State-of-the-Art Review

Anticoagulation: The Present and Future

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Summary: Thrombin is a central bioregulator of coagulation and is therefore a key target in the therapeutic prevention and treatment of thromboembolic disorders, including deep vein thrombosis and pulmonary embolism. The current mainstays of anticoagulation treatment are heparins, which are indirect thrombin inhibitors, and coumarins, such as warfarin, which modulate the synthesis of vitamin K-dependent proteins. Although efficacious and widely used, heparins and coumarins have limitations because their pharmacokinetics and anticoagulant effects are unpredictable, with the risk of bleeding and other complications resulting in the need for close monitoring with their use. Low-molecular-weight heparins (LMWHs) provide a more predictable anticoagulant response, but their use is limited by the need for subcutaneous administration. In addition, discontinuation of heparin treatment can result in a thrombotic rebound due to the inability of these compounds to inhibit clot-bound thrombin. Direct thrombin inhibitors (DTIs) are able to target both free and clot-bound thrombin. The first to be used was hirudin, but DTIs with lower molecular weights, such as DuP 714, PPACK, and efegatran, have subsequently been developed, and these agents are better able to inhibit clot-bound thrombin and the thrombotic processes that take place at sites of arterial damage. Such compounds inhibit thrombin by covalently binding to it, but this can result in toxicity and nonspecific binding. The development of reversible noncovalent DTIs, such as inogatran and melagairan, has resulted in safer, more specific and predictable anticoagulant treatment. Oral DTIs, such as ximelagatran, are set to provide a further breakthrough in the prophylaxis and treatment of thrombosis. Key Words: Anticoagulation—Thrombin—Heparin—Coumarin—Direct thrombin inhibitor (DTI)—Ximelagatran.

Coagulation is the body's primary defense mechanism for the prevention of bleeding after tissue injury. Once triggered, coagulation consists of a series of stepwise, coordinated reactions involving specific plasma proteins and blood cells, culminating in the formation of an insoluble fibrin clot (1). A key factor within this system is thrombin (2), which constitutes the final common mediator of both the intrinsic and the extrinsic coagulation pathways, and mediates the proteolytic cleavage of fibrinogen to fibrin molecules, which subsequently become cross-linked (Fig. 1). In addition, thrombin promotes platelet activation and therefore plays a major role in the different stages of thrombus formation (3). Furthermore, thrombin not only stimulates coagulation by activating the cofactors of tenase and prothrombinase complexes (e.g., factors VIII and V), but also modulates coagulation and fibrinolysis by the thrombomodulin/protein C pathway, and by the alteration of endothelial functions. Thrombin also activates inflammatory processes...
FIG. 1. Physiologic action of thrombin. Fibrinogen binds to exosite 1 and is cleaved by the active catalytic site of thrombin to produce fibrin. Involving blood leukocytes and vascular wall cells (2), and is involved in tissue repair through the activation of several cell types, including endothelial cells, monocytes, and fibroblasts, resulting in cell proliferation, chemotaxis, and cytokine production (4). Thrombin also initiates the proliferation of vascular smooth muscle cells at the site of injury and modulates the effects of growth factors.

Thus it can be seen that thrombin is a central bioregulator of coagulation, and is capable of both anticoagulant and procoagulant activities. As a consequence of its pivotal and ubiquitous roles in hemostasis, thrombin is a key target for the therapeutic prevention and treatment of thromboembolic disorders, including deep vein thrombosis and pulmonary embolism.

CURRENT ANTICOAGULATION TREATMENT OPTIONS

The current mainstays of anticoagulation treatment of thromboembolic disorders are heparins, which exert their effects via the indirect inhibition of thrombin, and coumarins (also known as vitamin K antagonists).

Warfarin, the most commonly used coumarin derivative, achieves its anticoagulant effect by modulating the synthesis of vitamin K–dependent proteins, resulting in the synthesis of defective coagulation factors without any coagulant activities (5). Warfarin is administered orally, with a bioavailability of almost 100%; however, more than 98% is plasma protein bound. In addition, as a result of interactions with dietary vitamin K, concomitant medications, and cytochrome P450–dependent metabolism, there is high variability among individual responses to warfarin treatment (Table 1). Consequently, individual dosing regimens must be tailored to the needs of each patient.

