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The Act of Balancing Bleeding versus Thrombosis

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Patients with severe hemostatic defects are only partially protected from thrombosis. Conversely, those with thrombosis and the need for anticoagulant therapy may also suffer from bleeding. Thus, while treating patients at one extreme of the hemostatic spectrum, their counterparts must not be neglected, and the art of balancing the therapy between these extremes needs to be refined. It is of the utmost importance to evaluate the balance between pro-hemorrhagic and prothrombotic risk factors in optimizing long-term prophylaxis in patients with, for example, atrial fibrillation. Tests for global hemostatic capacity may help estimate the risks in some of these patients. Familiarity with, and access to, a variety of hemostatically active drugs is crucial for proper management of various bleeding complications.

Thrombosis in hemophilia

Substantial resources are expended to control bleeding in patients with hemophilia or the severe form of von Willebrand's disease. With specialized hemophilia treatment centers and coagulation factor concentrates, results have been remarkable, the prognosis for these patients improved, and their life expectancy increased from 16 years at the beginning of the 20th century to almost normal today. Substitution therapy is, however, a risk factor for thrombotic events that may occur in patients with the most severe forms of these bleeding disorders.¹ The second important risk factor for thrombosis in these patients is indwelling catheters that are typically used in children with hemophilia.²

Acute coronary syndromes were seldom described in patients with hemophilia until recently. This was at least partly because they rarely reached old age. With improved survival, however, myocardial infarction (MI) and death due to ischemic heart disease have become realities among patients with hemophilia, albeit at a lower incidence.³ In fact, the risk of death from MI has been estimated to be one-fifth of the expected number.⁴ Thus, some protection against MI is certainly gained by having a congenital coagulopathy. Patients with the severe form of hemophilia have been observed with very severe coronary heart disease at the time of their first clinical manifestation.

Although patients with the severe form of hemophilia or von Willebrand's disease are well aware of their propensity to bleed, individuals with the mild form of these diseases are rarely reminded of their hemostatic defect. The mortality rate from intracranial bleeding is paradoxically higher in patients with mild compared to severe hemophilia in Sweden.⁵ At our institution in Stockholm, Sweden, we have found that patients with a mild bleeding disorder, bewildered by their diagnosis of acute MI, have forgotten to communicate that they have a history of bleeding diathesis before therapy with thrombolytic agents was started. Such a combination inevitably results in bleeding complications.

Treatment of thrombotic events in hemophilia

How can thrombolytic or multiple anti-aggregant therapy (including glycoprotein [GP] IIb/IIIa inhibitors and ADP-receptor blockers) be given safely in the presence of a congenital coagulopathy? Although the hemostatic defect provides some protection against thrombosis, it is impossible to calculate to what extent the reduction in the dose of an antithrombotic or antiplatelet agent should be.



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Table 1: Suggested treatment protocol for patients with a congenital bleeding disorder and MI

	Antithrombotic treatment	Hemostatic treatment
Intensive care period or until discharge	Thrombolysis and/or GP IIb/IIIa inhibitor and/or heparin and/or ADP-receptor blocker and aspirin	Factor concentrate in continuous infusion aiming at 0.5 IU/mL*
Discharge – 1 month	ADP-receptor blocker and low-dose aspirin	Factor concentrate 20 IU/kg i.v. 3 times/week
After 1 month	Low-dose aspirin	If bleeding disorder in severe form – continue as above

*Monitor plasma factor level once daily, adjust infusion rate accordingly
MI = myocardial infarction

Likewise, if a coronary stent is inserted, there is little understanding of the possible local protective effect against thrombotic occlusion provided by the hemostatic defect.

The only rational solution in this balancing act is to replace the missing factor and then start treatment or prophylaxis against thrombosis as indicated. Since substitution therapy in hemophilia and the more severe forms of von Willebrand's disease is costly and since high doses of factor concentrates have been associated with thromboembolic complications,^{6,9} it would be ideal to maintain the plasma level at the lower limit of normal. However, because the traditional mode of administration of factor concentrate utilizes intravenous bolus doses, high peak levels have to be reached to keep the trough level at the lower limit of normal. Venous thromboembolism has occurred with this mode of replacement therapy.

