Heparin in Interventional Radiology: A Therapy in Evolution

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ABSTRACT

Interventional radiology techniques made possible by the antithrombotic properties of heparin have revolutionized treatment for a myriad of disorders. Newer low-molecular-weight heparins (LMWHs) offer several advantages over unfractionated heparin (UFH), especially in chronic settings. They are increasing in popularity for use during vascular procedures. However, LMWH shares limitations with UFH such as heterogeneity, nonspecificity, and induction of thrombocytopenia. These drawbacks have led to a search for the next generation of antithrombotic agents. Homogeneous drugs targeting specific coagulation cascade molecules are now available. The number of alternative anticoagulant drug combinations presents clinicians with a confusing array of choices. The strengths and weaknesses of UFH, LMWH, and direct antithrombin agents are presented. The promising future of LMWH and hirudins is discussed.

KEYWORDS: Heparin, low-molecular-weight heparin, interventional radiology, hirudin, bivalirudin, anticoagulation

Objectives: Upon completion of this article, the reader should be able to (1) summarize the different anticoagulants used in interventional procedures, (2) discuss the relative advantages of each, and (3) select the appropriate anticoagulant for use in a specific setting.

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Intravascular procedures using indwelling catheters and sheaths would be impossible without inhibition of the coagulation cascade. Synthetic surfaces of catheters and wires themselves are intrinsically thrombogenic. Tissue damage from vessel punctures, sutures, and angioplasty exposes tissue factor, providing a powerful trigger for coagulation. Even ionic contrast material is known to be thrombogenic. Heparin has long been used to overcome these factors, and its antithrombotic properties have proved indispensable for most interventional procedures.[1–3] Interventional radiology techniques made possible by heparin have revolutionized the treatment for a myriad of disorders. Such therapies have often supplanted the more traditional surgical approaches.

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Table 1 Comparison of Current Antithrombotic Agents

Property	Unfractionated Heparin	Low-Molecular-Weight Heparin	Hirudin/Bivalirudin
Activity against thrombin	Antithrombin dependent	Antithrombin dependent (only long chains active)	Direct inhibition
Anti–factor Xa activity	Antithrombin dependent	Antithrombin dependent	None
Active against clot-bound thrombin	No	No	Yes
Reversal agent	Protamine	Protamine (partial reversal)	No
Purity	Heterogeneous	Heterogeneous	Homogeneous
Dose response	Nonlinear, unpredictable	Linear, predictable unless obese or renal failure	Linear, predictable unless antihirudin antibodies
Clearance	Saturable protein binding + renal	Renal	Enzymatic cleavage + renal
Monitoring	aPTT, ACT	Anti–factor Xa assays	aPTT, ACT
Heparin-induced thrombocytopenia	Yes	Yes (less often than UFH)	No

ACT, activated clotting time; aPTT, activated partial thromboplastin time; UFH, unfractionated heparin.

However, the increasing number of anticoagulant drug combinations has led to many divergent approaches in the absence of standard methodologies.[4] The large number of patients presenting with acute coronary syndrome has enabled cardiologists to conduct clinical trials more readily than radiologists. Consequently, the growing body of interventional cardiology literature concerning methods of anticoagulation proves to be an indispensable resource.

In many hospitals, unfractionated heparin (UFH) remains the mainstay of therapy. It is a familiar drug to physicians and has a long history of successful employment in many specific applications. However, it has serious disadvantages related to its heterogeneous composition, unpredictable pharmacokinetics, and potentially severe side effects. Although low-molecular-weight heparin (LMWH) offers several advantages over UFH, especially in the setting of chronic use, it shares some of the same limitations. This has led to the search for the next generation of antithrombotic agents.

New agents that have the advantage of being homogeneous compounds are now available. These drugs are more selective in their molecular targets. Hirudin, the active principle in the salivary secretion of leeches, and its synthetic derivative bivalirudin are direct thrombin inhibitors. Fondaparinux sodium (Arixtra®, Organon Sanofi-Synthelabo LLC, West Orange, NJ) is a new more anti-Xa specific agent. There are anti–tissue factor agents now in development. The variety of antiplatelet agents and their indications continues to grow.[5] However, initial data on these new compounds have been somewhat ambiguous, as many require concurrent administration of other drugs to achieve therapeutic efficacy. Their use is also limited by the lack of reversal agents to counter their anticoagulant effect. Given the familiarity with heparin, its proven track record, and its extremely low cost, it is unlikely any of these agents will completely supplant heparin in the near future.

Understanding the biochemical nature of both UFH and LMWH is critical to appreciating the functional distinction between these related compounds. It also allows better assessment of the potential role to be played by the newer targeted agents. Table 1 provides an overview of the three classes of anticoagulants to be discussed.

