VIKRAM R. PARALKAR, MD
University of Pennsylvania
RONALD N. RUBIN, MD
Temple University

Anticoagulation: An Update for Primary Care

Dr Paralkar is a hematology-oncology fellow at the University of Pennsylvania.
Dr Rubin is professor of medicine at Temple University School of Medicine and chief of clinical hematology in the department of medicine at Temple University Hospital, both in Philadelphia.

ABSTRACT: Heparin and warfarin have been mainstays of anticoagulation for decades. Advantages of these agents include their low cost and ready reversibility of anticoagulant effect; however, their major drawbacks are an increased risk of major bleeding and the need for monitoring. Low molecular weight heparins pose less of a bleeding risk than unfractionated heparin and usually do not require monitoring, although their use is restricted in patients with renal failure and they have questionable reversibility. Examples of newer anticoagulants are the synthetic heparin derivatives, the direct thrombin inhibitors, and the factor Xa inhibitors. These agents tend to have more stable and predictable pharmacokinetics than the older anticoagulants, but they are also more expensive.

Key words: anticoagulants, anticoagulation, heparin, LMWH, warfarin

In the *Timaeus,* Plato proposed the presence of fibers "scattered about in the blood . . . designed to maintain the balance of rare and dense, in order that the blood may not be so liquefied by heat as to exude from the pores of the body, nor again become too dense and thus find a difficulty in circulating through the veins." The idea of the fluidity of blood as the product of a balance "of rare and dense" was a remarkable one for his day, and almost two and a half millennia after his words, our far more comprehensive understanding of the mechanism of coagulation continues to recognize this delicate balance and the intricate pathways that maintain it.

Jay McLean and William Henry Howell of The Johns Hopkins University isolated in 1916 a fat-soluble anticoagulant phospholipid in liver (hepar) that they termed heparin. Two decades later, the first human trials proved that purified heparin was safe and effective in humans; since then, it has become one of the mainstays of modern therapeutics.[1]

The indications for anticoagulation have multiplied greatly since the early days of heparin, as have the drugs that have become available for that purpose. In this article, we review these agents and weigh their pros and cons (**Tables 1, 2,** and **3**).

ANTICOAGULANTS: AN OVERVIEW

Until a decade ago, anticoagulants were classified into parenteral and oral agents. This classification is gradually becoming outdated, as anticoagulants are now classified based on their biochemistry. Nonetheless, the great majority of parenteral agents are thrombin inhibitors, and most oral anticoagulants are vitamin K antagonists.

Thrombin inhibitors are classified as direct or indirect inhibitors based on the manner in which they inhibit thrombin activity. In the native state, antithrombin III does not significantly inactivate thrombin, but it undergoes conformational change in the presence of heparin to form a heparin-antithrombin complex that binds irreversibly to thrombin and inhibits its activity, in addition to catalyzing the inactivation of thrombin factor Xa and other clotting factors.

Table 1 – Pros and cons of indirect thrombin inhibitors

Indirect thrombin inhibitors	Pros	Cons
Unfractionated heparin	•Short half-life •Anticoagulant effect can be rapidly reversed •Low cost •Long history of clinical use	•Increased risk of major bleeding •Increased risk of heparin-induced thrombocytopenia (HIT) •Delay in hospital discharge
Low molecular weight heparins	•Stable and predictable pharmacokinetics •Monitoring usually not required •Can be administered on outpatient basis •Lower incidence of HIT than unfractionated heparin	•Longer half-life than unfractionated heparin •Weight-based dosing restriction •Renal failure restriction •Questionable reversibility

Direct thrombin inhibitors, on the other hand, inhibit thrombin molecules directly by binding to their active sites.[2]

INDIRECT THROMBIN INHIBITORS

Unfractionated heparin. Heparin is a glycosaminoglycan found in the secretory granules of mast cells.[3] It catalyzes the inhibition of several coagulation proteases by antithrombin III, which is synthesized in the liver and circulates in plasma and inhibits activated coagulation factors of the intrinsic and common pathways, including thrombin, Xa, and IXa. Heparin increases the rate of the thrombin-antithrombin reaction at least 1000-fold and probably 10,000-fold.

