult. This is also reflected in guidelines: indeed, the ASH/ISTH/WFH/NHF guidelines, published in 2021, recommend to diagnose VWD type 1 in individuals with levels of VWF <30%, but also in individuals with VWF 30-50% and bleeding symptoms.³ This recommendation was not part of the UK guidelines published in 2014, which prefer to define low levels of VWF (but not VWD) for levels in the range 30-50%.⁴ This difference is understandable in view of the different health systems and reimbursement policies that are in place in the USA and in the UK, as discussed by Makris.⁵ Nevertheless, the same individual could be diagnosed with VWD type 1 in the USA or alternatively with an increased risk of bleeding associated with low levels of VWF (probably associated to blood group O) in the UK.

Our study evaluated a large cohort of patients affected by low levels of VWF, VWF type 1 and VWF type 2, followed at the A. Bianchi Bonomi Hemophilia and Thrombosis Center in Milan, Italy. VWF and FVIII both increased with age in the whole group. The

increase became linear after the age of 40 years (3.68 and 7.44 IU/dL per decade for VWF activity and FVIII, respectively). In type 2 VWD, FVIII increased with age, whereas an increase of both VWF activity and FVIII were shown in patients with type 1 VWD and low levels of VWF. We could not evaluate whether the increase of levels is reflected in a change in the bleeding phenotype, because type 1 VWD and low VWF (associated with the most relevant increase of VWF levels) are associated with mild bleeding symptoms, frequently present only after some haemostatic challenge such as surgery or trauma, making a comparison of the number of bleeding events in different time intervals difficult. Moreover, some bleeding symptoms typical for VWD, such as easy bruising, can also appear in healthy older individuals, resulting from hypodermis atrophy and skin thinning.

Our data on VWD type 1 and low levels of VWF are confirmed by a recent paper: Atiq et al combined two European cohorts of patients affected by low levels of VWF (LoVIC cohort) or VWF type 1 (WIN cohort) and showed the increase of VWF in patients affected by low levels of VWF, and in around 50% of the patients affected by VWF type 1 (with 23% of the patients reaching normal levels of VWF antigen, defined as 50 IU/dl).⁶

We usually consider bleeding disorders as monogenic diseases: e.g., in severe haemophilia A, a single mutation of F8 gene, such as inversion of intron 22, causes a complete disruption of factor 8 synthesis with severe FVIII:C deficiency in plasma (<1 IU/dL) and a severe bleeding phenotype. The same is true for type 3 VWD. In contrast, it is clear from these data, that mild and moderate bleeding disorders are not monogenic diseases, but different factors and genetic characteristics contribute to the bleeding phenotype. For this reason, clinicians should evaluate risk factors for bleeding, not by following a stepwise approach as is current practice, but by offering a complete evaluation of coagulation proteins, platelet function, and evaluation of the fibrinolytic system. This approach, though, would be expensive and not easily implemented in clinical practice, since some tests (for example platelet aggregation and secretion tests) are not available in all laboratories and are both expensive and cumbersome. A more pragmatic approach might be a global test on native blood to evaluate the bleeding risk. The use of native blood instead of plasma would be most physiologic, since also red blood cells and leukocytes participate to the haemostatic system. New tests with this purpose are currently under evaluation.

Nevertheless, it is important to recognize that countries with different economic resources could opt for different approaches; for example in Western countries, young women with heavy menses and mild bleeding symptoms such as easy bruising could

be offered diagnostic tests to exclude low levels of VWD, mild platelet disorders and increased fibrinolysis; these women would receive, independently of the laboratory results, treatment with a combined hormonal contraceptive pill or intra-uterine device releasing progesteron to control heavy menses, which are often associated with a low quality of life. The laboratory results would be relevant to offer some advice (and possibly treatment with tranexamic acid) in case of future surgeries or delivery. In countries with limited resources, young women with heavy menses could be pragmatically treated with a combined hormonal contraceptive pill to control the symptom, without offering any diagnostic tests, since these would be extremely expensive and their results would be related to mild bleeding disorders.