DVT, deep venous thrombosis; PE, pulmonary embolism; UFH, unfractionated heparin; HIT, heparin-induced thrombocytopenia; LMWH, low-molecular-weight heparin.

<table>
<thead>
<tr>
<th>Agent</th>
<th>Advantages</th>
<th>Disadvantages</th>
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<tbody>
<tr>
<td>Warfarin (and other coumarins)</td>
<td>Long-standing status as the gold standard for secondary DVT/PE prophylaxis Oral administration</td>
<td>No reliable basis for dosage selection in individual patients Difficulty in management (monitoring and dose adjustments) Slow onset and offset of action Narrow therapeutic window Dietary restrictions Risk of bleeding</td>
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<tr>
<td>UFH</td>
<td>Fast acting Good efficacy</td>
<td>Potential for the development of HIT Parenteral administration Unpredictable anticoagulant effect due to nonspecific binding of UFH to proteins and cells Risk of bleeding complications Risk of thrombocytopenia and osteoporosis Indirect action via antithrombin Unpredictable and variable bioavailability when administered subcutaneously</td>
</tr>
<tr>
<td>LMWH</td>
<td>Once or twice daily dosing Does not require laboratory monitoring Good efficacy</td>
<td>Parenteral administration High cost High rate of bleeding complications Risk of thrombocytopenia and osteoporosis Indirect action via antithrombin</td>
</tr>
<tr>
<td>Hirudin</td>
<td>Good efficacy Fast acting</td>
<td>Parenteral administration Risk of bleeding Lack of suitable agent for rapid reversal of anticoagulant effect</td>
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of each patient, with the added requisite of frequent monitoring to ensure that an adequate level of anticoagulation is maintained. Subtherapeutic levels may result in thromboembolic events, whereas supertherapeutic levels may result in serious bleeding (3). Although warfarin treatment has been shown to be effective in preventing recurrent venous thromboembolism, its use is associated with a significant risk of bleeding (5), which, in some countries, accounts for up to 40% of reported drug-induced deaths (6). The relative risk of hemorrhage is reported to increase with patient age (>65 years) and with the higher drug doses (7). Because it takes 2 to 7 days before the full antithrombotic response to warfarin is achieved, additional anticoagulant treatment is required during the initiation of therapy. Typically, this is provided by the coadministration of heparin or its derivatives.

Heparin, like warfarin, is an indirect thrombin inhibitor. Unfractionated heparin (UFH) inhibits thrombin by enhancing the activity of antithrombin, an endogenous thrombin inhibitor (8). Unfractionated heparin is administered as intravenous (IV) or subcutaneous injections two to three times daily. However, although efficacious, UFH has pharmacokinetic, biophysical, and biologic limitations (9) that restrict its use in the clinical setting (Table I). Of particular concern is the development of heparin-induced thrombocytopenia (HIT), a disease triggered by an immune response to heparin. It has been estimated that HIT develops in 8 to 28% of patients treated with heparin (10). Some of these problems have been overcome with the development of low-molecular-weight heparins (LMWHs), which are derived from UFH by enzymatic or chemical degradation (11). Low-molecular-weight heparins have longer plasma half lives as compared with UFH, thus allowing for once- or twice-daily dosing instead of twice- or thrice-daily dosing. Because LMWHs have a more predictable anticoagulant response, their use does not require routine laboratory monitoring; however, their utility is limited by the need for subcutaneous administration (9). In addition, the discontinuation of heparin (either UFH or LMWH) in the treatment of unstable angina, for example, is associated with a thrombotic rebound and the clustering of recurrent ischemic events (12). This reactivation of the thrombotic process is thought to result, in part, from the inability of these compounds to inhibit clot-bound thrombin. Thrombin bound to fibrin remains enzymatically active, triggers its cellular responses, and serves as a reservoir of active thrombin. Once heparin treatment is stopped, this active thrombin is then capable of reinitiating the coagulation process. There is also a risk of subsequent development of HIT, which may be life threatening when severe thrombocytopenia is accompanied by severe thromboembolic events (8).

