Hemorrhagic disorders of fibrinolysis: a clinical review

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Summary. Hyperfibrinolytic bleeding can be caused by a deficiency of one of the inhibitors of fibrinolysis (plasminogen activator inhibitor type 1 [PAI-1] or α2-antiplasmin [α2-AP]), or an excess of one of the activators of fibrinolysis: tissue-type plasminogen activator or urokinase-type plasminogen activator. This review focuses on the clinical implications of these disorders. The bleeding phenotype of fibrinolytic disorders is characterized by delayed bleeding after trauma, surgery and dental procedures. Bleeding in areas of high fibrinolytic activity is also common, such as menorrhagia and epistaxis. Patients with α2-AP deficiency present with the most severe bleeding episodes. Recently, it was discovered that hyperfibrinolytic disorders are associated with a high rate of obstetric complications such as miscarriage and preterm birth, especially in PAI-1 deficient patients. Hyperfibrinolytic disorders are probably underdiagnosed because of lack of knowledge and lack of accurate diagnostic tests. A substantial part of the large group of patients diagnosed as ‘bleeding of unknown origin’ could actually have a hyperfibrinolytic disorder. In the case of a high index of suspicion (i.e. because of a positive family history, recurrent bleeding or uncommon type of bleeding such as an intramedullary hematoma), further testing should not be withheld because of normal results of standard hemostatic screening assays. Timely diagnosis is important because these disorders can generally be treated well with antifibrinolytic agents.

Keywords: alpha2-antiplasmin; fibrinolysis; hemorrhagic disorders; obstetric labor complications; plasminogen activator inhibitor 1.

Introduction

Primary hemostasis, secondary hemostasis and the fibrinolytic system are the three main components of blood coagulation. These complex processes are integrated to serve a major common goal to stop unwanted bleeding and to prevent unnecessary clot formation. This review focuses on the fibrinolytic process, particularly on the hemorrhagic diathesis, which occurs when the fibrinolytic pathway is accelerated. In general, fibrinolysis is the process of fibrin clot solubilization. This process is accurately regulated by activators, inhibitors and cofactors to maintain a delicate balance. An overview of this balance is illustrated in Fig. 1. The key component of fibrinolysis is plasmin, a serine protease that degrades fibrin. The zymogen plasminogen is the pro-enzyme for plasmin and can be converted by tissue-type plasminogen activator (tPA) or urokinase-type plasminogen activator (uPA). tPA is synthesized and secreted primarily by endothelial cells, and its release is regulated by multiple stimuli, including thrombin [1–3]. In the absence of fibrin, tPA is a very weak activator of plasminogen; however, its catalytic efficiency is greatly enhanced in the presence of fibrin. In this situation fibrin stimulates its own degradation [3]. uPA can effectively activate plasminogen both in presence and absence of fibrin but has much lower affinity for fibrin as compared with tPA [1,3]. Once formed, plasmin cleaves fibrin, generating fibrin degradation products (FDP) [1]. Inhibitors, on the other hand, are present to balance the fibrinolytic homeostasis. Thrombin-activatable fibrinolysis inhibitor (TAFI) attenuates plasmin generation after being activated by thrombin, plasmin or thrombomodulin-bound thrombin. TAFI removes the carboxy-terminal lysine residues from fibrin, resulting in a decreased plasmin generation and stabilization of fibrin containing thrombi [1,3]. Plasminogen activator inhibitor type 1 (PAI-1) is an inhibitor of tPA and uPA. Inhibitors of plasmin are α2-antiplasmin (α2-AP) and α2-macroglobulin (α2-M). The main physiological plasmin inhibitor is α2-AP. In the situation when plasmin is formed in excess in respect to α2-AP, plasmin is neutralized by α2-M [2]. Figure 2 illustrates the interplay between activators and inhibitors of fibrinolysis in vivo upon formation of a fibrin...
clot after damage of the endothelium. Pathophysiological conditions of fibrinolysis with an increased risk of bleeding disorders are a decreased inhibition of fibrinolysis as a result of deficiency of one of the main inhibitors (α2-AP and PAI-1) or an increase in plasminogen activation as a result of excess tPA or uPA. The abundant presence of uPA can be caused by increased expression of uPA in platelets, known as Quebec platelet disorder.

Deficiency of TAFI would theoretically lead to hyperfibrinolysis because of decreased inhibition of the fibrinolytic pathway but has never been described in literature. TAFI-deficient mice did not show a bleeding tendency [4]. On the contrary, high levels of TAFI have been described in patients with a bleeding tendency [5]. However, because TAFI is activated by thrombin, coagulation disorders leading to decreased formation of thrombin can cause decreased activation of TAFI, leading to hyperfibrinolysis. It is suggested that this contributes to the bleeding phenotype in patients with a coagulation factor deficiency, as in hemophilia or in factor XI deficiency [6,7].

Diagnosis of a hyperfibrinolytic bleeding tendency is challenged by the lack of currently available and validated laboratory tests. A difficulty in the development of

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a fibrinolysis screening assay is the low baseline fibrinolytic capacity as a result of the presence of fibrinolysis inhibitors in plasma. This can be partially resolved by acidification of the plasma, shifting the plasma to a more fibrinolytic nature (less PAI-1 dependent) [8]. One of the most frequently used laboratory screening assays is the euglobulin clot lysis time (ECLT), recording the time till visual lysis of the euglobulin fraction in a tube. It is usually shortened in cases of increased fibrinolysis. However, because of a lack of global validation, a normal euglobulin clot lysis time does not exclude hyperfibrinolysis. Thromboelastography (TEG) and rotation thromboelastometry (ROTEM) assess viscoelastic changes after recalcification and addition of coagulation activators to citrated whole blood. They are mainly used as point-of-care coagulation tests in massive blood loss in the emergency department or in the operating room. However, their reproducibility is poor and they require specialized equipment [9]. Plasma turbidity assays measure changes in optical density after the initiation of coagulation. They are sensitive for plasma levels of all fibrinolytic proteins except for tPA, as tPA is added to induce lysis [10]. Prolonged plasma clot lysis times measured by this method are associated with hypofibrinolysis and have been shown to increase the risk of venous and arterial thrombosis. Shortened clot lysis times, on the other hand, may reflect various hemorrhagic states induced by hyperfibrinolysis [9,10]. The global fibrinolytic capacity in whole blood is another assay of fibrinolysis. An advantage of this method is that no fibrinolytic activators are added. This assay is sensitive for abnormalities in t-PA activity, PAI-1 activity, fibrinogen and TAFI activity [9,11]. Global assays may be helpful in the future; however, they are not available for clinical use at the moment. TAFI, α2-AP, PAI-1, tPA and uPA can all be measured in blood using confirmation assays and allow quantification of antigen and activity levels, but these assays are not available in every laboratory and there is no consensus about the cutoff level to define deficiencies. Treatment of hemorrhagic diatheses due to hyperfibrinolysis occurs with antifibrinolytic agents such as tranexamic acid or e-aminocaproic acid. These are lysine analogues that block the lysine-binding sites of plasminogen, inhibiting binding of plasminogen to fibrin, leading to decreased plasminogen activation [12]. In this review, we will discuss the main disorders of fibrinolysis causing a bleeding tendency and their associated clinical implications, laboratory diagnosis and treatment.