VWF and bleeding

Even though VWD has been described more than 100 years ago, the diagnosis and treatment of this disease have not progressed much in the last 10 years, particularly when compared with the new therapies developed for haemophilia, which completely changed the treatment of these patients.

Patients affected by VWD may present with rare but potentially severe bleeding manifestations at older age, due to gastro-intestinal bleeding, often associated with angiodysplasia. This clinical situation (angiodysplasia in older age) can also affect individuals with normal levels of VWF, but the bleeding severity is worse in patients affected by VWD. The observations of the role of VWF in angiogenesis,^{7,8} argue in favour of a pathogenetic mechanism in VWD. In particular, a role for high molecular weight multimers was advocated based on the higher prevalence of gastro-intestinal bleeding in VWD characterized by loss of high molecular weight multimers than in other forms of VWD.^{9,10}

Due to the rarity of type 3 and type 2 VWD, few data are available regarding the efficacy of VWF concentrate prophylaxis in patients with severe gastro-intestinal bleeding.

Previous studies have shown that prophylaxis is less efficacious for gastro-intestinal bleeding than for hemarthrosis (49% vs 86%).¹¹⁻¹³ If we hypothesize that VWF deficiency causes an increased angiogenesis that leads to angiodysplasia, we would also expect that the vascular remodeling initiated by the prophylactic regimen would take some time. For this reason, the effectiveness of prophylaxis should be evaluated after a minimum follow-up of 12 months (which unfortunately is not available in the published studies). Furthermore, we know that all plasma-derived VWF/FVIII concentrates which were used in the few published studies, lack high molecular weight multimers, and this could be another reason for their poor efficacy in patients with

gastro-intestinal bleeding, especially in the short-term. The new recombinant VWF concentrate, which is characterized by ultra-large multimers, was recently evaluated in the prophylaxis regimen in a small group of severe VWD patients (n=23), but no data are available regarding the specific efficacy in treating and preventing gastro-intestinal bleeding.¹⁴

For this reason, guidelines on the treatment of gastro-intestinal bleeding in congenital and acquired VWD can be based only on expert opinion. In our paper, we discussed 3 patients affected by congenital VWD and 2 patients by acquired VWD where different therapeutic approaches were used. In particular, one patient affected by type 3 VWD showed a good response to prophylaxis with VWF/FVIII concentrate, but the efficacy of this treatment was not complete in the first year. This observation corroborates the hypothesis that VWF concentrate might model with time the angiogenetic process.

However, in a patient affected by mild type 1 VWD, prophylaxis with VWF concentrate did not prevent gastro-intestinal bleeding while a rescue treatment (tamoxifen in this case, prompted by the breast cancer that the patient had developed) did prevent the bleeding. In this case, the role of VWF levels on the pathogenesis of the gastro-intestinal bleeding was probably only marginal. It is indeed well known that older patients, not affected by any bleeding disorder may also present with acute and chronic gastro-intestinal bleeding, sometimes requiring chronic blood transfusions.

In the case of acquired VWD, the underlying disorder is the main driver in choosing the treatment. In case of increased clearance mediated by monoclonal gammopathies, the use of intravenous immunoglobulin is highly effective, but its use is off-label, due to the lack of randomized clinical trials. In case of increased clearance of VWF because of increased shear stress such as in heart valves defects (or similarly in ECMO or LVAD), other strategies are recommended.¹⁵

In acquired von Willebrand syndrome associated with increased clearance of VWF, the use of desmopressin (DDAVP) that releases the natural storages of VWF from endothelial cells, could be useful. We tested the response to DDAVP in a case series of 18 patients with acquired von Willebrand syndrome, finding a complete and sustained response after 4 hours in 38% of the patients. This finding is clinically important, since DDAVP is not expensive and can be administered subcutaneously. Most importantly, DDAVP releases VWF characterized by ultra-large multimers that are very active in haemostasis. This effect of DDAVP could possibly ensure a better haemostatic effect than what could be deduced from the VWF ristocetin cofactor activity tests (which do not reflect the multimer VWF profile in plasma). In our case-series, most patients could be treated with DDAVP for mild-moderate bleeding events

or surgeries associated with low-moderate bleeding risk, in association with tranexamic acid. It is important to underline that coronary spasm was described as a rare side effect of DDAVP. For this reason, its use in older patients, such as those affected by acquired von Willebrand syndrome is not always feasible or recommended. In this setting, a cohort study, with at least 10 years of follow-up, enrolling patients with congenital VWD and gastro-intestinal bleeding appears necessary to better understand the natural evolution of this symptom, in particular regarding the response to first treatment such as prophylaxis with VWF concentrate, the life-long risk of recurrent gastro-intestinal bleeding and the possible use of alternative rescue treatments.

