

INVITED REVIEW

# Approach to the diagnosis and management of mild bleeding disorders

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**Summary.** Symptoms suggestive of the presence of a mild bleeding tendency are commonplace. Whilst the majority with such symptoms are healthy, it is important to identify those with bleeding disorders in order to manage symptoms, to minimize risk from invasive procedures and to avoid unnecessary exposure to blood products. Thorough clinical assessment remains the cornerstone of the diagnostic strategy for mild bleeding disorders, although the sensitivity and specificity of the clinical history and examination are limited. When clinical suspicion is aroused the use of a staged protocol of laboratory investigations is appropriate, but the limitations of currently available tests of primary hemostasis and blood coagulation must be recognized if diagnostic errors are to be avoided. Whilst there is considerable current interest in global assays of hemostasis and coagulation, none has yet been demonstrated conclusively to be more effective than the more standard approach. Iatrogenic bleeding has increasing prominence in clinical practise. The expanding use of anticoagulants and platelet inhibitor drugs has resulted in an increased proportion of the population being at risk of abnormal bleeding. Knowledge of the levels of risk associated with particular drugs and combinations, and the advantages and hazards of interruption of drug use for planned interventional procedures, are essential in order to reduce the incidence of iatrogenic bleeding. Prevention and treatment of hemorrhage in subjects with mild bleeding disorders includes the application of general measures, including attention to surgical technique, measures specific to the precise diagnosis, and less specific treatments that enhance hemostasis and coagulation or inhibit fibrinolysis. The last of these includes the widely prescribed drugs desmopressin, aprotinin, epsilon aminocaproic acid and tranexamic acid. Data are now available on their efficacy and safety in a range of clinical situations.

**Keywords:** bleeding disorders, coagulation screening tests, hemostatic therapies.

## Introduction

Discrimination between normality and a pathological bleeding tendency can be a significant challenge. Even when there is a degree of certainty over the diagnosis of a minor bleeding disorder the prediction of bleeding risk in relation to interventions is an inexact science. A balance must be struck between unwarranted treatment, possibly engendering a risk of thrombosis, and excessive bleeding, which may result in exposure to blood products.

Here we consider the diagnosis and management of those bleeding disorders that are of a severity that may render them virtually subclinical and in which spontaneous severe hemorrhage is a rarity. As this definition includes many acquired bleeding disorders and congenital disorders other than those caused by severe coagulation factor deficiency or major defect in platelet function, the topic is broad.

Among the conditions listed in Table 1, the severity of bleeding may be quite variable. An obvious example is hemophilia A, in which a severe phenotype with spontaneous bleeding accompanies factor levels of 1% or less, whereas the condition is clinically milder if the factor (F) VIII concentration is > 3%. In other disorders there is a less clear relationship between the level of factor deficiency and the clinical phenotype, for example in FXI deficiency, where some subjects with FXI of less than 20% remain asymptomatic and others with somewhat higher plasma concentration suffer mild to moderate bleeding. Considerable clinical heterogeneity is seen in FXIII deficiency also. Perhaps the best example of heterogeneity is in congenital dysfibrinogenemias. Although umbilical stump bleeding, soft tissue and central nervous system hemorrhage is prominent in some, others are asymptomatic and still others have a prothrombotic state. It follows that the term 'mild bleeding disorder' is a classification based on clinical symptoms or presence of known acquired diseases or treatments associated with bleeding, rather than results of laboratory analysis. It broadly includes those conditions in which there is increased bleeding associated with trauma, including operative trauma, and a tendency to easy skin bruising, epistaxis or

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**Table 1** Mild bleeding disorders

	Acquired	Congenital
Disorders of primary hemostasis	Due to pharmacological platelet inhibitors Thrombocytopenias Primary bone marrow diseases (myeloproliferative, myelodysplastic, leukaemic, plasma cell dyscrasias) Severe renal failure	Most von Willebrand disease Some qualitative platelet disorders
Disorders of coagulation/fibrinolysis	Hepatocellular failure Vitamin K deficiency Due to pharmacological anticoagulants Coagulation factor inhibitors	Some coagulation factor deficiencies, including hemophilia carrier state Antiplasmin deficiency
Other	Scurvy	

menorrhagia, but in which spontaneous life-threatening or organ-threatening bleeds do not generally occur. As such it overlaps with normality.

