A Brief Review of 50 Years of Perioperative Thrombosis and Hemostasis Management

Serena Valsami and Lars M. Asmis

Perioperative thrombosis and hemostasis management has changed dramatically over the past 50 years. From two anticoagulants and one anti-aggregant, the number of currently available drugs has recently increased several-fold, leaving clinicians with the problem of choosing the optimal agent. Individualized preoperative assessment of bleeding risk based on bleeding history and testing limited to high-risk patients is an emerging concept. Based on the identification of risk factors for venous thromboembolism (VTE), pharmacologic and non-pharmacologic strategies for perioperative VTE prophylaxis have had a major impact on patient outcome. For patients undergoing surgery who are treated with anticoagulants and anti-aggregants, “bridging” strategies have been proposed. Bleeding management strategies have shifted focus from replacing lost blood volume to new approaches aimed at preventing blood loss, reducing the potential complications of blood loss, and preventing the transfusion of blood products. For some areas of perioperative thrombosis and hemostasis management, randomized controlled trial (RCT) data are emerging, but the database remains insufficient to date. Clearly, more RCTs need to be published for perioperative thrombosis and hemostasis management to become an evidence-based approach.

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EDITOR’S NOTE

This is a “special” article celebrating the 50th anniversary of Seminars in Hematology. Dr Serena Valsami from the University of Athens, Greece and Dr Lars Asmis from the University of Zurich, Switzerland, in a comprehensive review, discuss management of perioperative thrombosis and hemostasis. Identification of risk factors and development of new drugs greatly changed the incidence and evolution of thrombotic and hemorrhagic complications, which was the “nightmare” of patients and surgeons. The value of prospective randomized clinical trials in the elaboration of guidelines in this matter is clearly seen in this well-written review.

INTRODUCTION

The management of patients undergoing a surgical procedure has changed considerably over the past 50 years. This brief review will focus on some of the key changes in the field of perioperative thrombosis and hemostasis management, discussing where the field set out 50 years ago, what changed since then, and where it is today.

DEVELOPMENTS IN ANTICOAGULANTS

In the 1960s when Seminars in Hematology was founded, the mainstay of anticoagulant therapy was unfractionated heparin and vitamin K antagonists (VKAs). In the first half of the past 50 years much was learned about the mechanism of action of these drugs, while in the second half new molecules were added to the palette of available anticoagulants.

Heparin was discovered by McLean in 1916 and was isolated from dog livers (Greek for liver: hepar), which gave the anticoagulant its name.1 VKAs were determined to be a cause of a hemorrhagic disease in cows by Charles Link. They were first used as a potent poison for rodents. It was not until the 1950s that the drug found its way into clinical medicine.

In 1968, Abildgaard showed that the protein antithrombin was necessary for heparin’s anticoagulant action, illustrating that the heparins were indirect anticoagulants.2 Warfarin inhibits coagulation by disturbing hepatic post-translational modification of coagulation factors (FII, FVII, FIX, and FX) and inhibitors (proteins C and S). Without the postranslationally added carboxyl groups,
these factors cannot bind to the surface of activated platelets and thus are dysfunctional. Because neither anticoagulant family, the heparins and the vitamin K antagonists (VKAs), binds directly to the active center of coagulation factors, they are called indirect anticoagulants. One of the problems with unfractionated heparins (5–30 kd; mean molecular weight [MW], 15 kd) was that they did not have a fixed dose-response relationship. This was in part due to unspecific binding of these long, negatively charged molecules to many other targets, including acute-phase reactants, platelets, and endothelial cells. Monitoring was necessary to titrate the correct dose in each patient.

Fractionation or isolation of smaller heparin fragments provided a solution to the dose-response problem. By generating mixtures of small fragments of heparin (2–9 kd; mean MW, 4–6 kd) the product obtained a fixed dose-response relationship and weight-based dosing was possible. Monitoring was no longer obligatory. The exact mechanism of heparin action was elucidated in the late 1970s by the finding that heparins bind to antithrombin through a unique pentasaccharide motif. Only molecules that harbor this pentasaccharide sequence are biologically active in coagulation inhibition. The exact sequence was identified by Choy in 1985.\(^3\) This paved the way to the generation of a synthetic pentasaccharide, fondaparinux.