Methodology

A systematic search was undertaken in PubMed and EMBASE for relevant articles from the past until 22 August 2017. Articles in English and some other languages (e.g. Dutch, French and German) were included. The used search terms are shown in Data S1 in Supplementary Material. Articles describing at least one clinical symptom of at least one patient with a hemorrhagic disorder of fibrinolysis were included in the analysis calculating the incidences of clinical symptoms. Two authors (J.S. and M.N.) independently screened articles for relevance. Discrepancies were resolved through consensus with a third author (S.S.). References of identified articles were cross-checked for other relevant articles. The search strategy identified 1397 articles. After removal of duplicates, 1101 articles were screened for eligibility based on title and abstract. The study flow diagram is shown in Fig. 3. The kappa agreement for study selection was 0.98, indicating excellent agreement between the investigators. A total of 77 articles were identified, accounting for a total of 181 relevant cases with information on the clinical symptoms. Of these cases, 14 patients were homozygous for α2-antiplasmin deficiency and 104 were heterozygous carriers. Thirty-six patients had a PAI-1 deficiency, 23 Quebec platelet disorder and four tPA excess. Patients with a primary TAFI deficiency were not found. Incidences of clinical symptoms and information on the diagnosis and treatment of each of the disorders are discussed hereafter.

α2-antiplasmin deficiency

Background α2-antiplasmin (α2-AP) is the main physiological inhibitor of plasmin [2]. The deficiency can lead to the abundant presence of plasmin and therefore induce hyperfibrinolysis and bleeding. α2-AP is a member of the serpin family of enzyme inhibitors, and it is synthesized in the liver [13]. The gene for α2-AP is located on chromosome 17 [14]. The first case of α2-AP deficiency was published in 1978 in a patient with post-traumatic as well as spontaneous bleeding. The deficiency was then named Miyasato disease after the patient’s surname. By studying the family, it was noted that this disorder was most likely inherited autosomal recessive [15]. The prevalence of α2-AP deficiency is unknown, but it is very rare.

Clinical manifestations An overview of bleeding symptoms in patients with a homozygous α2-AP deficiency can be found in Fig. 4. [15–30] These numbers were extracted from 14 cases. A homozygous deficiency usually leads to serious bleeding symptoms, mostly post-trauma and post-surgery or after dental extractions. A few of the included patients in Fig. 4(A) did not have a hemostatic challenge; therefore, the prevalence of 43% post-surgery bleeding is likely to be an underestimate, as well as the percentages for post-trauma and post-dental extraction bleeding. Only three adult women have been described with a homozygous α2-AP deficiency. Therefore, the prevalence of menorrhagia could not be calculated. However, two of these three women experienced menorrhagia so it appears to be a relevant issue [17,24,29]. Interestingly, multiple patients have been described with intramedullary hematomas, an uncommon type of bleeding [21,22].
A total of 104 individuals with a heterozygous α2-AP deficiency were found. These individuals either had bleeding symptoms or were family members of a known homozygous patient [17,19,20,24,26–29,31–45]. Sixty-six of 104 heterozygous individuals were asymptomatic. The number of symptomatic heterozygous individuals is likely to be an overestimate caused by publication bias. Interestingly, severe bleeding tendencies such as gastrointestinal bleeding and umbilical cord bleeding have also been described in individuals with a heterozygous α2-AP deficiency [31,38]. The most common bleeding symptoms in individuals with a heterozygous α2-AP deficiency were post-surgery and post-traumatic. Although the occurrence of menorrhagia and postpartum bleeding could not be calculated, because many articles do not give details on whether participants were male or female, these symptoms appear to occur quite often as well [34,36,38,40,42]. All of the heterozygous individuals had α2-AP levels of

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Fig. 4. Prevalence of bleeding symptoms in patients with (A) homozygous α2-antiplasmin deficiency, (B) PAI-1 deficiency and (C) Quebec platelet disorder. Symptoms other than post-traumatic and post-surgery were only scored if occurring spontaneously. PAI-1, plasminogen activator inhibitor type 1. *Of women >12 years of age. **Of patients who had dental extractions. ***Of patients who had a serious accident. ****Of patients who experienced deep cut(s) [15–30,52–55,75–75,82].

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around 50%. A study in patients with acquired α2-AP deficiency showed that clinical hyperfibrinolysis only occurred at plasma levels of α2-AP below 60% [46]. It is unknown whether women with a heterozygous α2-AP deficiency experience high rates of obstetric complications, as almost no adult women with pregnancies have been described. There are some reports of relevant obstetric bleeding complications in both homozygous and two heterozygous women, leading to miscarriage and preterm delivery [29,34,38]. In summary, homozygous α2-AP deficiency is associated with a severe bleeding tendency and possibly a high rate of female-specific bleeding problems. Bleeding manifestations in individuals with a heterozygous α2-AP deficiency are less often described in the literature; however, they do occur.

**Diagnosis and treatment** Ignorance about α2-AP deficiency might lead to underestimation of the diagnosis. This can be aggravated by the lack of abnormalities in screening assays. The euglobulin clot lysis time is usually shortened but can be normal in both carriers and homozygous patients [15,17–20,23,25,26,31,33,37,38]. A reason for this low sensitivity for α2-AP deficiency can be the lack of enrichment of α2-AP in the euglobulin fraction after acidification of plasma [47]. When a deficiency is suspected based on a shortened clot lysis time and/or suspicious history, directed α2-AP confirmation assays should be performed. A deficiency can be either quantitative (type I), causing a coincidental decrease in α2-AP activity and antigen, or qualitative (type II), causing low activity levels with normal or only slightly decreased antigen concentrations [12]. The treatment of bleeding episodes consists of antifibrinolytic agents. Antifibrinolytic agents can also be used as prophylaxis before invasive procedures [12,13]. The use of fresh frozen plasma (FFP) has also been described; however, the variable activity of α2-AP in FFP and the possible adverse event of dilutional coagulopathy as a result of volume overload make this a less attractive option [12,13,35]. Currently, in many countries, FFP is being replaced by omniplasma; however, omniplasma has lower α2-AP levels and shorter ROTEM lysis times with a reduction of more than 50% when compared to FFP. Therefore, the use of omniplasma is not recommended in the treatment of α2-AP deficiency [48]. Desmopressin acetate may induce secretion of plasminogen activator and should therefore be avoided [35].