SAFETY

As observed with the use of warfarin, a major safety concern for anticoagulant treatment is bleeding. A fine balance must be maintained to prevent overdosing (leading to bleeding) while avoiding underdosing (inadequate anticoagulant effect). To achieve this, the ideal anticoagulant should be easily absorbed, giving predictable and reproducible plasma levels, thus maintaining an effective and "safe" anticoagulant effect. As with any anticoagulant, in emergency situations rapid reversal of the anticoagulant effect may be required; thus a drug with a half-life requiring twice-daily dosing may be an optimal compromise between convenience and safety (13).

As a consequence of these drawbacks, research has been undertaken to develop direct thrombin inhibitors (DTIs) (3, 14). The first DTI to be made available for clinical use was hirudin, a 65-amino acid polypeptide that was originally obtained from the salivary glands of the leech (Hirudo medicinalis). Hirudin is a potent and specific inhibitor of thrombin, forming a stoichiometric (1:1) and extremely slowly reversible complex. It binds to both the active site and substrate recognition site (exosite 1) of the thrombin molecule (15) (Fig. 2). Because of this bivalent binding, hirudin is one of the most potent inhibitors of thrombin, binding in a slow, two-stage process (association rate constant $1.4 \times 10^{-8}$/M/s) to form an essentially irreversible complex (inhibition constant $K_i$).

![Diagram](hirudin.png)

**FIG. 2.** Hirudin binds to thrombin at exosite 1 and at the active site, forming an essentially irreversible complex.
Thrombin belongs to a large family of serine proteases including trypsin, chymotrypsin, and plasmin. Cross-reactivity of a DTI with these other enzymes can result in safety concerns and possible toxicity. However, high selectivity for thrombin, with the avoidance of interactions with related fibrinolytic enzymes, may reduce the high incidence of bleeding observed with less selective agents, e.g., warfarin (25). This effect can be explained as nonspecific inhibition of thrombotic enzymes and can actually prevent clot formation, thus promoting bleeding.

High potency/affinity for thrombin

Once the coagulation system is triggered, the generation of thrombin is rapid; therefore, to be pharmacologically effective, DTIs should be fast acting (26). This has proven to be problematic for certain thrombin inhibitors such as L-370,518 (23), α-ketoamide transition state analogues (25), and efegatran (26), which possess slow, tight-binding kinetics. Another potential drawback with slow-binding inhibitors was described by Elg et al. (27), who reported that these compounds give steep dose-response curves resulting in narrow therapeutic windows.

Wide therapeutic window

The narrow therapeutic window of safe and effective plasma concentrations of warfarin, in addition to its unpredictable pharmacokinetics and pharmacodynamics, establishes the need for routine monitoring of the anticoagulant effect of warfarin (8). Based on the results of monitoring, doses have to be adjusted to avoid overtreatment (risk of severe bleeding, the main complication of oral vitamin K antagonist therapy) or undertreatment (failure to prevent clot formation or clot progression). Unfractionated heparin also has a narrow therapeutic window (8). In developing an ideal anticoagulant, therefore, a wide therapeutic window is a prerequisite for effective and safe use without routine laboratory monitoring.

Predictable and reliable pharmacokinetic and pharmacodynamic profiles

Unpredictable pharmacokinetic and pharmacodynamic profiles impact severely on the safety of anticoagulants, with the subsequent caveat that the therapeutic use of such agents (e.g., warfarin and UFH) requires regular monitoring. Hence, the development of an agent with predictable pharmacokinetics and pharmacodynamics, with minimal inter- and intrapatient variability, would remove the need for monitoring and dose titration.

Inhibition of both free and clot-bound thrombin

One of the current limitations of heparin and warfarin is the inability of these agents to inhibit clot-bound thrombin. Once a thrombus is formed, thrombin is able to bind to fibrin and can remain active inside the clot, where it is protected from inhibition by antithrombin (28). The fibrin clot thus acts as a reservoir for enzymatically active thrombin, which retains its ability to interact with various substrates and cells, including propagation of coagulation, inflammation, and restenosis. Inhibition of both free and clot-bound thrombin is therefore regarded as essential for the development of an effective DTI.