Even though hirudin, derived from the medicinal leach (\textit{hirudo medicinalis}), was one of the first anticoagulants to be described in the late 19th century, it could not be used for clinical anticoagulation in view of the narrow therapeutic window and lack of adequate monitoring tests.\(^4\) Hirudin found an application as an alternative anticoagulant in case of heparin-induced thrombocytopenia (HIT).\(^5\) HIT is an antibody-mediated adverse drug effect with antibodies directed against complexes of heparin and platelet factor 4 that was described in 1958 by Weismann and Tobin.\(^6\) Hirudin derivatives, such as lepirudin and bivalirudin, still are used for this indication. These anticoagulants are characterized by directly attacking the active sites of thrombin or FIIa. The molecule binds directly to the so-called serine protease domain, thereby inhibiting the activated coagulation factor. All of these direct anticoagulants had the problem that they could only be used parenterally. The search for new oral agents began.

The first new oral direct anticoagulant that made it into clinical practice was ximelagatran, a direct thrombin inhibitor. In view of its hepatotoxicity, the drug was withdrawn again from the market in 2006. The next direct thrombin inhibitor to be approved by a large national health agency was dabigatran, with initial indication for the prevention of venous thromboembolism (VTE) in hip or knee replacement surgery in 2008 in Canada and Europe and later for prevention of stroke in atrial fibrillation by the US Food and Drug Administration (FDA) in 2010. Argatroban is another direct thrombin inhibitor that has gained market approval.

Another class of direct oral anticoagulants, the direct inhibitors of FXa, soon followed. Rivaroxaban gained approval by Canadian and European health authorities for VTE prevention in hip and knee replacement in 2008. In 2011 it became FDA-approved for the treatment of deep vein thrombosis (DVT) and stroke prevention in atrial fibrillation. The FDA approved the treatment of DVT and pulmonary embolism in 2012. Apixaban, edoxaban, and other related compounds have or are in the process of obtaining health agency approval for various indications.

**DEVELOPMENTS IN ANTIPLATELET AGENTS**

In the 1960s aspirin was the main antiplatelet agent in clinical use. Aspirin (acetylsalicylic acid) was first produced by Felix Bayer in 1897 and almost immediately found wide application as an anti-inflammatory and antipyretic drug.\(^7\) Almost 50 years later, in 1938, its impact on impairing hemostasis was noted in patients treated with aspirin who experienced prolonged bleeding after tonsillectomy. In the 1950s, aspirin was then prescribed to prevent coronary and cerebral thrombosis in high-risk patients, with remarkable results.\(^8\) The effect of aspirin on the hemostatic properties of human platelets, by inhibition of adenosine diphosphate (ADP)-induced secondary platelet aggregation, was shown by different groups during the 1960s.\(^9,10\) Shortly after that, aspirin’s full mechanism of action through cyclooxygenase inhibition was elucidated.\(^11,12\) In the 1980s, aspirin received approval by the FDA for the secondary prevention of arterial vascular disease and in the same time period, the ISIS-2 trial proved its efficacy in treating myocardial infarction. Currently, aspirin remains an established part of the treatment and secondary prevention of arterial thromboembolism.\(^13\) However, there are issues regarding aspirin that remain unresolved, including the use of aspirin for primary prevention of atherovascular disease and the clinical relevance of suboptimal platelet response to aspirin or aspirin resistance.\(^14,15\)