**Plasminogen activator inhibitor type 1 deficiency**

**Background** Plasminogen activator inhibitor type 1 (PAI-1) is the principal inhibitor of tPA and uPA [2]. Like α2-AP, PAI-1 is a member of the serpin family [2]. A variety of cells synthesize PAI-1, including hepatocytes, adipocytes and endothelial cells [49]. The PAI-1 gene is located on chromosome 7, and its expression can be induced by several factors such as insulin [50]. Although the principal function of PAI-1 is inhibition of fibrinolysis, it has other functions in inflammation as an acute phase protein. In contrast to low PAI-1 levels, high PAI-1 levels are associated with atherosclerosis and coronary artery disease, metabolic syndrome, fibrosis and poor prognoses in several cancer types [51]. When evaluating a patient for PAI-1 deficiency, both antigen and activity levels should be analyzed, as the deficiency can be both qualitative or quantitative. The first case of a bleeding disorder as a result of a qualitative PAI-1 deficiency was described by Schleef *et al.* in 1989, followed by the first reported quantitative deficiency in 1991 [52,53]. It is an autosomal recessive disorder [54]. The prevalence of PAI-1 deficiency is not known as it has only been described in case reports. However, two studies showed that the incidence of PAI-1 activity < 1.0 U mL⁻¹ and < 2.0 U mL⁻¹ in healthy populations was as high as 10–13% and 21%, respectively [55,56]. These data suggest that many individuals with low PAI-1 activity are asymptomatic. The prevalence of a bleeding disorder caused by PAI-1 deficiency is low. However, accurate diagnosis is hampered by a lack of accuracy of the currently available activity assays in the lowest range [50].

**Clinical manifestations** The bleeding tendency of patients with a PAI-1 deficiency is shown in Fig. 4(B) [30,52–55,57–75]. A total of 36 patients with a PAI-1 deficiency have been described, including both qualitative and quantitative deficiencies. Most patients experienced post-trauma and post-surgery bleeding. Two cases could not be included in the analysis of this review, because aside from their PAI-1 deficiency, they also had another disorder that could explain their specific bleeding symptoms, and both of the articles did not report any other symptom [76,77]. When only taking into account the 17 women ≥ 12 years of age that have been described, nine of them experienced menorrhagia, making this a common symptom. Obstetric complications appear to occur often in women with a PAI-1 deficiency. The reason for this is not entirely clear, although animal studies have suggested that PAI-1 and the accompanying proteolytic process play a role in degradation of the follicular wall during ovulation, as well as in fertilization, embryo implantation, embryogenesis and angiogenesis [54,78]. A total of 17 described pregnancies and outcomes were found. As shown in Fig. 5, there is a high rate of miscarriage and preterm birth, with only 24% of described pregnancies reaching term. Vaginal bleeding during pregnancy was common, occurring in 54%, as well as postpartum bleeding, with a prevalence of 27% [54,65,67,69,70,73]. These numbers might be an overestimation as a result of publication bias. However, in the case of missing information about bleeding complications, pregnancies were considered as being normal to compensate for the possible overestimation bias. Family investigation revealed only...
symptoms in a minority of the heterozygous family members [58,59,63,66]. However, Del Rosario et al. described a heterozygous individual with severe bleeding symptoms including spontaneous hemarthrosis [79]. In summary, homozygous PAI-1 deficiency is associated with major bleeding problems and obstetric complications, whereas heterozygous PAI-1 deficiency is usually asymptomatic.

**Diagnosis and treatment** The actual diagnosis of a PAI-1 deficiency is often delayed as a result of normal screening tests and impaired recognition of the disorder. The currently available assays for PAI-1 activity are not discriminative in the lowest range, as the normal limit of these assays ranges to zero [50]. PAI-1 antigen levels are even more difficult to interpret, as these assays do not discriminate between complexed PAI-1 and free PAI-1. Furthermore, the diurnal variation of PAI-1, with highest levels in the early morning and lowest in the afternoon, can make accurate diagnosis more complicated [80]. The diagnosis of PAI-1 deficiency is further complicated by the fact that the euglobulin clot lysis time is not always shortened despite the fact that PAI-1 is enriched in the euglobulin fraction [52,53,60,61,63,64,66,70,73]. In addition, tPA activity can be high; however, a normal value does not exclude the diagnosis [52,58,61,63,71,72]. Treatment of PAI-1 deficiency consists of antifibrinolytics. They can be used as treatment for an acute bleeding, as a preventive measure before an invasive procedure and for limiting the amount of menstrual blood loss or epistaxis [50,59,70].

**Urokinase-type plasminogen activator excess**

**Background** The Quebec platelet disorder (QPD) is the only described disorder with hyperfibrinolysis caused by excess of urokinase-type plasminogen activator (uPA). It is caused by a tandem duplication of a 78-kb genomic segment that includes the PLA2 gene, leading to overexpression of uPA. It is an autosomal dominant disorder with a high penetrance [81]. Most known cases have been traced to a single family of French ancestry in Quebec, Canada [82]. The hyperfibrinolysis is caused by increased expression and storage of uPA in platelets [83]. The genetic defect causes increased transcription of the PLA2 allele during megakaryocyte differentiation located on chromosome 10 [84]. The first case was described in 1984, although at the time bleeding was thought to be caused by a qualitative platelet factor V deficiency. Therefore, the disorder was first called factor V Quebec [85]. The prevalence of the disorder worldwide is unknown; however, in Canada it is estimated at 1 : 655 000 and in Quebec 1 : 220 000 [86].

**Clinical manifestations** The bleeding history of the QPD family has been described in detail by McKay et al [82]. Twenty-three patients with the disorder were described (see Fig. 4C for their bleeding symptoms). As in the other fibrinolytic disorders, bleeding after dental extractions, surgery and trauma was frequently reported. A total of nine pregnancies were described, none of which ended in miscarriage. None of the patients reported antenatal bleeding; however, two women needed transfusion after giving birth. As in PAI-1 deficiency, some patients reported impaired wound healing, which was associated with lower platelet counts [82]. One separate case of QPD from Pakistan was not included in the review, because the diagnosis was only based on reduced aggregation with epinephrine. Although often seen in QPD, this is not considered specific for this disorder [87].

**Diagnosis and treatment** As this disorder is autosomal dominant with a high penetrance, the family history will be positive most of the time and raise a suspicion in cases of bleeding. The disorder is characterized by increased platelet content of uPA, which is released upon platelet activation. In a resting condition, uPA in plasma is normal or only moderately increased [81]. The disorder can be accompanied by an unexplained mild thrombocytopenia.
Screening assays for coagulation are usually normal, although factor (F) V can be mildly deficient. Platelet FV is reduced [85]. Functional platelet tests often reveal a characteristic pattern of absent aggregation with epinephrine and a reduced platelet aggregation with ADP and collagen, probably because of the overexpression of uPA and subsequent activation of plasminogen in platelets. Plasmin then can degrade von Willebrand factor, FV and fibrinogen [81,88]. Whole-blood clot lysis time is normal and urinary uPA is not increased [89,90]. As the genetic defect has been unraveled and other diagnostics are variable and complicated, it is now recommended to perform a PCR assay for the QPD mutation when diagnosis is suspected [91]. Patients with bleeding complications should be treated with antifibrinolytic therapy. The administration of platelets does not reduce bleeding [88,90].