### The diagnosis of mild bleeding disorders

Most commonly the clinician is faced with the patient who:

- 1 has suffered apparently excessive or frequent unprovoked bleeding, most commonly epistaxis or menorrhagia, or at parturition;
- 2 has suffered unexpected or apparently excessive bleeding after an intervention, such as dental extraction; or who
- 3 has a family history of apparently excessive bleeding.

Traditionally, the clinical approach includes the use of a detailed clinical history and examination combined with the deployment of laboratory screening tests in order to reach a diagnosis, to allow prediction of individual bleeding risk and to guide clinical management. However, there is very little evidence regarding the diagnostic efficiency of the clinical history used for this purpose and all of the coagulation screening tests have significant limitations.

#### The bleeding history

The major issues to be determined are:

- 1 Is a pathological bleeding tendency present?
- 2 Is it congenital/familial or acquired?
- 3 Is it principally a defect of primary hemostasis (platelet or vessel wall dependent) or of fibrin formation and stability (dependent on the fluid phase of coagulation)?
- 4 Is there systemic disease causing or exacerbating any bleeding tendency?
- 5 Is increased bleeding induced or exacerbated by pharmaceutical use?

The principal presentations are easy bruising, spontaneous mucosal bleeding, menorrhagia and excessive bleeding after trauma, often surgical trauma or parturition. The significance of these symptoms is increased when they occur in combination. In relation to postoperative bleeding in the acute situation, it is important to assess the patient from the bedside. For example, a frequent situation is excessive bleeding from a surgical wound raising suspicions of systemic hemostatic failure. However,

when, simultaneously, other sites of tissue injury such as drain insertion sites and vascular access sites are not bleeding abnormally, the bleeding is more likely to be due to surgical causes than to a systemic bleeding disorder. A comprehensive clinical assessment is important for other reasons. For example, easy bruising occurs in some conditions in which there is no systemic coagulopathy or defect of primary hemostasis and is due to an abnormality of blood vessels or their supporting tissues. In Ehlers-Danlos syndrome there may be excessive bleeding after trauma and a history of joint hyperextensibility. In some forms there is a risk of massive hemorrhage from spontaneous vessel rupture. In Cushing's syndrome there is easy bruising, usually without abnormal bleeding at other sites. A similar pattern of bruising, without systemic bleeding, occurs with chronic corticosteroid use, even with inhaled steroids. In senile purpura bruising typically occurs on the wrists and hands after minor trauma, or even spontaneously. All can be easily overlooked without full assessment, leading to over-investigation and even misdirected treatment.

Bruising is often the sole hemorrhagic manifestation in psychogenic purpura. Skin bruising may be severe and typically occurs only in accessible sites. Frequently, the bruises do not follow the normal pattern of resolution but may persist for several weeks. Women are more commonly afflicted by this form of dermatitis artefacta, which can lead to extensive but fruitless laboratory tests.