In 1974 a P2Y\(_{12}\) antagonist, a thienopyridine derivative named ticlopidine, was first discovered. Ticlopidine gained FDA approval in 1991. Its antithrombotic action was found to be equally effective to that of aspirin for the treatment of patients with atherovascular disease. Unfortunately, ticlopidine was associated with serious side effects, including bone marrow toxicity and thrombotic thrombocytopenic purpura. This drug was soon replaced by a second thienopyridine, clopidogrel.\(^16,17\) In 1996, clopidogrel proved its clinical efficacy versus aspirin in patients at risk for ischemic events and was approved for clinical use 2 years later. Clopidogrel is a prodrug that requires oxidation by two-stage hepatic cytochrome (CY) P450 to generate its active metabolites, which inhibit platelets for the lifespan. This explains the delayed onset of platelet inhibition (4–8 hours) by clopidogrel. The variability of the antiplatelet drug effect and the clinical efficacy of clopidogrel therapy were associated with the cytochrome P450 2C19 (CYP2C19) genotype.\(^18,19\) The third thienopyridine approved in 2011 was prasugrel, which requires
one-stage activation and exerts an antiplatelet effect within 2–4 hours. Compared to clopidogrel, prasugrel has a greater platelet-inhibiting effect, which is not influenced by polymorphisms of cytochrome CYP2C19 but is associated with a higher incidence of bleeding.20 Ticagrelor, unlike the thienopyridines, is a direct and reversible P2Y12 antagonist that does not require activation by liver enzymes. Ticagrelor was found to be effective in patients with clopidogrel resistance. However, it was associated with side effects such as bleeding, ventricular arrhythmias, and dyspnea.21,22 Abciximab, tirofiban, and eptifibatide are parenteral antiplatelet drugs acting through glycoprotein (GP)IIb/IIIa inhibition. All three GPIIb/IIIa antagonists are active in preventing ischemic events complicating percutaneous coronary interventions and in the treatment of acute coronary syndromes.23

PREOPERATIVE ASSESSMENT OF BLEEDING RISK

In the 1960s and 1970s, preoperative coagulation testing was the rule. Beck described a preoperative screening program for the prevention of unexpected hemorrhage in surgical patients. From this prospective study, he concluded that a detailed history, the prothrombin time, and determination of platelet count “were suitable for the specific detection of bleeding tendencies.”24 However, a few years later Eika et al showed a complete lack of correlation between results of preoperative screening tests (activated partial thromboplastin time [aPTT], prothrombin time, platelet count, and bleeding time) and perioperative blood loss.25 Larger prospective trials followed in the 1980s. Rohrer et al compared two patient groups of 514 “screening tests” and 605 “indicated tests” (based on bleeding history). They too concluded that preoperative screening for coagulopathies not suspected on the basis of detailed clinical information are unnecessary and should not be done.26 MacPherson et al published data on 111 asymptomatic patients in whom the four above-mentioned tests were performed and in 1,872 patients in whom unexpectedly large perioperative transfusions were reported. The authors concluded that in the absence of a positive bleeding history, preoperative screening would appear unnecessary.27 In the mid 1990s, Houry et al performed a prospective multicenter study evaluating the four tests in 3,242 patients. Four groups were distinguished according to presence or absence of positive bleeding history and normal or pathologic perioperative screening tests.28 Postoperatively all four groups had similar bleeding risks. The authors concluded that perioperative screening should not be performed routinely. Towards the end of the 1990s further studies showed that preoperative bleeding time lacked clinical benefit and that preoperative von Willebrand testing provided a low yield and limited ability to predict bleeding.29,30 A meta-analysis by Eckman et al confirmed the lack of sensitivity or specificity for such preoperative testing strategies.31

A desirable preoperative screening strategy should primarily be sensitive. It should have the capacity to rule out patients at increased bleeding risk. The high-risk patients will require further testing. It should furthermore be specific in order to identify patients at low risk that do not need to be tested. It should have a favorable cost/efficiency ratio. It should increase patient safety and it should be practicable.