Continuous infusion of factor concentrates offers the possibility of safely maintaining the plasma level at, or only slightly above, the lower limit of normal.^{10,11} This method, although suggested by Brinkhous in 1954¹² and first attempted by McMillan et al in 1970,¹³ only gained widespread acceptance during the past decade.¹⁴ Highly purified and more stable factor concentrates and the availability of portable minipumps contributed to the feasibility of continuous infusion. A reduced requirement for factor concentrate due to the elimination of unnecessary peaks and, in some cases, a saturation-like phenomenon with progressive reduction of clearance, makes continuous infusion cost-effective.¹⁴

For the optimal treatment of a patient with a congenital bleeding disorder and acute MI (Table 1), the patient should receive substitution with a concentrate of the deficient coagulation factor, maintaining a plasma level of approximately 0.5 IU/mL during the period when thrombolysis or GP IIb/IIIa inhibitors are given and preferably during the entire period of intensive care in hospital to allow for emergent procedures that may become necessary. Thereafter, a more conventional prophylactic regimen with the same factor concentrate – administered as bolus doses of 20 IU/kg 3 times a week – should be given as long as a combination of clopidogrel and aspirin is needed. This combination therapy may be limited to only one month. Thereafter, secondary prophylaxis against MI depends on the congenital coagulopathy. For patients with mild bleeding disorders, low-dose aspirin seems to be tolerated without a need for substitution with factor concentrates.

Thrombosis and bleeding

Acquired bleeding tendency in a patient with thrombosis requires the clinician to navigate a narrow and treacherous

passage. Bleeding due to a clearly-defined defect in the hemostatic system is usually easy to manage by compensating for the deficiency of a coagulation factor in hemophilia, von Willebrand's disease, or one of the rare defects (deficiency of factor II, V, VII, X, XI, or XIII), transfusing platelets in thrombocytopenia, or repairing local damage to vascular integrity. In other cases, one must assess whether treatment of the thrombotic event or the bleeding takes priority. Overt bleeding of moderate severity may be managed by transfusions of red blood cells while antithrombotic treatment is given, whereas bleeding in the central nervous system does not allow for administration of any anticoagulant. Conversely, a thrombosis in the jugular vein caused by removal of a central line does not require treatment; however, pulmonary embolism with hemodynamic instability is immediately life-threatening. Fortunately, combinations of the most serious examples of bleeding and thrombosis are rare.

One option for treating combined bleeding and thrombosis is anticoagulation together with deamino-D-arginine vasopressin (DDAVP) and/or an anti-fibrinolytic agent.

DDAVP in thrombosis

The vasopressin analogue DDAVP (desmopressin) releases factor VIII and von Willebrand factor, but also tissue-plasminogen activator (t-PA), and improves the interaction between platelets and the vessel wall.¹⁵ The profibrinolytic effect is almost negligible. DDAVP does not improve the antithrombotic treatment when used as an adjunct to heparin.¹⁶ However, the prolongation of bleeding time induced by heparin is reversed by DDAVP and this seems to allow for anticoagulant therapy with heparin at the same time a bleeding complication is mitigated.¹⁷ In experimental models, the addition of DDAVP to heparin does not reduce its antithrombotic treatment effect.¹⁸ The dosing is shown in Table 2.

Unstable angina or recent MI is usually considered a contraindication to DDAVP, although its use in coronary artery bypass surgery to reduce blood loss has not been associated with a significant increase in the risk of thrombotic complications.¹⁹ DDAVP causes retention of water, especially after repeated administration and, therefore, water and sodium balance must be monitored. The reported tachyphylactic effect²⁰ – a diminishing effect with repeated dosing – may not be an important issue in the situation discussed here.