Pharmacokinetics and dosing. Heparin is not absorbed through the GI mucosa and therefore is given by continuous intravenous infusion or subcutaneous injection. It has an immediate onset of action when given intravenously; however, the bioavailability varies considerably when given subcutaneously, and the onset of action is delayed by 1 to 2 hours. The dose of heparin required to produce a therapeutic activated partial thromboplastin time (aPTT) varies because of differences in the concentrations of heparin-binding proteins in plasma. This results in a dual-phase pharmacokinetic profile (initial rapid clearance is due to nonspecific protein binding; followed by slower true metabolic clearance). Full-dose heparin therapy is usually administered by continuous intravenous infusion.

Pros. Heparin has a very short dose-dependent half-life (90 to 150 minutes), and its anticoagulant effect is reversed quickly after discontinuation. If immediate reversal is desired, protamine sulfate, a heparin binder, can be used. In addition to being one of the least expensive parenteral anticoagulants, heparin has been tested and used for multiple indications over many decades, although many of its traditional indications are now being usurped by newer agents.

Cons. Major bleeding occurs in 1% to 3% of patients treated with intravenous heparin for venous thromboembolism.[4] The risk of bleeding is increased in the presence of another risk factor for bleeding, such as use of antiplatelet agents, recent surgery, or GI bleeding. The risk of hemorrhage also increases with supratherapeutic aPTT values, but bleeding may occur at therapeutic levels.

Heparin-induced thrombocytopenia (HIT) is caused by circulating antibodies against heparin-platelet factor 4 complex. It occurs in fewer than 1% of patients who receive standard doses of heparin and even less frequently in patients treated with low molecular weight heparin (LMWH).[5] The risk of HIT rises with the increase in the dose of heparin used. Sequelae are commonly thrombotic—thromboembolism and arterial thrombosis (limb, myocardial, cerebral). Bleeding is a rare complication. The diagnosis of HIT is sometimes difficult, because patients with recent heparin exposure who experience a drop in platelet count may have other causes for thrombocytopenia (eg, sepsis, recent surgery, drugs). A high incidence of non-specific antibody formation has been observed after coronary artery bypass procedures, but the actual incidence of thrombocytopenia and/or thrombosis is much lower.

HIT should be suspected in patients who have received heparin for

5 or more days and whose platelet count has dropped below 150,000/μL or 50% without any other reasonable explanation. The ELISA is a sensitive test that detects antibodies immunologically but is not specific. The serotonin release assay, a far more specific test, detects antibodies if they are present at sufficient concentration to cause functional activation of platelets. However, it has a lower sensitivity, which varies based on the expertise of laboratory personnel and the selection of donor platelets.[6] As time passes, the assays are improving in sensitivity and specificity. The diagnosis of HIT should be made by integrating the results from one or more assays with clinical information, and especially taking into account the fact that medications, infections, and sepsis are common causes of thrombocytopenia in the inpatient setting.

HIT is treated by stopping all heparins, including intravenous flushes, and starting a direct thrombin inhibitor. Details about the various direct thrombin inhibitors and their selection criteria are discussed below. The duration of treatment remains unclear, although it has been observed that 52% of patients who initially have isolated thrombocytopenia develop objective evidence of thrombosis during the subsequent 30-day period, after which the risk of thrombosis plateaus.[7] Uncomplicated HIT should therefore be treated by switching to therapeutic doses of warfarin for 30 days. In complicated HIT, the duration of anticoagulation is determined by the length indicated for the particular clot.

Table 2 – Pros and cons of newer oral agents

Pros	Cons
•Oral administration	•Significant expense
•Very rapid onset of anticoagulant effect	•Compliance essential because effect quickly decays
•No coagulation test monitoring	•No antidote
•Early comparison data regarding bleeding, efficacy excellent	•Short history of clinical use

A *delay in discharge* can be another disadvantage of unfractionated heparin. Subcutaneous administration of heparin is not reliable for therapeutic anticoagulation, and considerable variability exists between therapeutic doses for different persons. Intravenous infusion with close monitoring of the aPTT is therefore required, requiring inpatient stay until therapeutic levels of an oral anticoagulant can be achieved.

Low molecular weight heparins. LMWHs are small fragments of unfractionated heparin with a molecular weight of 5000 daltons. Unlike unfractionated heparin, which has activity against both factor Xa and thrombin, LMWHs have greater activity against factor Xa.[8] Many LMWHs are now available (eg, enoxaparin, tinzaparin, dalteparin). Enoxaparin is the most studied and the most commonly used.