Pharmacoeconomic profile

Pharmacoeconomic outcomes of drug treatments become more and more important in both hospital and outpatient treatment. Compared with the current anticoagulant treatment options, the ideal agent should show enhanced pharmacoeconomic benefits. These could be achieved by the availability of oral administration, by removing the need for routine coagulation monitoring, by increasing drug efficacy, and by reducing the complications of treatment.
Oral administration

For the prophylaxis and treatment of thrombosis, long-term therapy is mandatory and is becoming increasingly accepted. A key element for successful long-term compliance to extended therapy is ease of administration, and clearly this can be aided by the use of an orally administered drug.

In addition to the properties discussed above, several other factors need to be considered when designing a new anticoagulant. These include minimal daily dosing, dose-dependent efficacy, no titration, no drug–drug interactions, and no plasma protein or food interactions.

A NEW HORIZON: NONCOVALENT DIRECT THROMBIN INHIBITORS

Following the introduction of hirudin, research has been undertaken to develop efficacious DTIs with improved tolerability. It has been postulated that because of their ability to inhibit clot-bound thrombin (17,29,30), DTIs may be more efficacious in comparison with low-dose UFH and LMWH. This is of relevance because, as already discussed, clot-bound thrombin remains enzymatically active. In a recent study, it was shown that clot-bound thrombin is relatively protected from inhibition by antithrombin-independent inhibitors (28). In addition, it has been demonstrated that lower-molecular-weight inhibitors such as D-phenylalanil-L-prolyl-L-arginylchloromethyl ketone (PPACK; molecular weight 524 Da) are able to inhibit clot-bound thrombin better than the larger thrombin inhibitors such as hirudin (molecular weight 7,000 Da) (28). Low-molecular-mass DTIs can also inhibit the thrombin-mediated aspirin- and heparin-resistant thrombotic processes that tend to take place at sites of arterial damage; inhibition of these processes can prevent occlusion of arteries (2).

Several different classes of DTI are being developed, including synthetic antithrombin peptides, irreversible inhibitors, and reversible inhibitors (31,32). Initially, research was directed to the development of agents that achieved their inhibitory effects by covalently binding to thrombin, e.g., DuP 714, PPACK, and efegefaran (13). Unfortunately, the presence of highly reactive electrophilic groups in these compounds, required for the irreversible, covalent binding, also resulted in toxicity, lack of selectivity for thrombin, and poor efficacy (24,26). Problems associated with nonspecific binding have been overcome partly with the development of the reversible, noncovalent inhibitors, which have superior selectivity and, owing to their fast-binding kinetics, lack the time-dependent onset of action that is common to the electrophilic inhibitors (26). Furthermore, it has been suggested that reversible DTIs such as inogatran (33) and melagatran (34) may produce superior safety profiles when compared with hirudin, because they only transiently inhibit the active site of thrombin (35) (Fig. 3). It has also been demonstrated that noncovalent DTIs do not interact with platelets and thus do not interfere with platelet-mediated wound repair (24). In addition, these agents have more predictable anticoagulant effects as compared with indirect thrombin inhibitors (3). Several promising noncovalent DTIs are emerging, including argatroban, BMS-186282, and melagatran.

Argatroban

Argatroban is a noncovalent DTI that is marketed in Japan for the treatment of acute cerebral thrombosis and hemodialysis in antithrombin-deficient patients. It is also used in arterial occlusive disease (36). Argatroban is a small (509 Da), reversible, active site-directed thrombin inhibitor, with a half-life of 15 to 30 minutes, that binds rapidly to thrombin with $K_i = 3.9 \times 10^{-8}$ mol/L for human thrombin (35). However, the clinical use of argatroban is limited owing to its need for parenteral administration, and development of an oral form is not expected. The drug was registered in the United States for use in HIT in the year 2000.

BMS-186282

BMS-186282 is a small, active site–directed thrombin inhibitor (37). It binds covalently to the active site of thrombin with high affinity ($K_i = 0.079 \mu$mol/L). In addition, BMS-186282 is highly selective for thrombin, which is thought to improve its safety profile, in comparison to less selective agents such as PPACK.

FIG. 3. Melagatran is a competitive, reversible inhibitor that binds directly to the active site of thrombin.

