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New Anticoagulants

Prevention of venous thrombosis (VTE), deep vein thrombosis (DVT) and pulmonary embolism (PE) are goals in the care of every hospitalized patient. Prevention of arterial and venous thrombi is a goal for every inpatient or outpatient at risk for thrombus formation and PE. Prophylaxis is always superior to treatment by any method of assessment—patient morbidity and mortality, cost of treatment, cost of lost productivity and cost of hospitalization.

Nearly every hospitalized patient has at least one risk factor for development of venous thrombi—aggregates of fibrin, activated platelets and trapped erythrocytes. The number of drugs approved for prophylaxis and treatment of VTE, DVT and PE were limited for many years to unfractionated heparin (UFH) and vitamin K antagonists (warfarin). The options for prophylaxis and treatment began to expand with the development and approval of low molecular weight heparins (LMWHs) and with better understanding of the molecular mechanisms of thrombogenesis, anti-thrombogenesis and anticoagulation. Better understanding of aspirin's platelet-inhibiting activity held clues leading to development of the thienopyridines such as clopidogrel. Better understanding of the molecular mechanisms of heparin's anticoagulant activity pointed the way to development of the pentasaccharides such as fondaparinux.

As understanding of the molecular basis of anti-thrombogenesis and anticoagulation continued to advance, a number of newer anticoagulants were developed, entered into trials, and neared approval for clinical use. The potential market for newer anticoagulants is large—e.g., in the U.S. alone, about two million inpatients and outpatients use warfarin as maintenance therapy to prevent thrombus formation associated with atrial fibrillation or after heart attack, stroke, bone fracture or surgery.

New oral anticoagulants currently well advanced in clinical trials include:

- Dabigatran, a factor IIa direct thrombin inhibitor;

- Apixaban, a direct factor Xa inhibitor; and,
- Rivaroxaban, a direct factor Xa inhibitor.

Idraparinux is a selective FXa inhibitor administered subcutaneously (SC).

Dabigatran Etexilate

Dabigatran is an oral inhibitor of fibrin formation from fibrinogen. It is absorbed from the gut and converted into an active metabolite. It is a fairly large molecule (molecular weight 628). After absorption from the gut, dabigatran has a bioavailability of 5% to 6%. Half-life in plasma is 14-17 hours. Renal clearance is 100%. Combined results of three Phase III clinical trials with more than 8,000 randomized patients showed dabigatran 150 mg and 220 mg similar to enoxaparin 40 mg or 60 mg in achieving end points of (1) preventing major VTE and VTE-related death, and (2) major bleeding. Dabigatran showed equivalent results to 40 mg enoxaparin in hip/knee surgery patients (RE-MOBILIZE trial), but failed to show equivalence to 60 mg enoxaparin. Dabigatran is approved for marketing in countries of the European Union.

Rivaroxaban

Rivaroxaban, like apixaban, is an oral factor Xa inhibitor with excellent bioavailability. Factor Xa inhibition may be a better target than thrombin for anticoagulation—e.g., FXa has few functions aside from coagulation, has a wider therapeutic window than thrombin, and exhibits no rebound thrombin generation whereas thrombin rebound is a negative aspect of thrombin inhibitors. Rivaroxaban has a molecular weight of 436, its half-life in plasma is 9 hours, and renal clearance is 65%.

In Phase III RECORD trials (Regulation of Coagulation in Major Orthopaedic Surgery Reducing the Risk of DVT/PE) in more than 10,000 patients, oral rivaroxaban 10 mg daily was significantly more effective for extended prophylaxis than a once-daily 40 mg SC dose of enoxaparin in preventing VTE in elective orthopedic surgery patients.¹

In the Phase II Oral Direct Factor Xa Inhibitor BAY 59-7939 in Patients with Acute Symptomatic DVT (ODIXa-DVT) study in 613 patients, superior efficacy/safety of oral rivaroxaban versus SC enoxaparin was shown across a three-fold range of daily dosing. Rivaroxaban was halted early in three patients who had elevated liver enzymes.²

A number of other PHASE III trials of rivaroxaban are ongoing.

Apixaban

Apixaban is an oral FXa inhibitor with excellent bioavailability. Its molecular weight is 460, half-life in plasma 9-14 hours and renal clearance 25%. In the Apixaban Prophylaxis in Patients Undergoing Total Knee Replacement Surgery (APROPOS) trial of 1,238 patients, apixaban 5, 10 or 20 mg per day qd or bid was compared with enoxaparin 30 mg SC bid and warfarin dose calculated for International Normalizing Ratio (INR) 1.8-3.0. Apixaban at doses of 2.5 mg bid or 5 mg qd had a promising benefit-risk profile compared with current standards of care for VTE prevention following orthopedic surgery.³

A number of Phase III trials of apixaban are ongoing.