Antifibrinolytic agents in thrombosis

Two specific antifibrinolytic agents – epsilon-aminocaproic acid (6-aminocaproic acid) and tranexamic acid – are lysine

Table 2: Hemostatic agents that may be given together with antithrombotic treatment to reduce active bleeding

Agent	Regimen	Potential problems
DDAVP (desmopressin)	0.2-0.3 mg/kg s.c. once daily	Fluid retention, hyponatremia, avoid in unstable coronary heart disease; tachyphylaxis
Tranexamic acid	10 mg/kg slowly i.v. every 8 h or 20 mg p.o. every 8 h	Nausea; avoid in DIC
Epsilon aminocaproic acid	5 g i.v. followed by 1-2 g/h	Nausea; avoid in DIC

DIC = disseminated intravascular coagulation

derivatives that compete for the lysine-binding site on plasmin. These have been approved and used for many years, especially for menorrhagia and other bleeding manifestations from mucous membranes in patients with disorders of primary hemostasis.²¹ Tranexamic acid is 6-10 times more potent and usually better tolerated, but has a longer half-life. It has an excellent preventive effect against bleeding after tooth extraction in patients on therapeutic doses of vitamin K antagonists.^{22,23} Tranexamic acid counteracts the conversion of plasminogen to plasmin, but is not effective when large amounts of plasmin are already circulating such as when there is bleeding caused by thrombolytic therapy. In this situation, the protease inhibitor, aprotinin, is required.

A frequently asked question is whether tranexamic acid causes or aggravates thrombosis. In a meta-analysis of 12 randomized clinical trials in hip or knee arthroplasty, pretreatment with tranexamic acid reduced the proportion of patients requiring blood transfusions without any increase in the risk of thromboembolism. Tranexamic acid is also beneficial for bleeding from sites other than the mucous membranes. This has also been observed in patients with hemophilia. Two cohorts of patients with hemophilia B were treated during the perioperative period with factor IX concentrate according to the same protocol; however, tranexamic acid was prohibited in one cohort. Most of the procedures were major orthopedic surgery. The mean blood loss was 379 mL versus 625 mL and blood transfusions were given to 0 of 9 patients versus 3 of 7 patients, for those receiving tranexamic acid versus those not receiving it, respectively.^{24,25} The typical dose of tranexamic acid is shown in Table 2, but it should be reduced in patients with renal or hepatic failure.

Antifibrinolytic agents should not be given to patients with disseminated intravascular coagulation since the resolution of microthrombi in vital organs may be delayed, resulting in aggravated multi-organ failure.²⁶

Vena cava filters

Although these devices reduce the short-term risk of pulmonary embolism, their benefit does not remain statistically significant after 2 years. There is no reduction in mortality and the risk of recurrent deep vein thrombosis (DVT) almost doubles during this period.²⁷ There are clear indications for insertion of such a filter, for example, in a patient with proximal DVT, symptomatic submassive or massive pulmonary embolism, at the same time as a very recent intracranial hemorrhage or within a few days of brain surgery. In such cases, a temporary filter should be used since anticoagulant therapy most likely can be started with escalating doses after 10-14 days. In this way, the long-term risk of recurrent DVT can be reduced.

For patients with progressive DVT in spite of therapeutic doses of heparin, low-molecular-weight heparin, or vitamin K antagonists, insertion of a filter is an option. However, many of these patients have overt or occult cancer and may be partly resistant to these drugs. Due to the lack of studies on optimal drug therapy in these often desperate cases, there are no guidelines; however, switching from vitamin K antagonists to low-molecular-weight heparin or higher doses of the latter has been effective in anecdotal cases and may be attempted before a filter is inserted.