Whilst there is no doubt that some bleeding symptoms are more commonly associated with disease, especially menorrhagia and bleeding after surgical interventions, it is equally certain that such symptoms do not always reflect the presence of a systemic disorder of coagulation or hemostasis. Also, a high proportion of healthy individuals report suggestive hemorrhagic symptoms in response to direct questioning. Very few studies have addressed this issue. In a study of unaffected relatives of subjects with the rare Quebec platelet disorder there was a high incidence of apparently significant bleeding symptoms [1]. For example, around one-third reported skin bruising without reason and in one half with nosebleeds they lasted longer than 15 min [2]. Despite this limitation, it has been demonstrated that the bleeding history may have diagnostic power, but that this is dependent on the precise questions asked. In their case-control study comparing patients

with a proven bleeding disorder with healthy volunteers and using a standardized questionnaire, Sramek and colleagues [3] showed that the presence of a positive family history and bleeding after traumatic events, other than parturition, identified subjects with a bleeding disorder. However, some reported symptoms were non-discriminatory, including gum bleeds, epistaxis and blood in the urine or stool. Overall, we conclude that the bleeding history is a useful, albeit rather blunt, screening tool.

Menorrhagia as a potential indicator of an underlying bleeding disorder has attracted particular attention, in part because a gynecological/endocrine cause is identified in fewer than half of sufferers. In one large cohort an inherited bleeding disorder was identified in 17% of women who had menorrhagia and normal pelvic examination [4]. Mild von Willebrand disease was the principal diagnosis, with mild FXI deficiency prominent also. Of clinical importance, the occurrence of menorrhagia since menarche and presence of additional bleeding symptoms were discriminatory. Edlund *et al.* [5] had previously reported a similar incidence of von Willebrand disease in a smaller cohort of Swedish women with menorrhagia. In a North American population Philipp and colleagues [6] reported a high incidence of apparent platelet function defects in women with menorrhagia, although the precise diagnoses were not established. Taken together these observational data suggest that persistent menorrhagia from menarche for which no alternative explanation is apparent may be a significant pointer towards the presence of a systemic bleeding disorder.

### Screening tests

When the bleeding history and/or family history are suspicious it is usual to proceed to a staged series of investigations to confirm an abnormality of primary hemostasis or coagulation and to determine a precise diagnosis. Generally, coagulation screening tests are performed first, sometimes with a skin bleeding time. However, because mild von Willebrand disease is a common diagnosis, specific tests for the condition may be included as part of the initial assessment. A typical approach is depicted in Table 2. It is essential to appreciate that the screening tests have limitations and may fail to detect significant disease, for example mild von Willebrand disease, deficiency of FXIII and alpha2-antiplasmin deficiency.

In interpreting screening tests some important considerations should be borne in mind:

- 1 Plasma clotting times are influenced by preanalytical variables such as difficult venepuncture, undisclosed heparin contamination and excessive citrate concentration due to erythrocytosis.
- 2 Normal ranges are established using the mean value and 2 standard deviations on samples from a representative population. As a result 2.5% of normal samples will have a slightly prolonged clotting time.
- 3 The skin bleeding time is poorly reproducible and does not predict bleeding risk. Its utility as a screening tool has been questioned.

**Table 2** An approach to laboratory investigation

First stage
Full blood count and ABO blood group, liver function test Prothrombin time and activated partial thromboplastin time. Mixing tests with pooled normal plasma if indicated Thrombin time and fibrinogen concentration von Willebrand factor antigen, factor VIII and ristocetin cofactor Standardized skin bleeding time Platelet aggregation with, at least, ADP, collagen, arachidonic acid, ristocetin
Second stage
The cause of thrombocytopenia should be determined, if present Prolonged PT/APTT: perform relevant factor assays, with inhibitor assays if indicated. A lupus inhibitor test should be performed in the face of isolated prolongation of the APTT Prolonged TT: perform Reptilase time and fibrinogen antigen Abnormal von Willebrand tests: repeat to confirm, with multimers if indicated. Repeat tests even if first stage results are normal, if there is clinical suspicion Repeat abnormal platelet aggregation tests. If results are suggestive, perform platelet granule secretion assay If all above normal/negative: perform a factor XIII screen and assay alpha2-antiplasmin

These considerations are of particular importance in relation to random use of coagulation screening tests preoperatively to predict bleeding in unselected patients. Current evidence does not support such an approach [7].