A strategy that addressed these criteria was that proposed by Koscielny et al, who published two large studies, each with approximately 5,000 patients. These studies suggested that performing a bleeding history on all patients preoperatively allowed for risk stratification into low- and high-risk categories. The high-risk category comprised 11% of the study population. A retrospective study suggested that a standardized bleeding history can identify patients at risk, while a prospective study suggested that risk category allocation-based investigation was possible (only a minority of approximately 10% were suggested to have perioperative laboratory testing) and that treatment based on that risk allocation resulted in perioperative transfusion rates that were not statistically significantly different.32,33

Since the turn of the century several bleeding history questionnaires have been validated and applied. Questionnaires have been proposed by Houry, Koscielny, the Austrian Society of Anaesthesiology Reanimation and Intensive Care (OeGARI), and others.33–35 These questionnaires address primarily the acquired bleeding diatheses, which are highly prevalent. If one suspects a hereditary bleeding disorder such as von Willebrand syndrome (vWSS) then the MCMMDM questionnaire has proven to be highly sensitive.36 To date, there is accumulating evidence strongly suggesting that generalized preoperative screening is costly and not efficient. Despite this evidence, generalized screening is prevalent. This has led authors to propose a solution in which bleeding history and additional risk factor define risk groups in which no testing, minimal testing (prothrombin time and platelet count), standard testing (aPTT, prothrombin time, fibrinogen), and extensive coagulation testing are proposed.37

PREVENTION OF VENOUS THROMBOEMBOLISM

Perioperative VTE was a relevant problem in view of a high morbidity and mortality in the 1960s. Fifteen percent to 40% of major surgery patients, 40%–60% of hip and knee arthroplasty patients, and 40%–80% of trauma patients suffer from VTE in the absence of preventive measures.38 Based on the discovery of risk factors for perioperative venous thrombosis and the finding that these risk factors were cumulative in nature, strategies for the prevention of VTE were sought. There are generally two forms of VTE prophylaxis: pharmacologic and mechanical. The effectiveness of oral anticoagulation (VKAs) in the prevention of DVT after hip surgery was described in
the early 1960s. Trials comparing unfractionated low-dose heparin 3x 5,000 IU subcutaneously with low-molecular-weight heparin (LMWH) were published in the late 1980s. A couple of years later, oral anticoagulation was proven effective in preventing DVT in major surgery. Large randomized controlled trials (RCTs) establishing the role for VKA in hip replacement surgery were published in the late 1990s. Trials with LMWH were performed only a few years later and these were followed by those for fondaparinux and new direct anticoagulants in the 2000s.

The duration of prophylaxis for hip and knee replacement initially was 7–10 days. This changed in the early 2000s for high-risk patient populations including total hip replacement (and later also cancer patients), where an extended prophylaxis—with an added 3 weeks on top of the original 7–10 days—was introduced.

The timing of pharmacologic VTE prophylaxis has been a major debate. In North America postsurgical start was propagated for LMWH, while in Europe the presurgical start was more frequently followed. For certain LMWHs this resulted in the adoption of different dosing schedules. In North America, for example, enoxaparine was licensed at 30 mg subcutaneously twice per day versus 40 mg subcutaneously once per day in Europe. With the advent of the novel direct anticoagulants in the late 2000s, this issue has become obsolete as studies were performed with a postoperative start of the pharmacological prophylaxis.

Mechanical measures of VTE prevention have also been evaluated. Graduated compression stockings and intermittent pneumatic compression devices have been shown to be effective as of the mid 1990s and were included in the relevant American College of Chest Physicians (ACCP) guidelines thereafter. It is of note that the effect of mechanical and pharmacologic VTE prevention appears to be additive. This is of importance in high-risk patients.

**PERIOPERATIVE THROMBOSIS RISK FACTORS**

Perioperative VTE ranging from simple DVT to pulmonary embolism (PE) and arterial thrombosis (ATE) were long thought to be a non-preventable side effects of surgery. The introduction of VTE prophylaxis in hip arthroplasty patients reduced the proximal DVT rate from 18%–36% and the fatal PE rate from 0.1%–2.0% to below 3.4%–4.8% and 0.6%, respectively. These numbers proved that VTE-related morbidity and mortality were preventable to a large extent.