This is also true for acquired von Willebrand syndrome. In this case, the first obstacle to overcome is the difficulty to obtain a correct diagnosis. To ensure the availability of advanced tests (such as VWF multimer profile, VWF pro-peptide measurement and possibly a general evaluation of clinical cases), a collaboration between highly specialized centers and general practitioners or general hospitals should be organized through the hemophilia centers. As for acquired hemophilia, which incidence has increased in the last years, this is certainly due to the population ageing and the availability of the diagnostic tests.

When diagnostic tools for acquired von Willebrand syndrome will be available in more centers, an international cohort study could give us a better understanding of this rare syndrome, focusing in particular on the incidence of bleeding events, on the correlation between bleeding events and residual levels of VWF, and on the success of treatment of the underlying disease to restore normal levels of VWF. This is particularly important in case of acquired von Willebrand syndrome associated with monoclonal gammopathies, which in most patients do not require any treatment, but can be associated with severe bleeding. In such cases the decision to start treatment of the underlying monoclonal gammopathy should be carefully evaluated, bearing in mind that it can also be associated with side-effects. However, only case reports or small case series are actually available to guide clinicians in their choices.

The collection of data on the natural evolution of gastro-intestinal bleeding associated with congenital and acquired VWD is particularly important, also because new treatments will possibly be available in the near future. Therapies rebalancing haemostasis such as concizumab, a monoclonal antibody directed against tissue-factor pathway inhibitor, or fitusiran, a molecule that silences antithrombin RNA, are candidates for treating patients with congenital or acquired VWD. Their use will need

to be evaluated together with the thrombotic risk in patients who are generally rather old and affected by comorbidities.

VWF and thrombosis

The role of VWF in increasing the risk of both arterial and venous thrombosis has been shown in several case-control and cohort studies. These studies are supported by the observations on VWF's role in mediating inflammation and cancer development. It is interesting to note that ABO blood group, which is an important determinant of VWF levels in plasma, also constitutes an important risk factor for cardiovascular disease and VTE.^{2,16}

Anticoagulation for 3 to 6 months is the indicated therapy in case of VTE. At the end of this period, clinicians must decide whether the risk of bleeding associated with the anticoagulant therapy is balanced by the benefit of preventing recurrent thrombosis. In such a clinical setting, we evaluated the use of global haemostasis assays (D-Dimer and thrombin generation) to assess the risk of recurrent VTE. Since its automation on a coagulometer with assays based on latex particles, the D-Dimer test is now widely available. High levels of D-Dimer, measured one month after discontinuation of anticoagulation, have been associated with an increased risk of recurrent VTE, and the evaluation of D-Dimer is currently included in several prediction models for recurrent VTE (DASH, HER-DOO2 and Vienna Prediction Model).¹⁷⁻²⁵

The thrombin generation potential test is another tool to evaluate the risk of recurrent VTE, since it measures the ability to produce thrombin in individual plasmas.^{26,27} Since D-Dimer is a degradation product of fibrin, it represents the presence of fibrin, while thrombin generation represents the potency of plasma to produce thrombin (and subsequently fibrin) in the presence of a trigger.