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Melagatran
Melagatran is a very small (429.5 Da), reversible, active site-directed thrombin inhibitor that is administered subcutaneously and is the active form of the orally administered DTI, ximelagatran (38). Melagatran is a potent inhibitor of thrombin, with a Ki of 0.002 μmol/L, and high selectivity against other serine proteases such as plasmin (Ki = 0.7 μmol/L) (34,39). In addition to directly inhibiting thrombin activity, melagatran has been shown to inhibit thrombin generation (40,41). In contrast to earlier anticoagulants such as heparin and warfarin, melagatran inhibits both free and clot-bound thrombin (27). This prevents evolution of the clot and destabilizes clot formation. The antithrombotic action of melagatran has been assessed in various animal models, and it has been shown to be efficacious in preventing and treating both arterial (27,42) and venous thromboembolism (43-45). The dose-response curve of inhibition of thrombus formation in a rat arterial thrombosis model was three times shallower than that of warfarin. Also, in a rat tail transection bleeding time model, warfarin provoked longer bleeding times (significantly greater than the control) compared with melagatran when each drug was given at a level causing 80% inhibition of thrombosis. Hence, the therapeutic window of melagatran doses (or plasma concentrations of melagatran) that would produce a beneficial antithrombotic effect without significantly increasing the risk of unwanted bleeding is wider than with warfarin (46).

Encouraging results have been obtained from studies in healthy volunteers, where melagatran demonstrated predictable pharmacodynamic and pharmacokinetic properties following IV and subcutaneous administration. This suggests that with melagatran treatment, unlike with warfarin and heparin, there is no need for routine monitoring. In addition, melagatran was well tolerated at all dose levels studied (47,48). However, as with other thrombin inhibitors, after oral administration bioavailability was low and variable, suggesting the need for an alternative oral dosage form (47).

ORAL AVAILABILITY: THE CHALLENGE
A major challenge in the development of new anticoagulants is the design of an agent that can be administered orally. There is an emerging awareness of the need for long-term thrombin inhibition to prevent the recurrence of thrombosis. Clearly, this challenge is met more easily with orally administered compounds, which also may help to increase long-term patient compliance. As the patient population requiring long-term use of anticoagulants is generally elderly, ease of administration is an important factor. However, despite the obvious advantages, the development of an orally administered DTI has proved to be challenging for a number of reasons.

For an agent to be orally administered, it is crucial that there is good absorption from the gastrointestinal tract. Bioavailability following oral administration can be significantly reduced by first-pass metabolism and by tryptase binding (24). In addition, once- or twice-daily dosing is desirable, which relies on suitable half-life duration and clearance characteristics (25). Plasma protein binding, which is always a consideration for any drug, is more important for thrombin inhibitors than for most agents because the primary effect compartment is the blood itself (24). Despite intensive research of the new thrombin inhibitors currently under investigation, few appear to have the potential for oral administration and only one of these, ximelagatran, has progressed into advanced clinical trials.

Ximelagatran
Oral DTIs represent a new class of anticoagulant. The first drug to reach advanced clinical trials is ximelagatran, a novel, reversible, active site DTI, of which melagatran is its active form (49). The development of ximelagatran may represent the first clinically useful oral anticoagulant since the development of warfarin over 50 years ago.

Ximelagatran was developed to overcome the limited intestinal absorption and, hence, low oral bioavailability of melagatran. In vitro permeability studies have shown that ximelagatran penetrates a cellular model of the gastrointestinal barrier (Caco-2 cells) approximately 80 times faster than melagatran (49). In addition, at neutral pH, ximelagatran is uncharged and is more lipophilic than melagatran (38,49), properties that contribute to improving the gastrointestinal absorption of ximelagatran. Preclinical studies have shown that after oral administration ximelagatran is rapidly biotransformed to melagatran, thus providing excellent antithrombotic effects (50).