Pharmacokinetics and dosing. The pharmacokinetics of LMWH is linear and more predictable than that of unfractionated heparin, and weight-adjusted, once- or twice-daily dosing regimens can be used. LMWH is usually administered by the subcutaneous route. The anticoagulant activity of LMWH can be monitored by measuring anti-factor Xa levels.

Pros. Because of the stable and predictable pharmacokinetics of LMWH, monitoring is not routinely required. It can be administered on an outpatient basis and allows early patient discharge with LMWH for "bridging" to an oral anticoagulant. The incidence of HIT is also much lower with LMWH than with unfractionated heparin.

Cons. Although LMWH is associated with a lower risk of bleeding than unfractionated heparin, it has a longer half-life (4.5 hours) and takes longer to be cleared from the body. For this reason, unfractionated heparin may be preferred for patients who have procedures or surgeries scheduled.

Weight-based dosing of LMWH is feasible only for patients who

Table 3 – Pros and cons of warfarin

Pros	Cons
•Low cost	•Increased risk of major bleeding (especially intracranial hemorrhage)
•Long history of clinical use	•Need for periodic INR monitoring due to drug and food interactions
•Oral dosing	•Teratogenicity
•Anticoagulant effect can be reversed with vitamin K	•Warfarin-induced skin necrosis (rare)

INR, international normalized ratio.

weigh less than 150 kg. For those who weigh 150 kg or more, unfractionated heparin is recommended. If LMWH is to be used, anti-factor Xa levels should be monitored.[9] A peak anti-factor Xa level (4 hours after administration) of 0.6 to 1 U/mL is therapeutic.

Enoxaparin accumulates in patients with a creatinine clearance of less than 30 mL/min; therefore, its use should be limited to patients with higher levels. Bridging with enoxaparin is not recommended for those whose creatinine clearance is less than 30 mL/min. Tinzaparin may be used in patients who have a creatinine clearance above 20 mL/min.

Finally, unlike unfractionated heparin, which is readily reversed by protamine sulfate, LMWH has questionable reversibility.

Synthetic heparin derivatives. *Fondaparinux* is a synthetic pentasaccharide that is chemically similar to heparin; it inhibits factor Xa but not thrombin. It is completely bioavailable with subcutaneous injection, with a half-life of 17 hours. Fondaparinux is 100% renally excreted and is thus contraindicated if the creatinine clearance is less than 30 mL/min.[10,11] Monitoring is not required. Fondaparinux has no antidote; however, factor VIIa has anecdotally been reported to help control bleeding.

Idraparinux binds antithrombin with greater affinity than fondaparinux. It has a half-life of 80 hours and is administered subcutaneously on a weekly basis. It has very stable pharmacokinetics, but the long half-life may be a disadvantage.

DIRECT THROMBIN INHIBITORS

Argatroban. This small peptide molecule competitively binds to thrombin and has a half-life of 40 to 50 minutes. It can be administered only by the intravenous route and achieves a steady state between 1 and 3 hours after initiation of infusion. The aPTT returns to normal between 1 and 2 hours after discontinuation. It should be noted that argatroban also increases prothrombin time (PT) and can complicate bridging to warfarin. Aiming, while bridging, for an international normalized ratio (INR) of greater than 4 is an imperfect but reasonable way to achieve an INR in the 2 to 3 range after discontinuation of argatroban. Because argatroban is cleared by the liver, significant dose adjustments may be required in patients with hepatic failure. Caution should be used in this setting and, if possible, a different anticoagulant should be given in the presence of hepatic failure.[12]

Lepirudin. This direct thrombin inhibitor is a polypeptide derived from leech salivary extract. Genetic engineering has resulted in its production from cloned cells. Lepirudin has a half-life of 1.3 hours and can be administered only through an intravenous route. Because it is cleared renally, lepirudin should be used with caution, if at all, in patients with renal failure; significant dose adjustments are required.[13] We seldom use lepirudin if the creatinine clearance is less than 30 mL/min. Antibodies may sometimes be produced against lepirudin, and this may be therapeutically problematic.

Bivalirudin. This direct thrombin inhibitor is also administered through the intravenous route and has a half-life of 25 minutes. About 80% is cleared by proteolysis and 20% by renal filtration. In patients with renal failure, a lower dose of bivalirudin should be used, with close monitoring.[14] This agent is used mainly in the invasive cardiology setting.