Tissue-type plasminogen activator excess

As previously mentioned, patients with a congenital PAI-1 deficiency may have high levels of tPA activity, with most of the time normal tPA antigen levels [52,58,61,63,71,72]. A total of four cases have been described with high levels of plasminogen activator and a bleeding tendency [92–94]. These patients had symptoms of excessive bleeding after trauma and surgery, and in some cases also spontaneous hematomas or easy bruising. Family members of a patient with an excess of tPA had high tPA levels and shortened euglobulin clot lysis time, without any bleeding symptoms [93]. One of the patients underwent liver transplantation for cirrhosis and was thereby cured of his bleeding disorder [94]. In addition, an abstract by Hampton et al. described a family of 12 members who showed elevated plasma activator levels, of whom nine had a history of excessive bleeding [95]. As a few of the above-mentioned cases of tPA excess were diagnosed before the discovery of PAI-1 deficiency in 1989, these cases can be misdiagnosed. However, two cases had normal PAI-1 activity and antigen level [93,94]. Given the sparse number of cases, it is currently unclear whether this can be considered a separate entity within the bleeding disorders. For diagnosis we recommend the use of an assay other than an antigen assay, as currently available antigen assays do not only measure the free form but also complexes between tPA and PAI-1.

Acquired disorders of fibrinolysis

Acquired disorders of fibrinolysis are an important cause of bleeding and mortality. In acute promyelocytic leukemia (APL), a deficiency of α2-AP or TAFI or excess of uPA can contribute to the bleeding tendency [46,96,97]. Fibrinolysis can be further increased in these patients as a result of high levels of annexin A2 expression on APL cells, leading to increased production of plasmin [98]. In cirrhosis, high levels of tPA as well as deficiency of α2-AP and TAFI have been described [99]. However, this may be rebalanced by a decline in antifibrinolytic factors, and typical hyperfibrinolytic bleeding in cirrhotic patients is rare [100]. In addition, acquired α2-AP deficiency has been described in a variety of diseases, including amyloidosis, gastric cancer, prostatic cancer, adenocarcinomas and nephrotic syndrome (as a result of renal loss) [46,99,101–103]. Trauma is also associated with high fibrinolytic activity, and a higher fibrinolytic activity correlates with a poor clinical outcome in these patients [104]. In addition, there are also iatrogenic causes of hyperfibrinolysis. Cardiopulmonary bypass provokes a state of hyperfibrinolysis caused by rapid thrombin generation and high circulating levels of epinephrine, bradykinin and vasopressin [105]. Thrombolysis, increasingly used for ischemic stroke and other indications, is also an important cause of iatrogenic hyperfibrinolysis. Risk factors for post-thrombolytic bleeding include advanced age, female gender and low bodyweight. For patients with a high risk of major bleeding, weight-adjusted doses and catheter-directed therapy should be considered to reduce the risk [106]. Post-thrombotic bleeding can be converted using reversal agents, especially in the case of intracranial bleeding <24 h after thrombolysis or ongoing coagulopathy demonstrated by hypofibrinogenemia. Possible reversal agents include cryoprecipitate, recombinant FVIIa, FFP or antifibrinolytic agents. Other options may be considered in specific patient groups (e.g. prothrombin complex concentrate in patients on vitamin K antagonists) [107]. Theoretically, omniplasma and fibrinogen concentrate are options for conversion as well; however, they have not been described in the literature for this indication.

Fibrinolysis in bleeding of unknown cause

There is a substantial number of patients with a bleeding tendency and positive family history for bleeding complications without a definite diagnosis after performing all available screening tests and conformational tests. Conceivably, there will be a subset of patients with a hyperfibrinolytic disorder amongst them. In addition, several studies have demonstrated an altered fibrinolytic balance in patients with a bleeding tendency of unknown cause. In a study of 270 patients with bleeding of unknown cause, patients had higher tPA activity levels and lower levels of tPA-PAI-1 complexes and lower PAI-1 levels, indicating a possible underlying hyperfibrinolytic disorder [5]. In a cohort of patients undergoing cardiac surgery, postoperative blood loss was associated with lower preoperative levels of PAI-1 and lower postoperative tPA-PAI-1 levels [108]. On the other hand, a study evaluating fibrinolysis in patients with a mild-to-moderate bleeding tendency of unknown cause showed no differences in PAI-1 levels between patients and healthy controls. In addition, low PAI-1 activity levels are common in a normal population and there is no significant difference between PAI-1 activity levels in patients with a
bleeding tendency compared with blood donors and healthy controls [5,56].

Conclusions

Although the prevalence of hyperfibrinolytic disorders as a cause of bleeding described in the literature is quite low, the bleeding tendency is usually characterized by a pattern of delayed bleeding upon trauma or surgery and mucocutaneous bleeding such as menorrhagia and epistaxis. However, a clinical differentiation with other bleeding disorders, such as platelet disorders or von Willebrand disease, can be difficult, as they frequently present with mucocutaneous bleeding as well. Bleeding complications caused by fibrinolytic disorders can be very severe and can lead to increased morbidity and mortality if not treated adequately with antifibrinolytic therapy.

In general, the group of fibrinolytic disorders can be divided into patients with excess of stimulators of fibrinolysis and patients with a deficiency of inhibitors. The most severe clinical phenotype is caused by α2-AP deficiency. It is noteworthy that PAI-1 deficiency is accompanied by obstetric complications through a still unexplained underlying mechanism. Concerning the other fibrinolytic disorders, the occurrence of obstetric complications is as yet unknown and therefore an interesting subject for future research.

Because of the lack of recognition of fibrinolytic disorders and the difficulties in assessing the right diagnosis, the prevalence of these disorders is probably higher than described thus far. An accurate diagnosis is severely hampered by the absence of a sensitive and validated test of fibrinolysis. This accounts for the PAI-1 antigen and activity level, but also for the euglobulin clot lysis time. Normal results of these tests do not rule out a hyperfibrinolytic disorder. Furthermore, these current fibrinolytic assays can only be undertaken in specialized laboratories. Global assays may overcome this problem as, in general, these assays are more sensitive and able to measure several pathways in just one test. Examples are assays that measure plasmin generation or plasma-based turbidity assays [109,110]. A disadvantage is that these assays are not widely available. Moreover, next-generation sequencing techniques of genes involving the whole spectrum of fibrinolytic disorders.

Fibrinolytic assays in patients with bleeding of unknown cause show inconclusive results. Overall, an imbalance in the fibrinolytic system could be the explanation for a bleeding tendency more often than currently anticipated, and more research in this field would be beneficial. Finally, without a proper and accurate diagnosis, bleeding complications cannot be treated with targeted therapy, leading to unnecessary use of inappropriate blood products and expensive factor concentrates. We suggest developing or validating new diagnostic tools to better monitor fibrinolysis in order to facilitate the use of adequate therapy for bleeding as a result of malfunctioning of the fibrinolytic cascade.