In clinical studies of ximelagatran, the oral bioavailability and metabolism into melagatran have been shown to be rapid and complete and, in contrast with warfarin, no food interactions were observed (51). Predictable pharmacodynamics of melagatran have been demonstrated following administration of oral ximelagatran and subcutaneous melagatran. Recent clinical trials of sequential therapy with subcutaneous melagatran and oral ximelagatran in the prophylaxis of venous thromboembolism after major orthopedic surgery suggest that ximelagatran and its active form melagatran are promising agents for the prevention of venous thromboembolism (52,53). Furthermore, a randomized, double-blind, double-dummy, parallel-group, multicenter trial (METHRO ID) involving 1,916 patients undergoing total knee or total hip replacement surgery has shown that the efficacy of the highest dose of melagatran (3 mg subcutaneously twice daily) and ximelagatran (24 mg by mouth)
twice daily) was superior to that of dalteparin. In addition, the compounds had a comparable tolerability profile (54).

CLINICAL APPLICATIONS

Because numerous thromboembolic risk factors exist, anticoagulants have a wide range of applications in disease conditions, many of which require long-term administration. In addition to their use in postoperative thromboembolic prophylaxis (after orthopedic, general, and vascular surgery), anticoagulants are also used in the treatment of existing thromboembolism and in the prevention of its recurrence. Other applications include preventing venous thromboembolism in hospitalized medical patients, in patients with cancer and in pregnancy, and in the prevention of systemic embolic events in patients with nonvalvular atrial fibrillation (AF), valvular heart disease, prosthetic heart valves, acute myocardial infarction, ischemic stroke, unstable infarction, and percutaneous coronary intervention.

Venous thromboembolism treatment and secondary prevention

Typically, treatment of venous thromboembolism involves coadministration of UFH (IV) or LMWH (subcutaneous) and warfarin or other coumarins (oral) until therapeutic levels of anticoagulation by warfarin are achieved, at which time heparin treatment is discontinued. Warfarin treatment is then continued for 3 to 6 months. The probability of recurrence of thromboembolism within 1 year following the discontinuation of warfarin treatment is 5 to 10% (55,56). Despite this relatively high risk, longer-term anticoagulant therapy is not commonly recommended because the risk of adverse events such as bleeding associated with warfarin is perceived to outweigh the benefits, although recent studies have confirmed the benefits of prolonged thromboembolic prophylaxis in the outpatient setting (57). Perhaps long-term oral anticoagulant therapy will become a more realistic option with the advent of an orally active agent that does not require monitoring and that has reduced bleeding risks.

Medical and cancer patients

Hospitalized patients with general medical conditions such as congestive heart failure, chronic obstructive pulmonary disease, or infections are also at moderate risk for the development of venous thromboembolism, and a higher risk is associated with the need for critical care. Venous thromboembolism is also a common complication in patients with cancer, due to a hypercoagulable state attributable to the malignancy or to chemotherapy, radiotherapy, or central venous lines. In medical patients with risk factors for venous thromboembolism, heparin or LMWH are the currently recommended agents for thromboprophylaxis (58).

Pregnancy and thrombophilia

Maternal deep vein thrombosis and pulmonary embolism or fatal pulmonary embolism are relatively common during pregnancy. The risk is escalated in pregnant women who also have thrombophilia due to congenital deficiencies: for example, in those with antithrombin, protein C or protein S deficiencies, and in those with factor V Leiden gene mutations. Because there are safety concerns with the use of warfarin in pregnancy, heparin or LMWH is most commonly used, but both are inconvenient, expensive, and associated with risks of bleeding, osteoporosis, and HIT. The heparinoid, danaparoid, is an alternative in those who develop HIT. Because DTIs cross the placenta, these agents have not been studied in pregnancy to date (59).

Atrial fibrillation

Prevention of thromboembolic stroke in patients with nonvalvular atrial fibrillation (AF) is a major indication for long-term anticoagulation with warfarin. Cerebral embolism is the pathogenic mechanism behind 16 to 20% of all ischemic strokes and is most commonly associated with AF (60). Atrial fibrillation becomes an increasingly important risk factor for stroke with advancing age, with an attributable risk of 23.5% in the 80- to 89-year-old age group (61). Anticoagulation should also be provided before elective cardioversion of atrial fibrillation. Overall, several studies of long-term antithrombotic therapy in AF show that adjusted-dose warfarin is more effective than aspirin in stroke prevention and is probably more effective than low-dose warfarin with or without concomitant aspirin. The risk of intracranial hemorrhage increases dramatically with warfarin above international normalized ratio (INR) values of 4.0 to 5.0; therefore, a target INR range of 2.0 to 3.0 is considered standard (62). The need to balance the efficacy and safety of warfarin has led to prophylaxis guidelines based on risk stratification, such that those with high or moderate additional risk factors for stroke should be given adjusted-dose warfarin, while aspirin is used in low-risk patients (62). Despite evidence for its benefit, effective prophylaxis remains underprovided to patients with atrial fibrillation (63). An oral DTI that has a predictable effect without the need for laboratory monitoring would facilitate greater provision of long-term anticoagulation for stroke prevention in all patients with atrial fibrillation.