STRUCTURE AND FUNCTION

Heparin

Heparins in medical use, along with closely related heparans, are a heterogeneous population of linear polysaccharides belonging to the glycosaminoglycan family. In vivo they exist in many varieties as components of membrane-bound proteoglycans covering the surface of nearly all cell types. They are also found extensively throughout the extracellular matrix. Their structural diversity arises from variation in carbohydrate composition, in the protein core of the associated proteoglycans, and from the random cleavage of the polysaccharide chain during heparin synthesis giving variable lengths.[6] Ubiquitous and biodiverse, heparins have been implicated in a wide range of biologic functions. Other recognized functions of heparins and heparans include alteration of vascular permeability, release of lipoprotein lipase from hepatic stores, modulation of vascular smooth muscle cell proliferation,[7] alteration of osteoblast-osteoclast balance, cell adhesion, and charge-based binding to plasma and membrane proteins that can affect the pharmacokinetics of other agents.[6]

Most familiar to clinicians is heparin's activation of the plasma serine protease inhibitor antithrombin (AT), leading primarily to the inactivation of clotting cascade factors Xa and thrombin (factor IIa). Of the coagulation cascade serine proteases, thrombin is most sensitive to inhibition, ~10 times more sensitive than

factor Xa. To a lesser degree, the heparin-AT complex also inhibits factors IXa, XIa, and XIIa. Besides its effect on the coagulation cascade, heparin can induce tissue factor pathway inhibitor secretion from vascular endothelial cells and consequently impair thrombus formation through inhibition of the tissue factor–VIIa complex. Heparin interacts with platelets to alter thrombus formation as demonstrated by in vitro experiments and by its effect on the prolongation of bleeding time.[8] It may have a further direct effect on endothelial cells to inhibit coagulation in the microvasculature. Highly concentrated endogenous heparins on endothelial cell surfaces promote elevated baseline intravascular AT activity maintaining vessel patency. In the context of vessel injury, plasma becomes exposed to tissue factor and to the much reduced concentration of heparins within the extracellular matrix. This leads to simultaneous extrinsic pathway activation and drop-off in AT activation, promoting thrombus formation. Paradoxically, exogenously administered heparin may inadvertently lead to a prothrombotic state in the microvasculature by competing with endogenous endothelial cell surface heparin for plasma AT.[6,9,10]

The structural diversity of heparins that permits their varied functions has important consequences for their anticoagulant activity. A distinct five-saccharide subunit that has an AT-specific binding domain must be present to provoke the conformational change in AT that leads to a 1000-fold increase in its activity. This AT binding domain is present in only approximately one third of heparin molecules in commercial preparations, and it is this fraction that is critical for antithrombotic activity. The short AT binding domain is both necessary and sufficient to activate AT inhibition of factor Xa.[6] However, heparin inhibition of thrombin relies upon spatially distinct, simultaneous binding to both AT and thrombin. Both the presence of the pentasaccharide AT binding subunit and a minimum heparin chain length of at least 18 saccharide subunits are mandatory for this function. Once it has catalyzed AT inactivation of thrombin, the heparin molecule is released from the trimolecular complex and can promote further reactions.

These structural properties restrict the utility of heparin in the context of established thrombus. Thrombin already bound to clot is no longer accessible to the heparin-AT complex and remains active.[11] Activated platelets also release platelet factor 4 (PF4), which inhibits the activity of heparin.[12] The direct thrombin inhibitor hirudin and its derivatives do not have these limitations.[13–16]

Like thrombin bound to clot, factor Xa is protected from heparin-AT when part of the prothrombinase complex.[8] It is therefore resistant to both UFH and LMWH in this context. The new pentasaccharide AT activator fondaparinux sodium will suffer from similar limitations. Only direct inhibitors of factor Xa that are AT independent have the potential to overcome this obstacle.[13]

Low-Molecular-Weight Heparin

LMWH is derived from heparin mixtures by several different proprietary methods. By virtue of these varying methods, commercially available LMWH products are even more heterogeneous in composition than their parent heparin population. This means that the results of clinical trials using a particular LMWH agent cannot be applied to the other drugs of this class without independent validation.[12] Because of their shorter chain lengths, most of the species within a LMWH preparation cannot facilitate thrombin inactivation by AT. They act predominately through AT-mediated inhibition of factor Xa. Whereas almost 100% of the UFH molecules capable of interacting with factor Xa can also interact with thrombin, only 25–50% of LMWH molecules have sufficient length to interact with both factors.[8]

Direct Thrombin Inhibitors

Hirudin is a 65-amino-acid peptide derived from the salivary secretion of leeches that inhibits thrombin in a 1:1 essentially irreversible fashion. Hirudin does not inhibit any other coagulation cascade proteins. It inhibits thrombin through two binding domains without requiring any cofactors.[17] The carboxy terminal domain binds to thrombin's substrate binding site, and the second domain blocks thrombin's catalytic site.