NEWER ORAL AGENTS

Rivaroxaban. This is an orally administered factor Xa inhibitor. Its bioavailability ranges from 60% to 80%. Peak plasma levels are achieved within 3 hours, and the half-life is 7 to 11 hours. It is partly renally excreted and is metabolized by CYP3A4. It does not routinely require monitoring, but its activity can be measured using factor Xa. There are no specific reversing agents.[15] Rivaroxaban was superior to enoxaparin for thromboprophylaxis after hip arthroplasty[16] and knee arthroplasty.[17] It was non-inferior to enoxaparin and vitamin K antagonists for symptomatic venous thromboembolism,[18] and non-inferior to warfarin in nonvalvular atrial fibrillation.[19]

Dabigatran. This is an orally administered factor IIa inhibitor. It achieves peak plasma levels in 2 hours, and its half-life is about 12 hours. It does not routinely require monitoring and is almost entirely renally excreted, but can also be removed by dialysis. It has no specific reversing agents.[15,20] In randomized trials, dabigatran was either non-inferior or inferior to enoxaparin for thromboembolism prophylaxis after knee arthroplasty.[21,22] It was non-inferior to warfarin for treatment of acute venous thromboembolism,[23] and, at lower doses, showed similar stroke and embolism risk reduction but less bleeding as compared to warfarin in atrial fibrillation.[24]

Apixaban. This is an orally administered factor Xa inhibitor. Peak plasma levels are achieved in 1 hour, and the half-life is 8 to 15 hours. It is metabolized by CYP3A4. There are no specific reversing agents.[15] In randomized trials, it showed conflicting efficacy as compared to enoxaparin, being inferior for thromboprophylaxis after knee arthroplasty[25] but superior for hip arthroplasty.[26] It showed similar outcomes to enoxaparin with vitamin K antagonists for acute venous thromboembolism.[27] In patients with atrial fibrillation, apixaban was superior to warfarin,[28] and for those unsuited for vitamin K antagonist therapy, apixaban was superior to aspirin in