### Can we do better? 'Global screening tests' in the diagnosis of mild bleeding disorders

There has been considerable interest in the possibility that tests that assess overall hemostatic and coagulation potential may be of value in screening for, and diagnosis of, bleeding disorders.

The PFA-100<sup>r</sup> device (Dade Behring Inc., Deerfield, IL, USA) simulates primary hemostasis at high shear. Small amounts of citrated blood are aspirated at a shear rate of 5000–6000 s<sup>-1</sup> through a capillary. The blood meets a membrane with a 150-µm central aperture coated with either collagen and epinephrine or collagen and ADP. Platelet adhesion and aggregation cause occlusion of the aperture. Results are reported as closure time in seconds. Closure time is influenced by preanalytical variables, which must be standardized, and the presence of anemia and thrombocytopenia. It is highly dependent on the concentration of von Willebrand factor. Numerous studies have examined closure times in congenital and acquired disorders of platelet function and these data have been extensively reviewed by a working group of the ISTH-SSC Platelet Physiology Subcommittee [8]. Although the test is sensitive to von Willebrand disease, its sensitivity is variable in congenital platelet disorders. The working party concluded that 'normal closure time can help exclude some severe platelet defects and moderate-to-severe von Willebrand disease, but if clinical suspicion is strong, further testing should be performed'. As such, the test lacks the sensitivity and specificity required for general utility as a screening tool. Nor does it have an established role in assessing bleeding risk associated with platelet suppressive therapy. Others have presented a contrary

view [9,10], arguing, based on extensive experience of clinical application of the test, that it is a useful screening tool and possibly predicts clinically effective bleeding. Nevertheless, we conclude that there is insufficient evidence at present for routine adoption of the method as a screening tool for bleeding disorders. Furthermore, it is acknowledged that its use to predict bleeding could lead to over-treatment [10]. We believe that, at best, the use of the device is an alternative to the standardized skin bleeding time in the investigation of possible bleeding disorder.

Thromboelastography or thromboelastometry measures the viscoelastic changes that occur during coagulation. The rate of fibrin polymerization and clot strength in whole blood or plasma are assessed. There is little evidence of utility as a screening tool for bleeding disorders. Its principal application is to provide some guidance on blood product use in hepatic and cardiac surgery [11–13]. The test has been used to detect coagulation changes in trauma patients, also [14].

Qualitative and quantitative analysis of clot waveform on MDA<sup>f</sup> (bioMerieux inc. Durham, NC, USA) coagulation analyzers has been used to assess the severity of coagulation dysfunction in disseminated intravascular coagulation, both clinically overt and subclinical [15,16]. No role in screening for bleeding disorders in other situations has emerged.

Over recent years, methods for the determination of the thrombin generation curve in plasma have been refined. The area under the thrombin generation curve, or endogenous thrombin potential, has been used to investigate risk of both bleeding and thrombosis [17]. The test appears to be sensitive to very low levels of some coagulation factors and the endogenous thrombin potential appears to relate to clinical bleeding tendency in that context [18]. It is sensitive to heparin anticoagulation also [19]. However, this approach has no proven place as a screening tool for bleeding disorders in general at present.

### Iatrogenic bleeding

Coumarins are a significant cause of bleeding and are widely used. For example, at least 500,000 subjects take warfarin in the UK, representing 1% of the population. Furthermore, the value of combinations of platelet suppressive agents in the management of cardiovascular disease is recognized increasingly. This use of antithrombotics is inevitably accompanied by an increased bleeding tendency. As a result the clinician is frequently faced with the need to assess the bleeding risk in subjects treated with these agents who require invasive interventions.

In relation to warfarin, the risk of bleeding is clearly linked to the International Normalized Ratio (INR). The most informative data are from the inception cohort reported by Palareti *et al.* [20]. Bleeding rates per 100 patient years were: fatal, 0.25; major, 1.1; and minor, 6.2; with a rising risk of bleeding with increasing age.