The recently published ACCP 2012 perioperative thromboembolic risk stratification of patients discerns three main categories for VTE prevention: an actutely ill hospitalized group (nonsurgical patients), a general and abdominal surgery (non-orthopedic patients) group, and an orthopedic surgery group (Figure 1A and B). Most of the thrombosis risk factors were identified over the past 50 years, along with the better understanding of the pathophysiologic coagulation mechanisms. They can be subdivided into modifiable and non-modifiable risk factors. Congenital risk factors are non-modifiable, while acquired risk factors can belong to either category (Table 1).

In 1965, antithrombin deficiency was the first form of inherited familial thrombophilia identified. During the 1980s, the congenital deficiency of each of the natural anticoagulants proteins C and S, both proteins having been identified in the 1970s, were for the first time associated with recurrent thrombotic tendency. In 1994 the inherited resistance to activated protein C was attributed to a point mutation in the factor V gene, called factor V Leiden. This was later shown to be the most frequent inherited thrombophilia, especially common in Caucasians. Approximately 2 years later, the point mutation in the prothrombin gene (G20210A), which was associated with an increased risk of VTE, was described by the same group.

Antiphospholipid syndrome (APS), an acquired hypercoagulable state affecting both the venous and the arterial vascular bed, was described in full in the 1980s after various previous reports of antibodies “circulating anticoagulants” in patients with systemic lupus erythematosus and thrombosis and a false positive test for syphilis. Currently, the Sydney criteria proposed are used to diagnose antiphospholipid antibody syndrome. Two sets of criteria need to be fulfilled. Any of the following three criteria need to be met to fulfill the clinical criterium: arterial thromboembolism, VTE, and/or recurrent abortions. In the presence of a positive clinical criterium, then one of the following laboratory criteria is sufficient for APS diagnosis: positive lupus anticoagulant, positive anticardiolipin antibodies (IgG or IgM), and/or positive anti-β2 glycoprotein antibodies (IgG or IgM). Treatment and diagnosis have been reviewed recently.

Increasing age has become an established risk factor for venous thrombosis. In 1966 Fleming et al reported an increased prevalence of fatal PE in healthy individuals above the age of 40. The same study identified obesity as a predisposing factor to PE, with 43% of fatal PE cases being overweight. Although obesity was suspected as a risk factor for VTE as early as the 1920s, a consensus for obesity as an independent risk factor in both men and women has only recently developed. Patients with a body mass index (BMI) of above 30 have a two times increased relative risk for VTE. The relative risk rises with increasing BMI above 30. In both developed and developing countries, where the prevalence of morbid obesity is continuing to rise, obesity and advanced age relevantly impact the perioperative thrombosis management.

Cancer was initially associated with thrombosis by Trousseau in 1863. Over the last decades the implementation of new anticancer treatments and prolonged overall survivor in cancer patients increased the need of proper perioperative assessment of this population.
Oral contraceptives gained FDA approval for the first time in 1960. Soon after that several concerns emerged regarding their association with thrombosis and PE, confirmed by epidemiological data in the 1970s. Similarly, hormonal replacement therapy has been associated with a threefold relative risk of DVT.

The surgical procedure itself represents a transitory hypercoagulable state, involving both venous and arterial thrombosis. Major orthopedic surgery is often complicated by VTE, whereas neurologic and vascular surgical procedures, in patients with atrial fibrillation, are associated with a greater risk for arterial thromboembolism, including stroke.