Recommendations for clinical practice

- Disorders of fibrinolysis should not be routinely tested for in patients with a bleeding tendency, because they are rare and laboratory diagnostics unreliable
- Fibrinolysis assays should be undertaken in a specialized laboratory when there is a high index of suspicion, raised by:
  - recurrent abnormal bleeding, mainly delayed bleeding post-trauma/surgery and mucocutaneous bleeding
  - positive family history of an established hyperfibrinolytic disorder
  - co-occurrence with reproductive failure
  - unusual bleeding sites (e.g. intramedullary hematomas or umbilical cord bleeding)
- In the future, diagnostics may be improved by the implementation of thrombin and plasmin generation assays and genetic tests using next-generation sequencing

Addendum

J. Saes performed the literature search. J. Saes, S. Schols and M. Nijziel selected studies. J. Saes extracted relevant information. J. Saes, S. Schols, M. Nijziel and W. van Heerde wrote the manuscript.

Disclosure of Conflict of Interests

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Supporting Information

Additional supporting information may be found online in the Supporting Information section at the end of the article:

Data S1. Search terms.

References

1 Cesarman-Maus G, Hajjar KA. Molecular mechanisms of fibrinolysis. Br J Haematol 2005; 129: 307–21.
2 Lijnen HR. Elements of the fibrinolytic system. Ann N Y Acad Sci 2001; 936: 226–36.
3 Rijken DC, Lijnen HR. New insights into the molecular mechanisms of the fibrinolytic system. J Thromb Haemost 2009; 7: 4–13.
4 Morser J, Gabazza EC, Myles T, Leung LL. What has been learnt from the thrombin-activatable fibrinolysis inhibitor-deficient mouse? J Thromb Haemost 2010; 8: 868–76.
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5 Gebhart J, Kepa S, Hofer S, Koder S, Kaufler W, Wolberg AS, Haslacher H, Quehenberger P, Eigenbauer E, Panzer S, Mannhalter C, Pabinger I. Fibrinolysis in patients with a mild-to-moderate bleeding tendency of unknown cause. Ann Hematol 2017; 96: 489–95.

6 Mosnier LO, Lisman T, van den Berg HM, Nieuwenhuis HK, Meijers JC, Bouma BN. The defective down regulation of fibrinolysis in haemophilia A can be restored by increasing the TAFI plasma concentration. Thromb Haemost 2001; 86: 1035–9.

7 Colucci M, Incampo F, Cannavo A, Menegatti M, Bonini SM, Zaccaria F, Seremaro N, Peyvandi F. Reduced fibrinolytic resistance in patients with factor XI deficiency. Evidence of a thrombin-independent impairment of the thrombin-activatable fibrinolysis inhibitor pathway. J Thromb Haemost 2016; 14: 1603–14.

8 van Geffen M, van Heerde WL. Global haemostasis assays, from bench to bedside. Thromb Res 2012; 129: 681–7.

9 Ilich A, Key NS. Global assays of fibrinolysis. Int J Lab Hematol 2017; 39: e142–3.

10 Meltzer ME, Lisman T, de Groot PG, Meijers JC, le Cesie S, Doggen CJ, Rosendaal FR. Venous thrombosis risk associated with plasma hypo-fibrinolysis is explained by elevated plasma levels of TAFI and PAI-1. Blood 2010; 116: 113–21.

11 Rijken DJ, Hoeger-de Nobel E, Jie AF, Ataman DE, Schalij MJ, Nieuwenhuis W. Development of a new test for the global fibrinolytic capacity in whole blood. J Thromb Haemost 2008; 6: 151–7.

12 Favier R, Aoki N, de Moerloose P. Congenital alpha(2)-plasmin inhibitor deficiencies: a review. Br J Haematol 2001; 114: 4–10.

13 Carpenter SL, Mathew P. Alpha2-antiplasmin and its deficiency: fibrinolysis out of balance. Haemophilia 2008; 14: 1250–4.

14 Welch SK, Francke U. Assignment of the human alpha 2-plasmin inhibitor gene (PLI) to chromosome 17, region pter-p12, by PCR analysis of somatic cell hybrids. Genomics 1992; 13: 213–4.

15 Koie K, Komiya T, Ogata K, Takamatsu J. Alpha2-Plasmin-inhibitor deficiency (Miyasato disease). Lancet 1978; 2: 1334–6.

16 Kluft C, Vellenga E, Brommer EJ. Homozygous alpha 2-antiplasmin deficiency. Lancet 1979; 2: 206.

17 Miles LA, Plow EF, Donnelly KJ, Hougie C, Griffin JH. A bleeding disorder due to deficiency of alpha 2-antiplasmin. Blood 1982; 59: 1246–51.

18 Kettle P, Mayne EE. A bleeding disorder due to deficiency of alpha 2-antiplasmin. J Clin Pathol 1985; 38: 428–9.

19 Kluft C, Nieuwenhuis HK, Rijken DC, Groenevelde E, Wijngaards G, van Berkel W, Dooijewaard G, Sixma JJ, alpha 2-antiplasmin Enschede: dysfunctional alpha 2-antiplasmin molecule associated with an autosomal recessive hemorrhagic disorder. J Clin Investig 1987; 80: 1391–400.

20 Puqueron X, Favier R, Richard P, Maillet J, Murat I. Severe postadenoidectomy bleeding revealing congenital alpha 2 antiplasmin deficiency in a child. Anest Analg 1997; 84: 1147–9.

21 Devaussuzenet VM, Ducou-le-Pointe HA, Doco AM, Mary PM, Montagne JR, Favier R. A case of intramedullary haematoma associated with congenital alpha 2-antiplasmin inhibitor deficiency. Pediat Radial 1998; 28: 978–80.

22 Takahashi Y, Tanaka T, Nakajima N, Yoshiba A, Fukui H, Miyauchi Y, Mi Y, Tamai S. Intramedullary multiple hematomas in siblings with congenital alpha 2-antiplasmin inhibitor deficiency: orthopedic surgery with protection by tranexamic acid. Haemostasis 1991; 21: 321–7.

23 Yoshioha A, Kamitsuji H, Takase T, Iida Y, Tsukada S, Mikami S, Fukui H. Congenital deficiency of alpha 2-antiplasmin inhibitor in three sisters. Haemostasis 1982; 11: 176–84.

24 Zarnovicanova M, Mocikova K. [A homozygous quantitative defect of alpha 2-antiplasmin in a family from central Slovakia]. Bratisl Lek Listy 2000; 101: 28–30.

25 Guermazi S, Khelif A, Conrad J, Ennabl S, Dellagi K. [Hemorrhagic syndrome and isolated alpha 2-antiplasmin deficiency. Apropos of a case]. Pathol Biologie 1997; 45: 483–6.

26 Aoki N, Saito H, Kamiya T, Koike K, Sakata Y, Kobakura M. Congenital deficiency of alpha 2-plasmin inhibitor associated with severe hemorrhagic tendency. J Clin Invest 1979; 63: 877–84.