Balancing risk factors in atrial fibrillation

Vitamin K antagonists provide a 68% risk reduction in stroke in patients with atrial fibrillation²⁸ compared to a modest 23% reduction with aspirin.²⁹ Still, only about half of patients considered eligible for vitamin K antagonists receive them as stroke prophylaxis,^{30,31} mainly due to the complexity of this treatment compared to aspirin, but also because of the fear of hemorrhage. The odds ratio for major bleeding on vitamin K antagonists in this type of patient is 1.9,³² but the absolute annual increase in major bleeding is a modest 0.3% and in intracranial bleeding 0.2%.³³

The Anticoagulation and Risk Factors in Atrial Fibrillation (ATRIA) cohort study demonstrated that these relatively benign incidences also appear applicable to patients who are not included in clinical trials.³⁴ In 13,559 patients with non-valvular atrial fibrillation, the hazard ratio for major bleeding in those treated with vitamin K antagonists did not differ significantly from 1.0, although there was a statistically significant increase in the risk of intracranial hemorrhage (adjusted hazard ratio 1.97).³⁴ When risks and benefits between the two prophylactic alternatives are compared, as shown by van Walraven,³⁵ treatment of 1000 patients with atrial fibrillation using vitamin K antagonists instead of aspirin prevents 23 ischemic strokes at a cost of 9 more major hemorrhages; thus, a net benefit of 14 major events.

Ideally, the choice of prophylaxis is tailored according to the guidelines³⁶ so that patients <65-years-old receive aspirin and those >75-years-old or between 65 and 75 years with additional risk factors are started on vitamin K antagonists. These risk factors include diabetes mellitus, hypertension, congestive heart failure and, most importantly, a history of stroke or transient ischemic attacks. However, the decision may be complicated by a history of bleeding. When the choice of prophylaxis is not clear-cut, a prediction score for bleeding, as reported by Beyth et al,³⁷ may be useful. For those at high risk of bleeding (ie, a score of 3 to 4), aspirin is preferred.

Anticoagulant therapy should be reassessed annually and after any event that results in hospitalization. Thus, if an

elderly patient with atrial fibrillation and taking vitamin K antagonist therapy is admitted with head trauma due to a fall, a review of the recent medical history may reveal repeated falls. Under such circumstances, aspirin is a safer alternative.

Another issue to assess at the annual visit is the stability of prothrombin time results. Improved management can be accomplished by using nomograms^{38,39} or computer software^{40,41} to support dosing, as well as a review of dietary habits and concomitant medications. The patient should be reminded to question the possibility of an interaction between vitamin K antagonists and any newly prescribed drug or medication purchased over-the-counter. Patients should also immediately report the use of antibiotics to the healthcare provider who is supervising their anticoagulant therapy since most antibiotics augment the effect of vitamin K antagonists.

Reversal of vitamin K antagonists

An important component of safer anticoagulant therapy is the management of imminent bleeding. Patients with a spontaneously long prothrombin time, corresponding to an international normalized ratio (INR) of ≥ 4.5 , are typically told to hold anticoagulant treatment for 1 or 2 days until the therapeutic range has been reached. In this situation, administration of 1 mg of oral phytonadion (vitamin K₁), in addition to skipping a dose of the vitamin K antagonist, is better than the latter alone in terms of the risk of bleeding during the following month.⁴² There is, however, a widespread reluctance to use vitamin K, likely due to the fear of thrombotic complications. Yet, with this small dose of oral vitamin K, thrombosis is rare and the INR almost never reverses to below the therapeutic range.⁴² In patients with overt bleeding, treatment with vitamin K is not sufficient because it takes about 6 hours until any effect is noticed and 12 to 24 hours until the full effect is achieved.⁴³ Patients with major bleeding and high INRs may receive plasma transfusions. It is crucial, however, to rapidly reduce the INR to ≤ 1.5 , independent of the indication for anticoagulation.