Figure 1. VTE prophylaxis in acutely ill hospitalized and in orthopedic patients (A) and in non-orthopedic (general and abdominopelvic surgery) patients (B) as proposed by ACCP 2012. Abbreviations: venous thromboembolism (VTE), high (hi), surgery (Sx), bleeding risk (BR), yes or high (+), no or low (−), no prophylaxis (No Px), pharmacologic prophylaxis (Ph Px), mechanical prophylaxis (Me Px), low molecular weight heparin (LMH), unfractionated heparin (UFH), fondaparinux (Fon), graduated compression stockings (GCS), intermittent pneumatic compression (IPC), dabigatran (Dab), apixaban (Api), Rivaroxaban (Riv). This scheme is a simplification of the recommendations given by ACCP 2012. The original documents should be consulted for detailed and accurate information. The figures given in B represent VTE risk: very low (<0.5%), low risk (~1.5%), high (~3%) and very high risk (~6%). “Ph Px later” refers to the recommendation of possibly starting pharmacologic thromboprophylaxis once and if the bleeding risk has diminished.
PERIOPERATIVE BRIDGING OF ANTAGGREGATION

The prevalence of therapeutic anticoagulation in the general population is approximately 1%. The main indications are atrial fibrillation, prevention of recurrent VTE, mechanical heart valves, and APS. Thus the need of perioperative management of patients on chronic anticoagulation is a relevant challenge. Bridging anticoagulation can be defined as the administration of short-acting anticoagulants consisting of subcutaneous LMWH or intravenous unfractioned heparin (UFH), for a 10- to 20-day period during interruption of VKAs. The first articles on bridging were published around the turn of the millennium. These and subsequent studies show that thrombotic risk needs to be counterbalanced against bleeding risk related to the patient and the surgical procedure. Several approaches to perioperative management of patients on antithrombotics have been published since the implementation of anticoagulation. In 2012, Siegal et al performed a meta-analysis of 34 studies. The question of whether bridging is associated with an improved outcome still cannot be finally answered. RCTs comparing bridging to no bridging in patients undergoing elective surgery are ongoing, and hopefully will answer this relevant question. For perioperative management of antithrombotic therapy, various strategies have been proposed. These rely heavily on expert opinion and RCT-based data are mostly lacking.

PERIOPERATIVE BLEEDING MANAGEMENT

Despite major advances in the past 50 years and in view of the associated morbidity and mortality, the management of perioperative bleeding remains a major challenge. This section will very briefly highlight some nonsurgical aspects of bleeding management. Originally, bleeding management focused on the restitution of blood components that were lost. Some current strategies focus more on preventing blood loss from the beginning. For the management of a bleeding patient, different blood products and hemostatic drugs are available (Table 2).

Transfusion medicine started out with whole blood as the only available product. Plasma as a liquid or a dried powder was the first available isolated blood component and was used starting from 1942 during World War II. Whole blood and plasma were initially stored in glass bottles. Plastic transfusion bags were invented in the 1950s and progressively replaced the bottles until the 1970s. Cryoprecipitates, products rich in von Willebrand factor and FVIII, were introduced in 1965. Plasma fractionation methods permitted the production of factor concentrates, Table 1. Venous Thromboembolism Risk Factors

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<thead>
<tr>
<th>Modifiable</th>
<th>Non-modifiable</th>
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<td>Surgery</td>
<td>Increasing age</td>
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<td>Trauma immobility (lower extremity paresis)</td>
<td>Previous VTE</td>
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<td>Cancer active or occult</td>
<td>Factor V Leiden</td>
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<td>Cancer therapy</td>
<td>Prothrombin mutation G20210A</td>
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<td>Venous compression</td>
<td>Hereditary antithrombin deficiency</td>
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<td>Pregnancy and postpartum period (6 weeks)</td>
<td>Hereditary protein S deficiency</td>
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<td>Estrogen-containing oral contraceptives or hormone replacement</td>
<td>Hereditary protein C deficiency</td>
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<td>Selective estrogen receptor modulators</td>
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<td>Erythropoiesis-stimulating agents</td>
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<td>Acute medical illness</td>
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<td>Inflammatory bowel disease</td>
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<td>Nephrotic syndrome</td>
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<td>Paroxysmal nocturnal hemoglobinuria</td>
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<td>Obesity</td>
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<td>Central venous catheterization</td>
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<td>Antiphospholipid antibody syndrome</td>
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Table 2. Pharmacological and Blood Component Pro-hemostatic Therapies

| Fresh whole blood |
| Red blood cells concentrates |
| Fresh frozen plasma |
| Platelet transfusion |
| Tranexamic acid |
| Desmopresin |
| Cryoprecipitate |
| Fibrinogen concentrate |
| Prothrombin complex concentrate |
| Activated prothrombin complex concentrate |
| Recombinant factor VIIa |