27 Hayward CP, Cina CS, Staunton M, Jurriaans E. Bleeding and thrombotic problems in a patient with alpha2 plasmin inhibitor deficiency. J Thromb Haemost 2005; 3: 399–401.

28 Kluft C, Vellenga E, Brommer EJ, Wijngaards G. A familial hemorrhagic diathesis in a Dutch family: an inherited deficiency of alpha 2-antiplasmin. Blood 1982; 59: 1169–80.

29 Maimo A, Garaglia I, Artoni A, Al-Humoos S, Peyvandi F. A novel mutation of alpha2-plasmin inhibitor gene causes an inherited deficiency and a bleeding tendency. Haemophilia 2008; 14: 166.

30 Morimoto Y, Yoshioka A, Imai Y, Takahashi Y, Minowa H, Kiriti T. Haemostatic management of intraoral bleeding in patients with congenital deficiency of alpha2-plasmin inhibitor or plasminogen activator inhibitor-1. Haemophilia 2004; 10: 669–74.

31 Kordich L, Feldman L, Porterie P, Lago O. Severe hemorrhagic tendency in heterozygous alpha 2-antiplasmin deficiency. J Thromb Haemost 2005; 3: 993–1001.

32 Ikematsu S, Fukutake K, Aoki N. Heterozygote for plasmin inhibitor deficiency developing hemorrhagic tendency with advancing age. Thromb Res 1996; 82: 129–16.

33 Hanss MM, Farcis M, Ffrench PO, de Mancourcourt P, Dechavanne M. A splicing donor site point mutation in intron 6 of the plasmin inhibitor (alpha2 antiplasmin) gene with heterozygous deficiency and a bleeding tendency. Blood Coagul Fibrinolysis 2003; 14: 107–11.

34 Dawley B, alpha H. Antiplasmin deficiency complicating pregnancy: a case report. Obstet Gynecol Int 2011; 2011: 698648.

35 Shahian DM, Levine JD. Open-heart surgery in a patient with heterozygous alpha 2-antiplasmin deficiency. Perioperative strategies in the first reported case. Chest 1990; 97: 1488–90.

36 Leebeek FW, Stibbe J, Knot EA, Kluft C, Gomes MJ, Beudeker M. Mild haemostatic problems associated with congenital heterozygous alpha 2-antiplasmin deficiency. Thromb Haemost 1988; 59: 96–100.

37 Stormorken H, Gogstad GO, Brossstad F. Hereditary alpha2-antiplasmin deficiency. Thromb Res 1983; 31: 647–51.

38 Griffin GC, Mammen EF, Sokol RJ, Perrotta AL, Stoyanovich A, Abildgaard CF. Alpha 2-antiplasmin deficiency. An overlooked cause of hemorrhage. Am J Pediatr Hematol Oncol 1993; 15: 328–30.

39 Knot EA, ten Cate JW, Lamping RJ, GieLK. Alpha 2-antiplasmin: functional characterization and metabolism in a heterozygote deficient patient. Thromb Haemost 1986; 55: 375–8.

40 Vijapurkar M, Mota L, Shetty S, Ghosh K. Menorrhagia and reproductive health in rare bleeding disorders: a study from the Indian subcontinent. Haemophilia 2009; 15: 199–202.

41 Igala M, Oukkach B, Khoubila N, Faez S, Benchekroun S. [A congenital alpha2-antiplasmin deficiency]. Ann Biol Clin 2013; 71: 93–5.

42 Lind B, Thorsen S. A novel missense mutation in the human plasmin inhibitor (alpha2-antiplasmin) gene associated with a bleeding tendency, Br J Haematol 1999; 107: 317–22.

43 Stibbe J, Knot EA, Leebeck F, Kluft C. 23 Heterozygote patients with α2-antiplasmin (α2-AP) Deficiency in 4 Dutch families. Fibrinolysis 1986; 1: 294.

44 Levi M, Peters M, Briet E. [Blind spots of the diagnostic hemostasis screen]. Ned Tijdschr Geneeskd 2000; 144: 457–60.

45 Cucuianu M, Crisnic I, Knauer O, Roman S. Severe bleeding in heterozygous alpha2-plasmin inhibitor deficiency. Rev Roum Biochim 1989; 26: 273–7.
Okajima K, Kohno I, Soe G, Okabe H, Takatsuki K, Binder BR. Direct evidence for systemic fibrinogenolysis in patients with acquired alpha 2-plasmin inhibitor deficiency. Am J Hematol 1994; 45: 16–24.

Smith AA, Jacobson LJ, Miller BL, Hathaway WE, Manco-Johnson MJ. A new euglobulin clot lysis assay for global fibrinolysis. Thromb Res 2003; 112: 329–37.

van Beers JJ, van Egmond LT, Wetzelis RJ, Verhezen PW, Beckers EA, van Oerle R, Sproink HM,Straat RJ, Henskens YM. Increased coagulation and fibrinolytic potential of solvent-detergent plasma: a comparative study between Omniplasma and fresh frozen plasma. Vox Sang 2016; 111: 33–42.

Yasar Yildiz S, Kuru P, Toksoy Oner E, Agibarsi M. Functional stability of plasminogen activator inhibitor-1. ScientificWorldJournal 2014; 2014: 858293.

Mehta R, Shapiro AD. Plasminogen activator inhibitor type 1 deficiency. Haemophilia 2008; 14: 1255–60.

Iwaki T, Urano T, Umemura K. PAI-1, progress in understanding the clinical problem and its aetiology. Br J Haematol 2012; 157: 291–8.

Dieval J, Nguyen G, Gross S, Delobel J, Kruithof EK. A lifelong bleeding disorder associated with a deficiency of plasminogen activator inhibitor type 1. Blood 1991; 77: 528–32.

Schleeff RR, Higgins DL, Pilzner E, Levi VJ. Bleeding diathesis due to decreased functional activity of type 1 plasminogen activator inhibitor. J Clin Investig 1989; 83: 1747–52.

Heiman M, Gupta S, Shapiro AD. The obstetric, gynecological and fertility implications of homozygous PAI-1 deficiency: single-centre experience. Haemophilia 2014; 20: 407–12.

Santamaria A, Borrell M, Mateo J, Vallve C, Fontcuberta J. What is the clinical impact of low plasminogen activator inhibitor-1 (PAI-1) activity? A case report and study of the incidence of low PAI-1 antigen in a healthy population. J Thromb Haemost 2007; 5: 1565–6.

Agren A, Wiman B, Stiller V, Lindmarker P, Sten-Linder M, Carlsson A, Holmstrom M, Odeberg J, Schulman S. Evaluation of low PAI-1 activity as a risk factor for hemorrhagic diathesis. J Thromb Haemost 2006; 4: 201–8.

Fay WP, Shapiro AD, Shih JL, Schleeff RR, Ginsburg D. Brief report: complete deficiency of plasminogen-activator inhibitor type 1 due to a frameshift mutation. N Engl J Med 1992; 327: 1729–33.