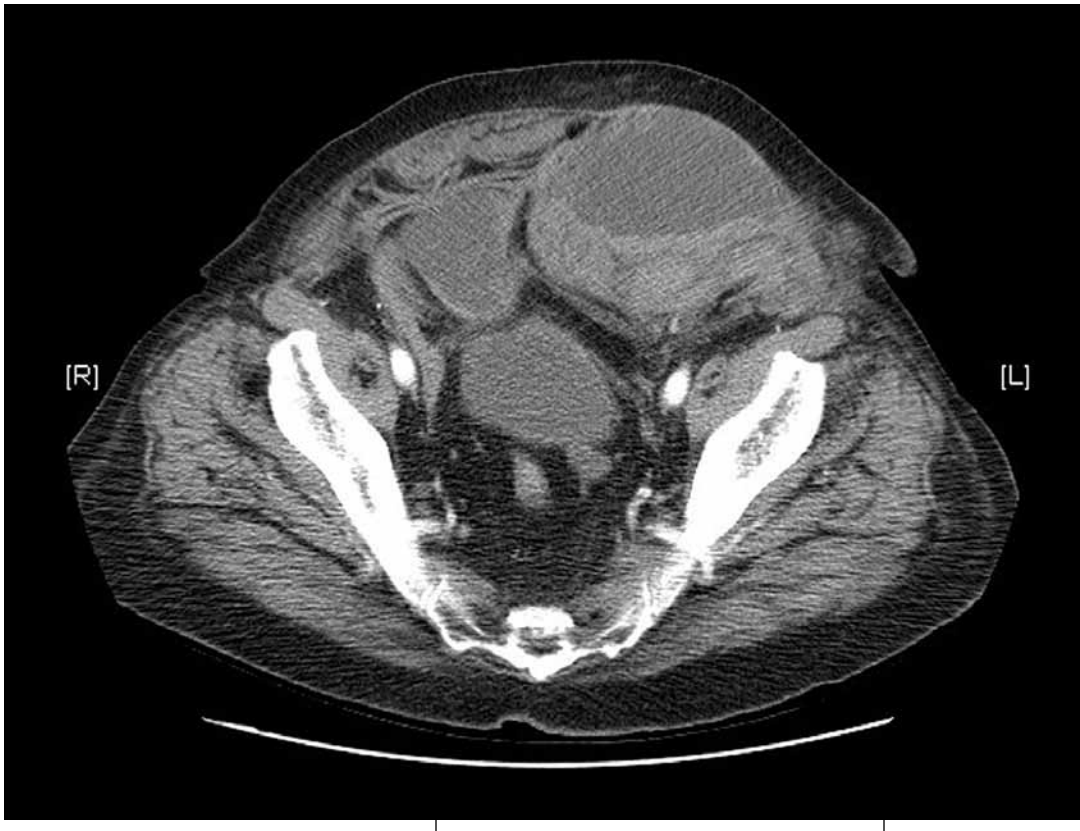

Figure – This abdominal CT scan shows a rectus sheath hematoma in an elderly man who had recently started aspirin and warfarin with an enoxaparin bridge for new-onset atrial fibrillation. His international normalized ratio was 4.1.

(Courtesy of Wael AlJaroudi, MD.)

reducing the risk of stroke or systemic embolism without increased bleeding.[29]

VITAMIN K ANTAGONISTS

Oral vitamin K antagonists were discovered in the early part of the 20th century when cattle that ate sweet clover were found to have sustained hemorrhage and even fatal bleeding on minor injury.[30] Warfarin is the only vitamin K antagonist available in the United States, although a variety of other preparations are used worldwide.

Pharmacokinetics and pharmacogenomics. Warfarin inhibits vitamin K epoxide reductase and prevents the terminal gamma carboxylation and subsequent activation of coagulation factors II, VII, IX, and X, and protein C and S. Some of the activated coagulation factors, particularly factor II, have long half-lives; thus, therapeutic anticoagulation is achieved only several days after initiation of warfarin. Average duration of action is 2 to 5 days.

Variability in the INR response to warfarin has been associated with genetic variability in the VKORC1 and CYP2C9 alleles in 10% of the population.[31] However, the pharmacokinetics of warfarin are complex even in those without identified genetic variability. Thus, warfarin therapy requires close laboratory monitoring in all patients, and especially in those who are on multiple medications. Genomic analysis to guide warfarin dosing is, at this time, unlikely to be cost-effective; further studies that demonstrate clinical relevance are necessary before genomic testing can be recommended prior to initiation of anticoagulation.

Warfarin has nearly complete bioavailability on oral administration. Its therapeutic index is narrow and varies between different indications.

Pros. Warfarin is very inexpensive and widely produced, and it has a 6-decade history of use and efficacy. Its oral dosing makes it easy to administer and has made it the default option for long-term anticoagulation.

Cons. In patients with a therapeutic INR, the risk of *major bleeding* is low, but in those with a supratherapeutic INR, the risk of hemorrhage—especially intracranial bleeding—progressively increases (**Figure**). Overall, the annual incidence of major hemorrhage related to warfarin is 2% to 5%, and it is the leading cause of iatrogenic hospitalization in general practice.[32] Increasing age is a major risk factor for warfarin-related bleeding. The use of warfarin requires close laboratory monitoring and close attention to diet and medications.

The anticoagulant effect of warfarin can be reversed by vitamin K. Oral vitamin K is more effective than subcutaneous, and is the route of choice when feasible.[33,34] Intravenous vitamin K should be used with caution because of the risk of anaphy-

laxis. Fresh frozen plasma can be used for rapid reversal of anticoagulation, although repeated transfusion may be required because the half-life of factor VII is short and it is cleared from the circulation before warfarin. Factor VIIa may have a role in the control of catastrophic bleeding.

Warfarin-induced skin necrosis is a rare complication caused by depletion of protein C. It is reported most commonly in patients who are heterozygous for protein C or S deficiency and after high-dose loading of warfarin. Lesions appear 3 to 10 days after initiation of warfarin and may involve the extremities, breasts, and adipose tissue. Treatment is generally supportive, with consideration of agents such as LMWH for continued anticoagulation. Larger lesions may require debridement.

Since loading with high doses of warfarin is no longer used in medical practice, this complication is rarely seen. Unless the patient has a known deficiency of protein C or S, bridging with heparin is not required for initiation of warfarin merely for the purpose of preventing this complication.

Teratogenicity is another disadvantage of warfarin; its use in pregnant women may cause birth defects, abortion, and fetal hemorrhage. Chondrodysplasia punctata results from the use of warfarin in the first trimester, and CNS abnormalities are seen with use during the second and third trimesters. Warfarin is therefore contraindicated in pregnancy. ■

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