Adapted from Keeling et al and Makris et al.
including non-activated concentrates (prothrombin complex concentrates, fibrinogen, FXIII, FVIII, and FIX) and activated concentrates (FVIII inhibitor bypassing agent).67 In 1969, Murphy and Gardner demonstrated the feasibility of storing platelets at room temperature, revolutionizing platelet transfusion therapy.68 Most recently, recombinant coagulation factor preparations both non-activated (FVIII, FIX, FXIII) and activated (recombinant human FVIIa) have become available.

The transfusion of blood products necessitates a risk benefit evaluation. History has shown that there are relevant risks associated with the transfusion of both cellular and cell-free blood products. Although hepatitis B virus (HBV) infection, called "serum hepatitis" at the time, was recognized as a complication of blood transfusion in survivors of World War II, it took nearly three decades to identify HBV the virus and develop HbSAg testing.69 In the early 1980s, there was a tragic epidemic of HBV, HCV, and human immunodeficiency virus (HIV) among hemophilia patients who had received contaminated concentrates prepared from large plasma pools.70 Donor blood testing for HIV started in 1985 and for HCV in the early 1990s.71,72 Efforts to implement pathogen-reduction technologies in blood, initially plasma and derivatives, started in the 1980s and are still ongoing.73

Currently, although transfusion of blood components is safer than ever, it remains hazardous. The transmission of known and emerging pathogens as well as non-infectious complications are unsolved problems.73,74 During the last decade several studies suggested that transfusion of blood components was associated with adverse clinical outcome, particularly increased morbidity and mortality. In a large meta-analysis published in 2008 regarding erythrocyte blood (RBC) transfusions in the critically ill, it has been shown that in 42 of the 45 studies, RBC transfusion was associated with unfavorable outcome of the patients, in two the transfusion benefits were equal to the risks, and only in one transfusion benefits were superior to the risks.75 Similarly RBC transfusions were associated with increasing mortality in trauma patients, burn victims, and liver transplantation patients, and in the treatment of acute coronary syndrome.76,77 A meta-analysis found that restrictive transfusion practices using thresholds of 7–8 g/dL versus higher thresholds are associated with fewer RBC units being transfused without evidence of adverse outcome on mortality, morbidity, functional recovery, and length of hospital stay. In addition, transfusion of RBCs, fresh frozen plasma (FFP), and mainly platelets results in a higher risk for postoperative and nosocomial infections.73,75 FFP transfusion has been associated with increased morbidity in different patient populations and with increased mortality in non-trauma patients.78,79 To date there is ongoing debate of how to manage the bleeding patients. There are approaches that propose transfusion strategies with high plasma to RBC ratios.80 Other approaches to perioperative bleeding management, for which relevant RCTs have been published recently, are early treatment with fibrinolysis inhibitors (CRASH-2 study in trauma), the targeted approach using factor concentrates and point-of-care testing (thromboelastography/metry), and the patient blood management concepts.81,82

**SUMMARY AND PROSPECTS**

Perioperative thrombosis and hemostasis management has evolved considerably over the past 50 years. The individual patient is at the center and optimal patient outcome should be its goal. Key challenges towards the achievement of that goal include the generation, validation, and implementation of evidence-based practices that integrate outcome-based research, individual risk-benefit evaluations, and public interests (cost of healthcare). As this field of medical expertise is growing increasingly complex, frequent interaction among and active communication between the patients, nursing staff, surgeons, anesthesiologists, intensive care physicians, hematologists, and other involved physicians is essential for continued success.

**REFERENCES**