Valvular heart disease, mechanical valves, and percutaneous coronary intervention

Long-term warfarin treatment is also used to prevent systemic embolism in patients with valvular heart disease and those with mechanical heart valves, although...
the decision to treat the former with warfarin requires careful assessment of the variables that influence the risk of thromboembolism and bleeding. Heparin or LMWH is administered until warfarin therapy attains the target INR (64,65). Heparin also has value in preventing arterial thrombus formation at the site of arterial injury following percutaneous coronary intervention (e.g., coronary artery bypass grafting), and bivalirudin has been recommended as an alternative (66).

**Acute myocardial infarction**

Prophylactic antithrombotic therapy in patients with acute MI can be used to prevent venous thromboembolism as well as mural thrombosis and systemic arterial embolism, which can cause stroke. The greatest risk for venous thromboembolism is during the few weeks following the acute MI, although the risk extends beyond this period. Early administration of heparin followed by either heparin, LMWH, or warfarin for up to 3 months is used for all acute MI patients at increased risk of systemic or pulmonary embolism who have not previously received thrombolytic therapy (67). Early therapy with IV thrombolytic therapy and aspirin has become accepted practice in selected patients with recent (<12 hours) acute MI (68). Following thrombolytic therapy, there is a risk of reoclusion. Furthermore, the thrombolytic agents may paradoxically lead to platelet activation and an increase in thrombin generation (69). A beneficial effect of early concomitant administration of IV heparin for 48 hours on the incidence of venous thromboembolism has been observed (67). The DTI hirudin has shown similar efficacy to heparin, when both were used in conjunction with thrombolytic therapy, in reducing the incidence of death, recurrent nonfatal MI or development of severe congestive heart failure or cardiogenic shock by 30 days in patients with acute MI (70).

**Ischemic stroke and unstable angina**

Approximately 5% of all early deaths following ischemic stroke are attributed to pulmonary embolism, and routine use of heparin, LMWH, or the heparinoid, danaparoid, is recommended for patients with recent stroke and impaired mobility (58). In patients with unstable angina, antiplatelet agents such as aspirin have been shown to reduce the rates of all-cause mortality or cardiac death and nonfatal MI. However, an additional benefit is obtained by treating patients hospitalized with unstable angina with aspirin plus heparin (IV) or LMWH, which should be continued for at least 48 hours or until the unstable pain pattern resolves (67). Hirudin plus aspirin appears to be more effective than UFH plus aspirin, although in view of the cost and apparently higher hemorrhagic risk, heparin remains the current therapy recommendation. In some studies extended therapy with moderate-intensity warfarin after initial heparin therapy has been shown to reduce the risk of death, MI, or refractory angina and the need for rehospitalization for patients with unstable angina, although the greatest benefit appears to be derived from early anticoagulation treatment with heparin (67).

**CONCLUSION**

Despite the obvious need for effective anticoagulant treatments, the use of such agents has, until recently, been hampered by methodologic (e.g., parenteral administration, coagulation monitoring, and dose adjustment) and safety (e.g., high risks of bleeding) concerns; however, with the emergence of oral DTIs, which has been evaluated in clinical trial programs, these problems can now be readdressed.

Anticoagulation therapy has undergone significant advancement with the development of DTIs (e.g., hirudin, argatroban, and melagatran). With the emergence of orally administered DTIs, such as ximelagatran, that are efficacious, well tolerated, and do not require monitoring, another breakthrough in the prophylaxis and treatment of thrombosis is imminent. Such agents are expected to facilitate widespread provision of anticoagulation to at-risk patients in multiple clinical applications.

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