The use of platelet suppressive agents, especially aspirin and clopidogrel, often in combination, is expanding as a result of

large randomized studies demonstrating efficacy in prevention of cardiovascular events. For example, the CAPRIE trial [21] demonstrated a significant decrease in risk of myocardial infarction, ischemic stroke and vascular death with prophylactic clopidogrel and the CURE [22] trial demonstrated additional benefit of clopidogrel added to aspirin therapy within 24 h of presentation with acute coronary symptoms. Furthermore, the efficacy of clopidogrel in preventing postintervention stent occlusion was confirmed in the CREDO trial [23]. As a result the number of subjects with an acquired, chronic mild bleeding disorder has increased markedly and reliable data on the degree of bleeding risk among this cohort begin to emerge.

Serebruany *et al.* [24] performed a meta-analysis of bleeding complications in over 300 000 patients enrolled in 50 randomized controlled trials. Within the limits of analysis of heterogeneous trials an estimate of overall bleeding rates was made. This was lowest for low dose (<100 mg daily) aspirin: 3.6% (95% CI, 3.3–3.9%). For other drugs, results were: dipyridamole 6.7% (5.8–7.55%) and clopidogrel 8.5% (8.1–8.8%). Glycoprotein IIb/IIIa inhibitors were associated with bleeding rates of >40%, with high rates of major bleeding. No assessment of combinations of drugs was made. Kapetanakis *et al.* [25] examined the rates of bleeding in subjects given clopidogrel and aspirin compared with those on aspirin only, prior to coronary artery bypass grafting. Addition of clopidogrel added to the bleeding risk as evidenced by an almost 5-fold greater likelihood of re-operation due to bleeding and an increased use of red cell and platelet transfusions. This conforms to the earlier findings of Ray *et al.* [26], who also demonstrated increased transfusion requirements in coronary artery bypass patients given clopidogrel within 7 days before operation. In contrast, analysis of data from the CAPRIE study revealed no excess of overall hemorrhagic events with long-term clopidogrel use in patients with symptomatic atherosclerosis compared with aspirin (9.27% vs. 9.28%, respectively). Unsurprisingly, aspirin users had more gastrointestinal bleeds [21]. The severity of the bleeding disorder induced by antiplatelet drugs, oral anticoagulants and combinations has been assessed in other populations also. Quilliam *et al.* [27] reported a higher risk of hospitalization for bleeding among a population of elderly stroke survivors using warfarin (OR 1.26, CI 1.11–1.43) and combination therapies (OR 1.07, CI 0.99–1.82) compared with non-users. These results are supported by those from a large observational study in elderly patients after myocardial infarction [28]. Sequentially increasing bleeding rates were observed, from 0.03 per patient-year to 0.09 per patient-year, associated with use of aspirin alone, aspirin with thienopyridine, aspirin plus warfarin and triple therapy. Finally, a moderate increase in bleeding risk when aspirin and warfarin are used together in elderly subjects with atrial fibrillation was demonstrated in a retrospective study by Shireman *et al.* [29].

The dilemma for the clinician is how to manage iatrogenic bleeding disorders, especially in the context of invasive procedures. Clearly this must be assessed on an individual basis. For example, in some situations associated with a high

risk of thrombosis the bleeding risk is secondary. This may be the case in patients with non-ST-elevation acute coronary syndrome; an analysis of data from the CURE study suggests that the benefits of starting clopidogrel therapy on admission outweighs the risks, even among those patients who proceed to coronary artery bypass graft surgery [22]. Similar considerations probably apply to patients with drug-eluting coronary stents, in whom discontinuation of combined antiplatelet therapy carries a high risk of stent thrombosis [30]. Even in lower risk patients, such as those on low-dose aspirin for stable coronary artery disease, withdrawal of aspirin is, unsurprisingly, associated with an increased risk of major adverse cardiac events, and the risk is magnified substantially in patients with coronary artery stents [31]. On the other hand, aspirin use is said to increase the risk of hemorrhage after head and neck surgery [32] and warfarin, but not antiplatelet drugs, to increase bleeding rates after colonoscopic polypectomy [33]. Recommendations have been made on which gastrointestinal endoscopic procedures require warfarin withdrawal [34].