In the thrombin generation assay, the formation of thrombin in a plasma sample is continuously measured by a fluorogenic substrate after initiation of coagulation, typically by tissue factor in the presence of calcium and phospholipids. The conditions of the assay, and specifically the concentration of tissue factor and phospholipids influence the sensitivity and specificity of thrombin generation and different conditions are generally used to evaluate hypo- or hypercoagulable states. Our colleague T.M Hackeng hypothesized that the sensitivity of the thrombin generation assay to detect hypercoagulability can be increased when there is a slow onset of thrombin generation, that can be obtained by adding a low tissue factor trigger concentration or by adding natural anticoagulants, such as thrombomodulin or activated protein C. Under these circumstances the TFPI/protein S anticoagulant system is a major determinant of

thrombin generation. Our study found an increased risk of a first thromboembolic event associated to increased thrombin generation, using the 3 different conditions that were tested. The strength of the association was variable, based on the conditions that were used, and low concentration of tissue factor was associated with the highest risk of VTE. Nevertheless, it must be considered that the variability of the test is higher using low concentration of tissue factor. The potential influence of in-vitro contact activation on the amount of thrombin generated is higher at low tissue factor concentration. To minimize this risk, we used TICA, a thermostable inhibitor of contact activation added to plasmas immediately upon defrosting and normalized thrombin generation parameters against a reference plasma sample. For these reasons, thrombin generation remains a laborious test which lacks standardization and clinical validation, performed in specialized laboratories.

Recently, a new, fully automated thrombin generation analyzer (ST Genesia by Stago) was released for clinical routine laboratories and it is commercialised with different kits to evaluate hypo or hypercoagulable states. This could be a new tool to globally evaluate the thrombotic risk.

We also tested the association between D-Dimer and the thrombin generation potential (alone or in combination) and recurrent VTE in the MEGA follow-up study.

We were able to identify three classes of risk of recurrent VTE: low risk for patients with low D-Dimer and low thrombin generation, intermediate risk for patients with either high D-Dimer and low thrombin generation or low D-Dimer and high thrombin generation, and high risk for patients with high D-Dimer and high thrombin generation. In the subgroup of patients with unprovoked VTE, the three levels of risk of recurrent VTE were confirmed. This distinction could be clinically useful since it allows to identify a group of patients with a first unprovoked VTE where stopping the anticoagulation could be considered safe, since their risk of recurrence of VTE is similar to that of patients with a first event of provoked VTE. Indeed, in this group, the bleeding risk of anticoagulation would out-weight the risk of recurrent VTE. Nevertheless, the majority of patients remain in the intermediate group, where the decision to carry on anticoagulation indefinitely, must be accurately weighed against the bleeding risk.

The main limitation of our study is the use of a home-made thrombin generation test, performed in a highly specialised laboratory, which could reduce the translational value of this study since most laboratories will not be able to perform the test routinely.

The recent introduction of a prophylactic dose (50% of the dose after 6 months of full anticoagulation) to carry on long-term anticoagulation with direct oral anticoagulants could also be a possible framework where the use of D-Dimer and the thrombin

generation potential could be tested to evaluate if they could be identified patients at higher risk of recurrent VTE.

CONCLUSION

VWF is a key factor in haemostasis for its role in preventing bleeding (through platelet adhesion, platelet aggregation and transportation of factor VIII), but it also increases the risk of arterial and venous thrombosis. In particular, VWF appears to be important in the thrombotic phenotype associated with inflammation and immunological response, as it was described in the COVID-19 pandemic. Besides, VWF has important features in regulating cancer spreading and angiogenesis.

Levels of VWF are regulated by genetic and acquired factors. The VWF increase with age is mainly due to acquired factors such as inflammation and decreased renal function. The great variability of VWF in the normal population due to blood group and age makes the diagnosis of type 1 VWD particularly challenging, especially in case of mild VWF deficiency. The increase of VWF and FVIII with age in patients affected by mild VWD must be evaluated, to guide replacement therapy with VWF concentrate or other haemostatic therapies.

Gastro-intestinal bleeding is a rare but often severe bleeding manifestation in patients with VWD. Its rarity is the cause of the lack of evidence-based guidelines, but a careful evaluation of the patient characteristics is the key to clinical choices in this setting.

The evaluation of thrombotic and bleeding risk is crucial after a first course of anticoagulation for VTE, to avoid recurrent thrombotic event, without exposing the patients to an excessive risk of bleeding. In this setting, the use of global assays such as D-Dimer and the thrombin generation appears promising, but they can only identify a minority of patients with a low or high risk of recurrent events.

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