Idraparinux

Idraparinux inhibits coagulation by selectively targeting factor Xa by binding to ATIII. It is derived from the pentasaccharide fondaparinux. Dosing is SC once a week. Plasma half-life is 80 hours, similar to that of antithrombin. It can be rapidly eliminated from circulation by binding to biotin, and the biotinylated molecule neutralized by avidin.

Phase III Van Gogh DVT and PE trials in 2,904 randomized patients with acute symptomatic DVT and 2,215 patients with PE, compared 2.5 mg SC idraparinux with LMWH followed by a VKA adjusted to achieve INR of 2.0-3.0. At 3 and 6 months, criteria for efficacy of idraparinux in VTE prevention was achieved. In the PE arm, pre-specified non-inferiority criteria for efficacy of idraparinux were not met at 3 months, and VTE incidence was lower than expected in patients treated with LMWH/VKA. In a 6-month extension of the Van Gogh trial, idraparinux was (1) found effective in preventing recurrent thromboembolism, (2) associated with increased risk for major bleeding versus placebo, and (3) after cessation of therapy, placebo patients previously treated with idraparinux had significantly less VTE occurrence.⁴

In the recently completed Amadeus trial in patients with atrial fibrillation, a significantly higher incidence of clinically relevant bleeding was seen in patients receiving idraparinux than those receiving VKA, with bleeding apparently more associated with older age and renal impairment.⁵

These anticoagulants and others also in development offer promise for a wider choice of anticoagulant options in the near future. Still needed is development of newer agents for parenteral delivery. Anticoagulants are inherently associated with a certain degree of risk for bleeding and drug-induced complications. There is, as well, sometimes necessity to halt or reverse the action of an anticoagulant.

The incidence of major bleeding cited in a trial must be considered in context with the definition of major bleeding in the patients enrolled in the study. In a study conducted in surgical patients, for example, it may be difficult to definitively separate procedure-associated bleeding from bleeding associated with an anticoagulant. Bleeding related to a procedure can vary greatly from patient to patient, making it difficult to establish a baseline for expected procedure-related bleeding.

Dabigatran etexilate, a thrombin inhibitor with a bleeding profile that compared well with enoxaparin, has been withdrawn from use in the U.S. because of liver toxicity. It continues to be approved for use in Canada and the European Union.

Fondaparinux has shown association with a higher incidence of major bleeding than enoxaparin in patients undergoing major orthopedic surgery, and is not widely used in orthopedic surgery patients in the U.S.⁶

In the pooled data of the various RECORD trials of rivaroxaban versus enoxaparin, rivaroxaban was associated with a slightly higher incidence of major bleeding at two weeks (1.5% vs 1.7%), but certain bleeding types were excluded from data.⁷

Summarizing all studies of bleeding associated with newer anticoagulants, no statistically significant increase has been seen in rates of major bleeding events—excepting the study of fondaparinux for prevention of VTE in orthopedic surgery patients.

Studies of apixaban have shown no unexpected adverse events, including elevated liver enzymes compared with enoxaparin in prevention of VTE in orthopedic surgery patients or in prevention of acute coronary syndrome.

When major bleeding occurs in a patient receiving an anticoagulant, the standard approaches to treatment are:

- Delay or discontinue the anticoagulant;
- Apply mechanical compression;
- Intervene surgically;
- Give fluid replacement and hemodynamic support; and,
- Give blood product or component transfusion.

No specific antidote exists for bleeding caused by newer anticoagulation agents. In the case of idraparinux, however, avidin is a specific antidote after the drug is biologically attached to biotin in the circulation. Avidin, a heterologous protein obtained from egg white, has a high affinity for biotin and no pharmacologic effects of its own. It has only a 10-20 minute half-life after injection and is cleared by the liver. Avidin is administered as an antidote by IV infusion of 100 mg over 30 minutes.

There have been studies indicating that factor VIIa may reverse the anticoagulant effects of fondaparinux and high-dose rivaroxaban.⁸

The economic costs of prophylaxis versus treatment of diseases such as VTE, DVT and PE are often discussed, but the basic concepts of “cost” are often faulty. When “cost” is presented in a study or an analysis, one should know how cost is defined. An analysis of the cost of treating VTE, for example, can often include manufacturing and marketing costs of drugs, variable indirect costs of operating a hospital, etc. However, these are not costs that a patient pays or a hospital charges. Thus, a typical cost analysis may bear no relationship to what a hospital charges or what a patient pays.