In a systematic review of warfarin withdrawal perioperatively, it was concluded that patients could undergo diagnostic endoscopy, arthrocentesis, cataract surgery and dental procedures without anticoagulant withdrawal but that withdrawal is necessary for many other procedures. However, the paucity of data supporting some of these decisions was noted [35]. Perhaps the most robust data on warfarin use are in dental surgery. Our interpretation of these data is that the risk of significant bleeding in patients undergoing outpatient dental procedures with an INR in the range 2 to 4 is low. Oral anticoagulant therapy should not be discontinued. The use of topical antifibrinolytic therapy to reduce bleeding in this context is described below.

In summary, subjects treated with antiplatelet and anti-thrombotic medications must be regarded as having a bleeding disorder, albeit iatrogenic. Management decisions to reduce bleeding risk whilst avoiding thrombotic complications are complex and must generally be considered individually.

When withdrawal of antithrombotics/antiplatelet agents is deemed essential prior to an invasive procedure consideration should be given to whether so-called bridging therapy should be implemented to reduce thrombosis risk, usually with low molecular weight heparin. In addition, the pharmacokinetics of the drug to be discontinued must be considered. For example, the glycoprotein IIb/IIIa inhibitors tirofiban and eptifibatid dissociate rapidly, with a short duration of action, whereas abciximab does not; aspirin, warfarin and clopidogrel all have a prolonged duration of action and require withdrawal several days before the hemostatic challenge, or reversal with vitamin K in the case of warfarin.

### **Prevention of excessive bleeding in mild bleeding disorders**

Minimizing blood loss during surgical procedures is important: uncontrolled bleeding results in an increased rate of re-operation with increased morbidity and mortality, and it

increases the probability of red cell transfusion. Although the viral safety of blood has improved in recent years transfusion is still associated with the risks of transfusion-transmitted infection [36] and other serious hazards. There are several ways to reduce perisurgical bleeding, including attention to surgical technique, general measures to optimize physiological hemostasis and the use of pharmacological agents that increase the levels of coagulation factors, including von Willebrand factor, inhibit fibrinolysis, or support clot stability.

#### *General and indirect measures*

The kinetics of clot generation are, of course, dependent on physiological conditions, including temperature and pH. Studies in animals confirm that hypothermia and acidosis delay coagulation [37,38]. This is particularly relevant after major trauma requiring immediate surgery, when tissue injury combined with hypothermia and acidosis contributes to the development of a coagulopathy. General measures to minimize the effect of hypothermia and acidosis on coagulation include re-warming techniques and the use of a staged surgical approach whereby short-duration essential surgical repair is carried out in preference to lengthy definitive surgery.

In patients undergoing uterine myomectomy, in addition to the beneficial effect of gonadotrophin releasing hormone agonist (GnRHa) analogue treatment [39], a recent Cochrane review concluded that there is benefit from the use of vaginal misoprostol, bupivacaine with epinephrine, vasopressin, use of a pericervical tourniquet and chemical dissection with mesna, although more trials are required [40].

The alpha2-adrenoreceptor dexamedetomidine has recently been shown to reduce bleeding after tympanoplasty and septorhinoplasty [41] and in a randomized controlled trial, cyanoacrylate surgical sealant reduced the time to effective hemostasis following vascular surgery [42].

The use of erythropoietin to normalize the hematocrit shortens the bleeding time in uremic patients [43]. It is likely that this results in less risk of bleeding from invasive procedures.