The risk of death or severe morbidity due to the bleeding far outweighs the risk of thrombotic complications without anticoagulation which, for mechanical heart valve prostheses, is approximately 8% per year.⁴⁴ For a patient with an average body weight, the volume of plasma needed to reverse a high INR to 1.5 or lower is at least 2 liters, but if rapidly transfused, this will provoke pulmonary edema in many elderly patients. Prothrombin complex concentrates (PCC) contain all the vitamin K dependent factors, are available in small volumes after reconstitution, and have been manufactured with at least one step of viral elimination as opposed to plasma. There may be hesitancy to use PCC due to the fear of thrombotic complications. However, in 6 cohort studies with PCC for reversal of vitamin K antagonists in patients with major hemorrhage – typically an intracranial hemorrhage – there was only 1 thrombotic complication in a

total of 118 patients⁴⁵⁻⁵⁰ and the hemostatic effect was always good. A large cohort study is presently being performed to substantiate these data. The dose of PCC required to reverse the INR down to a specific level can easily be calculated if the INR level is converted to a percentage scale.⁵¹

There is limited clinical experience with recombinant activated factor VIIa (rFVIIa) for reversal of vitamin K antagonists and reduction of the bleeding induced by these anticoagulants,⁵² but again, the risk of thrombotic complications needs further evaluation.

Reversal of new anticoagulants

A pentasaccharide – fondaparinux – has received widespread regulatory approval. Its long-acting sister compound, idraparinux, is in phase III clinical trials for DVT, pulmonary embolism, and atrial fibrillation. Theoretically, PCC should be a useful antidote in case of an overdose or major bleeding, but most experimental data are based on studies with rFVIIa.^{53,54} This reverses all the effects of the pentasaccharides on coagulation parameters. The dose of rFVIIa in these studies was 90 mg/kg, the most common dose in patients with hemophilia and inhibitors.

The orally available thrombin inhibitor ximelagatran has been approved in several European countries for prophylaxis against thromboembolism after orthopedic surgery. It has a half-life of only 5 hours. In cases of bleeding, it may be sufficient to discontinue the medication and treat symptomatically. Animal studies have indicated that activated prothrombin complex concentrate (APCC) reverses the anticoagulant effect with little risk of aggravating the thrombosis.⁵⁵

Clinical experience with the new anticoagulants is thus far extremely limited. Thrombosis may occur during treatment with rFVIIa, as well as with APCC.⁵⁶

Conclusion

In liver failure, the impaired synthesis of vitamin K-dependent coagulation factors, decreased clearance of pro-fibrinolytic factors, and thrombocytopenia caused by portal hypertension and hypersplenism, contribute to a tendency towards increased bleeding. Portal vein thrombosis in these patients may be attributed to an acquired low level of protein C, the vitamin K-dependent inhibitor of factor VIIIc, and factor Va. This scenario raises a series of questions. How should secondary prophylaxis against thrombosis be given? With reduced doses of vitamin K antagonists or low-molecular weight heparin? For how long?

In some types of surgery, the preferred hemostatic balance may be towards bleeding. For example, thrombus in the large blood vessels to a liver graft can jeopardize the outcome of the transplantation. Disseminated intravascular coagulation (DIC) is a condition with intravascular fibrin formation. It may lead to depletion of coagulation factors and platelets, resulting in bleeding. There is an

intermediate period when both continued deposition of fibrin and bleeding coexist. There are a multitude of coagulation factors, inhibitors, activation peptides, split products etc. that can be measured, but rarely fast enough to assess a critically ill patient. Furthermore, we do not have sufficiently sophisticated tools to calculate activated coagulation or deficient hemostasis to ascertain which predominates. The past decade has, therefore, witnessed a revival of global hemostatic tests, such as the endogenous thrombin potential,⁵⁷ overall hemostatic potential,⁵⁸ thromboelastography⁵⁹ and biphasic APTT waveform⁶⁰ – mainly for DIC. Thromboelastography is an old method that, with modernized instrumentation and user-friendly software, has become appreciated by many anesthesiologists. Further studies should evaluate how to optimize therapy when confronted with combined bleeding and thrombotic conditions.

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