Cost versus charge is one of the principles of cost analysis that should be considered, and failure to consider it is a pitfall leading to faulty analysis. Other principles/pitfalls include:

- Cost accounting versus cost effectiveness.
- From whose perspective is the analysis done—i.e., who pays?

- Fixed versus variable costs.
- Is cost derived from a community, institutional or departmental perspective?
- What is the end-point of the analysis?
- What are the basic assumptions for the analysis? Are the assumptions objective and honest?
- How sensitive is the conclusion of the analysis to the basic assumption?

An example of potentially faulty cost analysis is the cost of treating VTE annually in the U.S. About two million VTEs occur annually in the U.S., associated with 300,000 to 600,000 hospitalizations. The estimated direct annual cost of treating VTE is \$15-20 billion. Not taken into consideration in this analysis are indirect and hidden costs.

Indirect costs include the value of workdays and productivity lost when patients are hospitalized. Hidden costs include:

- Anticoagulation monitoring;
- Side effects and costs of (1) treating them as unexpected events, and (2) lost productivity due to extended hospital stay;
- Long-term complications such as post-thrombotic syndrome; and,
- Inability to apply a standard cost of treating VTE because costs can vary substantially from patient to patient.

A potential hidden cost in the future is the proposal of the Center for Medicare and Medicaid Services (CMS) to stop reimbursing for hospital-acquired VTE.

A 2002 study compiling data from 220 U.S. hospitals and 105,562 orthopedic surgery patients determined direct costs of preventing versus treating VTE. For all patients, the in-hospital cost of “no VTE” per patient was \$9,345. In comparison, the in-hospital, per-patient cost for patients with VTE was \$17,114, and the in-hospital, per-patient cost for patients with PE was \$18,521.⁹

Data compiled from studies of VTE in cancer patients show that the cost of treating VTE and PE is even higher than that for orthopedic surgery patients, in the same 2002 dollars used in the study of orthopedic surgery patients: \$41,620 to treat an in-patient presentation of VTE, and \$20,994 to treat early PE.

In terms of cost and diagnostic efficacy, which of the various options for diagnosing PE are the most advantageous? PE is the example for all conditions with high risk for morbidity, mortality, and high indirect and hidden costs. Decision analysis is a rational approach to making decisions when multiple variables must be considered.

Decision analysis can provide the data and perspective for a “decision tree”, an algorithmic type of decision making. Data must be objective and evidence-based if possible.¹⁰ Effective decision analysis should:

- Present options and their consequences;
- Quantify uncertainty using probabilities;
- Quantify the desirability of actions using utility of each action;
- Calculate the expected utility of each option; and,
- Choose the option that, on average, leads to the most desirable outcome.

A decision model for VTE prevention in medical patients using UFH or LMWH will present four possible outcomes for each agent: (1) no adverse event, (2) DVT, (3) bleeding, or (4) HIT. Analysis of cost distribution reveals that (1) the greatest cost savings is achieved by preventing HIT, and (2) LMWH is associated with lower overall cost because it is more effective in preventing HIT, although LMWH costs more per dose.

The take-home point of decision analysis is that it should always be system-based, should always use objective data, and should be founded on rational assumptions. Decision analysis should not be omitted for decision-making because decision makers are “comfortable” with current methods for making patient-care decisions.

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Standard of Practice

Making rational choices among anticoagulant drugs requires an increasingly large body of knowledge, experience and demonstrably good judgement. A number of anticoagulants newer than the low molecular weight heparins (LMWHs) are in trials or are process of being approved for use in prophylaxis of venous thromboembolism (VTE) and/or treating sequelae of deep-vein thrombosis (DVT) or pulmonary embolism (PE).

Physicians charged with responsibility for prevention and treatment of VTE and its sequelae should understand the mechanisms of hemostasis, thrombogenesis, coagulation and anticoagulation, and how anticoagulants interact with these mechanisms. Physicians should understand the clinical implications of direct thrombin inhibition, direct factor Xa inhibition and indirect factor Xa inhibition. Since physicians in

clinical practice will have little experience in using newer anticoagulants, critical assessment of data from clinical trials is essential to making good judgements based on a drug's safety and efficacy.

Clinical judgement should include awareness of economic implications of VTE prevention. While physicians may be most familiar with direct costs of prophylaxis such as comparative per-dose costs of anticoagulant drugs and associated direct costs such as monitoring for safety and efficacy, they should also be able to consider indirect operating costs, potential for additional costs if prophylaxis fails and a patient must be treated for thromboembolic disease or a complication of treatment, and hidden costs such as those borne by a patient is loss of productivity.