Lee MH, Vosburgh E, Anderson K, McDonagh J. Deficiency of plasma plasminogen activator inhibitor 1 results in hyperfibrinolytic bleeding. Blood 1993; 81: 2357–62.

Fay WP, Parker AC, Condrey LR, Shapiro AD. Human plasminogen activator inhibitor-1 (PAI-1) deficiency: characterization of a large kindred with a null mutation in the PAI-1 gene. Blood 1997; 90: 204–8.

Minowa H, Takahashi Y, Tanaka T, Naganuma K, Ida S, Maki I, Yoshioka A. Four cases of bleeding diathesis in children due to congenital plasminogen activator inhibitor-1 deficiency. Haemostasis 1999; 29: 286–91.

Matsui H, Takahashi Y, Matsunaga T, Tanaka-Horie T, Minowa H, Sugimoto M, Tsukino R, Mii Y, Giddings J, Yoshioka A. Successful arthroscopic treatment of pigmented villonodular synovitis of the knee in a patient with congenital deficiency of plasminogen activator inhibitor-1 and recurrent haemarthrosis. Haemostasis 2001; 31: 106–12.

Kuhli C, Luchtenberg M, Scharrer I, Hattenbach LO. Massive subhyaloidal hemorrhage associated with severe PAI-1 deficiency. Graefes Arch Clin Exp Ophthalmol. 2005;243:963–6.

Zhang ZY, WangZY, Dong NZ, Bai X, Zhang W, Ruan CG. A case of deficiency of plasma plasminogen activator inhibitor-1 related to Ala15Thr mutation in its signal peptide. Blood Coag Fibrinolysis 2005; 16: 79–84.

Jankun J, Skrzypczak-Jankun E. Bleeding diathesis is associated with an A15T heterozygous mutation in exon 2 of the plasminogen activator inhibitor type 1. Exp Ther Med 2010; 1: 575–7.

Smith C, Thornton YS. Pregnancy complicated by plasminogen activator inhibitor type 1 deficiency. South Med J 2010; 103: 1299–60.

Iwaki T, Tanaka A, Miyawaki Y, Suzuki A, Kobayashi T, Takamatsu J, Matsushita T, Umemura K, Urano T, Kojima T, Terao T, Kanayama N. Life-threatening hemorrhage and prolonged wound healing are remarkable phenotypes manifested by complete plasminogen activator inhibitor-1 deficiency in humans. J Thromb Haemost 2011; 9: 1200–6.

Iwaki T, Nagahashi K, Kobayashi T, Umemura K, Terao T, Kanayama N. The first report of uncontrollable subchorionic and retroplacental haemorrhage inducing preterm labour in complete PAI-1 deficiency in a human. Thromb Res 2012; 129: e161–3.

Bauduer F, Menard F, Mimoun A. Plasminogen activator inhibitor type 1 deficiency revealed by severe bleeding after prostatectomy in a 76-year-old male. Blood Coagul Fibrinolysis 2015; 26: 350–1.

Hirose J, Takedani H, Kubota M, Kinkawa J, Noguchi M. Total hip arthroplasty and total knee arthroplasty in a patient with congenital deficiency of plasminogen activator inhibitor-1. Haemophilia 2016; 22: e237–9.

Repine T, Osswald M. Menorrhagia due to a qualitative deficiency of plasminogen activator inhibitor-1: case report and literature review. Clin Appl Thromb Hemost 2004; 10: 293–6.

Stankiewicz AJ, Crowley JP, Steiner M. Increased levels of tissue plasminogen activator with a low plasminogen activator inhibitor-1 in a patient with postoperative bleeding. Am J Hematol 1991; 38: 226–9.

Takahashi Y, Tanaka T, Minowa H, Okubo Y, Sugimoto M, Nakajima M, Miyauichi Y, Yoshioka A. Hereditary partial deficiency of plasminogen activator inhibitor-1 associated with a lifelong bleeding tendency. Int J Hematol 1996; 64: 61–8.

Iwaki T, Nagahashi K, Takano K, Suzuki-Inoue K, Kanayama N, Umemura K, Urano T. Mutation in a highly conserved glycine residue in strand 5B of plasminogen activator inhibitor-1 causes polymerisation. Thromb Haemost 2017; 117: 860–9.

Largent V, Deneyes V, Brichard B, Chantrain C, Vermulen C. Bleeding diathesis in a child with normal screening tests: think about fibrinolysis. Eur J Pediatr 2005; 164: 587–8.

Rughani AI, Holmes CE, Penar PL. A novel association between a chronic subdural hematoma and a fibrinolytic pathway defect: case report. Neurosurgery 2009; 64: E1192; discussion E.

Goddeau RP Jr, Caplan LR, Alhazzan AA. Intraparenchymal hemorrhage in a patient with osteogenesis imperfecta and plasminogen activator inhibitor-1 deficiency. Arch Neurol 2010; 67: 236–8.

Bowkley CW, Dubel GJ, Haas RA, Soares GM, Ahn SH. Uterine artery embolization for control of life-threatening hemorrhage at menarche: brief report. J Vasc Interv Radiol 2007; 18: 127–31.

Bajou K, Herkenne S, Thijsen VL, D’Amico S, Nguyen NQ, Bouche A, Tabruyn S, Srahna M, Carabin YJ, Nivelles O, Paques C, Cornellissen I, Lion M, Noel A, Gils A, Vinckier S, Declerck PJ, Griffioen AW, Dewerchin M, Maritional JA, et al. PAI-1 mediates the antiangiogenic and profibrinolytic effects of 16K prolactin. Nat Med 2014; 20: 741–7.

Del Rosario MTH. The case of a late bleeder plasminogen activator inhibitor-1 deficiency. Ann Hematol Oncol 2015; 2: 1068.

Angleton P, Chandler WL, Schmer G. Diurnal variation of tissue-type plasminogen activator and its rapid inhibitor (PAI-1). Circulation 1989; 79: 101–6.

Hayward CP, Rivard GE. Quebec platelet disorder. Expert Rev Hematol 2011; 4: 137–41.
Hepatitis C virus (HCV) infection and the risk of thrombosis: a systematic review of the evidence. *J Thromb Haemost* 2004; 2: 159–65.

Kahr WH, Zheng S, Sheth PM, Pai M, Cowie A, Bouchard M, Podor TJ, Rivard GE, Hayward CP. Platelets from patients with the Quebec platelet disorder contain and secrete abnormal amounts of urokinase-type plasminogen activator. *Blood* 2001; 98: 257–65.

Diamandis M, Paterson AD, Rommens JM, Veljkovic DK, Blavignac J, Bulman DE, Waye JS, Derome F, Rivard GE, Hayward CP. Quebec platelet disorder is linked to the urokinase plasminogen activator gene (PLAU) and increases expression of the linked allele in megakaryocytes. *Blood* 2009; 113: 1543–6.

Tracy PB, Giles AR, Mann KG, Eide LL, Hoogendoorn H, Rivard GE. Factor V (Quebec): a bleeding diathesis associated with a qualitative platelet Factor V deficiency. *J Clin Invest* 1984; 74: 1221–8.