#### *Direct pharmacological enhancement of coagulation*

Enhancing coagulation or inhibiting fibrinolysis prior to or during a hemostatic challenge has been pursued by clinicians over many years. However, it might be predicted that such a strategy would result in enhancement of the postoperative prothrombotic state. Most of the data available on efficacy relate to antifibrinolytic drugs but there are also studies on the role of the synthetic vasopressin analogue desmopressin (DDAVP), fibrin sealant and recombinant FVIIa.

The use of tranexamic mouthwash [44–46] (as well as gelatin sponges with sutures [47]) is beneficial in patients undergoing dental procedures during coumarin therapy. The American College of Chest Physicians' guidelines recommend use of tranexamic acid or epsilon aminocaproic acid (EACA) mouthwash without interruption of coumarin therapy [48].

A Cochrane review [49] reported on eighty-nine studies of antifibrinolytics administered preoperatively. The majority were in cardiac surgery, with others in orthopaedic, liver transplantation and vascular surgery. Most evaluated aprotinin, with fewer assessing the effect of tranexamic acid or EACA. The authors concluded that aprotinin reduces the need for red cell transfusion and re-operation because of bleeding, without serious side-effects. Similar trends were observed for both tranexamic acid and EACA. Within the aprotinin studies, the benefit was more pronounced in patients receiving a continuous infusion, for cardiopulmonary bypass only. The data on orthopaedic surgery were fairly scant, but a more recent meta-analysis of 43 randomized controlled trials concluded that both aprotinin and tranexamic acid reduce the requirement for red cell transfusion [50]. However, the safety of aprotinin has been questioned. For example, in a recent observational study of almost 4000 patients undergoing coronary artery bypass graft surgery, Mangano and colleagues [51] reported a statistically significant reduced long-term survival among patients who received aprotinin compared with those who received EACA, tranexamic acid or no hemostatic medication. In summary, aprotinin appears to be effective in reducing bleeding during and after major surgery but there are concerns regarding safety. It may be that EACA and tranexamic acid are also effective and possibly safer but this question can be answered only through the conduct of randomized controlled trials with long-term follow-up.

DDAVP is effective in preventing bleeding in mild hemophilia A and type 1 VWD. The hemostatic effect is due to the approximately three- to 4-fold elevation of VWF and VIII:c levels. Serious side-effects are rare but the drug is contraindicated in patients under 2 years of age, because of the risk of hyponatremia, as well as in adults with symptomatic atherosclerosis. In patients without hereditary bleeding disorders there is no evidence for a benefit in the use of DDAVP as prophylaxis [52].

In 14 studies (388 patients) where fibrin sealant was used, perioperative blood loss and exposure to allogeneic blood appeared to be reduced [53]. The non-blinded nature of these studies and potential risks associated with exposure to a pooled plasma product need to be borne in mind.

Finally, in one study of elective open prostatectomy the use of recombinant VIIa resulted in reduced blood loss compared with placebo [54].

### Management of bleeding episodes in mild bleeding disorders

The management of bleeding in von Willebrand disease and mild hemophilia and due to warfarin is extensively covered elsewhere [55–57]. The evidence base for the management of bleeding in most other mild bleeding disorders is scant. Bleeding in patients on antiplatelet drugs is managed by withdrawal of the drug and in severe cases by platelet transfusion. The use of tranexamic acid, DDAVP and platelet transfusion in patients with assorted mild inherited

platelet disorders has been reviewed [58]. The evidence base for the use of DDAVP is most developed in patients with storage pool disorders [59]. Whether shortening of skin bleeding time after DDAVP administration in qualitative bleeding disorders translates into reduced bleeding is unproven, however.

The bleeding diathesis in renal failure is characterized by a defect of primary hemostasis. Control of acute bleeding is probably best achieved by red cell transfusion to correct the hematocrit and dialysis, but DDAVP shortens the bleeding time and may be of benefit [60].

### Disclosure of conflict of interests

The authors state that they have no conflict of interests.

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