Blavignac J, Bunimov N, Rivard GE, Hayward CP. Quebec platelet disorder: update on pathogenesis, diagnosis, and treatment. *Semin Thromb Hemost* 2011; 37: 713–20.

Abbasi AH, Shaiik H, Hussain SA. Quebec platelet disorder. *J Coll Physicians Surg Pak* 2010; 20: 549–50.

Hayward CP, Rivard GE, Kane WH, Drouin J, Zheng S, Moore JC, Kelton JG. An autosomal dominant, qualitative platelet disorder associated with multimerin deficiency, abnormalities in platelet factor V, thrombospondin, von Willebrand factor, and fibrinogen and an epinephrine aggregation defect. *Blood* 1996; 87: 4967–78.

Diamandis M, Veljkovic DK, Derome F, Rivard GE, Hayward CP. Evaluation of urokinase plasminogen activator in urine from individuals with Quebec platelet disorder. *Blood Coag Fibrinolysis* 2008; 19: 463–4.

Diamandis M, Veljkovic DK, Maurer-Spurej E, Rivard GE, Hayward CP. Quebec platelet disorder: features, pathogenesis and treatment. *Blood Coagul Fibrinolysis* 2008; 19: 109–19.

Paterson AD, Rommens JM, Bharaj B, Blavignac J, Wong I, Diamandis M, Waye JS, Rivard GE, Hayward CP. Persons with Quebec platelet disorder have a tandem duplication of PLAU, the urokinase plasminogen activator gene. *Blood* 2010; 115: 1264–6.

Booth NA, Bennett B, Wijngaard G, Grieve JH. A new lifelong hemorrhagic disorder due to excess plasminogen activator. *Blood* 1983; 61: 267–75.

Aznar J, Estelles A, Vila V, Reganov E, Espana F, Villa P. Inherited fibrinolytic disorder due to an enhanced plasminogen activator level. *Thromb Haemost* 1984; 52: 196–200.

Humphries JE, Goniais SL, Pizzo SV, Williams ME. Life-long bleeding diathesis: effect of orthotopic liver transplantation. *Am J Clin Pathol* 1994; 102: 816–20.

Hampton JWOF, Bannerjee D, Klamaz E, Delaney R. Plasma activator of plasminogen: cause of a familial bleeding diathesis. *J Clin Invest* 1972; 51: 42A.

Meijers JC, Oudijk EJ, Mosnier LO, Bos R, Bouma BN, Nieuwenhuis HK, Fijnheer R. Reduced activity of TAFI (thrombin-activatable fibrinolysis inhibitor) in acute promyelocytic leukaemia. *Br J Haematol* 2000; 108: 518–23.

Bennett B, Booth NA, Croll A, Dawson AA. The bleeding disorder in acute promyelocytic leukaemia: fibrinolysis due to u-PA rather than defibrination. *Br J Haematol* 1989; 71: 511–7.

Mene1 JS, Cesarman GM, Jacovina AT, McLaughlin MA, Lev EA, Hajjar KA. Annexin II and bleeding in acute promyelocytic leukaemia. *N Engl J Med* 1999; 340: 994–1004.

Leebeek FW, Rijken DC. The fibrinolytic status in liver diseases. *Semin Thromb Hemost* 2015; 41: 474–80.

Lisman TPRJ, Porte RJ. Pathogenesis, prevention, and management of bleeding and thrombosis in patients with liver diseases. *Res Pract Thromb Haemost* 2017; 1: 150–61.

Meijer K, Williams EC. Fibrinolysis and acquired alpha-2 plasmin inhibitor deficiency in amyloidosis. *Am J Med* 1985; 79: 394–6.

Meijer K, Smid WM, Geerards S, van der Meer J. Hyperfibrinogenolysis in disseminated adenocarcinoma. *Blood Coag Fibrinolysis* 1998; 9: 279–83.

Taberner DA, Ralston AJ, Ackrill P. Acquired alpha 2 antiplasmin deficiency in glomerular proteinuria. *BMJ (Clin Res Ed)* 1981; 282: 1121.

Raza I, Davenport R, Roukie C, Plutton S, Manson J, Spoons C, Khan S, De’Ath HD, Allard S, Hart DP, Pasi KJ, Hunt BJ, Stanworth S, MacCallum PK, Brohi K. The incidence and magnitude of fibrinolytic activation in trauma patients. *J Thromb Haemost* 2013; 11: 307–14.

Yavari M, Becker RC. Coagulation and fibrinolytic protein kinetics in cardiopulmonary bypass. *J Thromb Thrombolysis* 2009; 27: 95–104.

Daley MJ, Murthy MS, Peterson EJ. Bleeding risk with systemic thrombolytic therapy for pulmonary embolism: scope of the problem. *Ther Adv Drug Saf* 2015; 6: 57–66.

Yaghì S, Willey JZ, Cucchiara B, Goldstein JN, Gonzales NR, Khatri P, Kim LJ, Mayer SA, Sheth KN, Schwamm LH. Treatment and outcome of hemorrhagic transformation after intravenous alteplase in acute ischemic stroke: a scientific statement for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke* 2017; 48: e343–61.

Ozolina A, Strike E, Jaunakskne I, Krumina A, Bjertnaes LJ, Vanags I, PAI-1 and t-PA/PAI-1 complex potential markers of fibrinolytic bleeding after cardiac surgery employing cardiopulmonary bypass. *BMC Anesthesiology.* 2012; 12: 27.

van Geffen M, Loof A, Lap P, Boezeman J, Laros-van Gorkom M, van der Velden E, van der Kley S, Lamers C, van den Heuvel D, van der Meer J, van der Boeck P, van Gelder J, van der Heide J, van de Berg H, van der Linden M, van der Doef J, van der Meer J. Treatment of disseminated intravascular coagulation in patients with acute myocardial infarction: a prospective, randomized, double-blind, placebo-controlled trial. *J Thromb Haemost* 2017; 15: 1255–64.

Yavari M, Becker RC. Coagulation and fibrinolytic protein kinetics in cardiopulmonary bypass. *J Thromb Thrombolysis* 2009; 27: 95–104.

Ozolina A, Strike E, Jaunakskne I, Krumina A, Bjertnaes LJ, Vanags I, PAI-1 and t-PA/PAI-1 complex potential markers of fibrinolytic bleeding after cardiac surgery employing cardiopulmonary bypass. *BMC Anesthesiology.* 2012; 12: 27.

van Geffen M, Loof A, Lap P, Boezeman J, Laros-van Gorkom BA, Brons P, Verbruggen B, van Kraaij M, van Heerde WL. A novel hemostasis assay for the simultaneous measurement of coagulation and fibrinolysis. *Hematology* 2011; 16: 327–36.

Lisman T. Decreased plasma fibrinolytic potential as a risk for venous and arterial thrombosis. *Semin Thromb Hemost* 2017; 43: 178–84.

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