Bivalirudin (Angiomax®, The Medicines Company, Parsippany, NJ) is a smaller synthetic protein containing hirudin's thrombin-binding carboxy terminal and a second 4-amino-acid sequence targeting thrombin's catalytic site.[18] Activity of hirudin and its derivatives is AT independent, is not inhibited by activated platelets, and can target thrombin bound to clot or endothelial cell surfaces.[14–16] This gives them a theoretically superior ability to inhibit the extension of established clot and to provide anticoagulation in the microvasculature. In experimental systems using animal models, these AT-independent thrombin inhibitors were superior to heparin in blocking thrombosis at sites of deep arterial injury.[13,19,20]

PHARMACOKINETICS

Heparin

The heterogeneity of heparin preparations complicates dosing. Wide variation of chain lengths in commercial preparations leads to mixed clearance kinetics. Longer molecules are cleared more rapidly through charge-based saturable binding to plasma proteins, cellular surfaces,

and the extracellular matrix. In contrast, shorter molecules persist longer in the circulation and are renally cleared with slower first-order kinetics.[8] The protein binding clearance mechanism predominates at doses across much of heparin's therapeutic range. This leads to low initial bioavailability with increasing dose until the saturation threshold is reached, followed by a rapid, unpredictable rise in serum concentration.[21–23] Because of the rapid clearance of larger molecules, over time a preponderance of shorter chain molecules are present, leading to a smaller proportion of molecules capable of inhibiting both factor Xa and thrombin.[8] Route of administration further complicates heparin pharmacokinetics. Intravenous (IV) injection is associated with both higher initial bioavailability and more rapid clearance. Subcutaneous administration leads to reduced and less predictable bioavailability but prolonged duration of action.[24]

Interpatient responses to a constant heparin dose further complicate bioavailability. Differences in patients' body mass, plasma protein levels, and endogenous heparins can lead to dramatic, unpredictable modification of heparin metabolism and antithrombotic activity. Intrapatient variability also confounds dosing. The response of a single patient to a fixed dose of heparin can fluctuate because of malignancy, pregnancy, infection, and inflammation. In addition, some individuals have decreased susceptibility to the anticoagulant effects of heparin, a phenomenon termed heparin resistance.[25]

Dosing nomograms are employed to optimize rapid achievement of therapeutic anticoagulation. In a randomized trial, Raschke et al demonstrated that patients treated with a weight-based dosing nomogram (80 units/kg body weight bolus followed by 18 units/kg per hour infusion) achieved therapeutic levels earlier and had a lower incidence of recurrent thromboembolism than patients treated with a standard care nomogram (5000-unit bolus, 1000 units per hour infusion).[26] Despite this, there has been limited success with dosing nomograms, in part because of interpatient variability and heparin resistance but also because of limitations in laboratory measurements. Such measurements are confounded by concomitant use of other drugs to prevent clot formation. The traditional measure of activated partial thromboplastin time (aPTT) demonstrates a high degree of interinstitutional variation and is not immediately available in an interventional setting. An alternative measure, the activated clotting time (ACT), is rapidly available but correlates only loosely with clinical outcome, and its validation has been primarily through uncontrolled retrospective studies.[12,27] Consequently, frequent monitoring of the aPTT, although fraught with its own problems, is widely used to adjust heparin doses to attain an acceptable therapeutic level.

Low-Molecular-Weight Heparin

Clearance of LMWH is almost entirely renal and displays linear kinetics. LMWH has a much higher bioavailability than UFH, ~90% of the administered dose, and a more predictable dose response.[28–32] This gives LMWH the advantage of being administered on a per kilogram basis in the subacute setting without a need for specific laboratory monitoring. However, the use of LMWH in patients with renal failure or morbid obesity is complicated by less predictable dosing and clearance kinetics.[33–35] Provided that the patient's weight or renal impairment remains stable, dose optimization needs to be performed only once.

Directly measuring the degree of anticoagulation with LMWH is more problematic than with UFH. The aPTT predominately measures thrombin inhibition and is therefore altered only at very high doses of LMWH. Patients receiving LMWH therefore pose a special problem because standard screening regiments do not reveal them to be anticoagulated.[36] Preliminary data obtained with dalteparin plus glycoprotein (GP) IIb/IIIa inhibitors in coronary studies suggest that thrombotic complications are increased with anti-Xa levels less than 0.6.[12,37] On the other hand, a higher degree of bleeding has been observed at steady-state anti-Xa levels greater than 0.8 IU/mL.[38–42] Although there are more specific anti–factor Xa assays, they are not widely available and demonstrate substantial intralaboratory variability. Furthermore, the recommendations for target degree of inhibition of Xa, although based on limited data,[12,43] are restrictive.

Hirudins

Bivalirudin is cleared through a combination of enzymatic cleavage and renal excretion. In studies to define an optimal dosing regimen, it demonstrated a predictable dose-response curve and good bioavailability.[11,44] Peak plasma concentrations are reliably attained within a few minutes of IV administration. The degree of anticoagulation can be assessed using the ACT, and there is much less variability in results than with heparin dosing. Given its renal route of excretion, adjustment should be made in the context of renal failure.[45]

REVERSAL OF ANTICOAGULATION

Heparin

In cases with severe heparin-associated bleeding or when rapid postintervention reversal of anticoagulation is desirable, protamine is the antidote of choice.[46] Protamine, a derivative of salmon sperm, binds to heparin, forming an inactive complex that is rapidly cleared, normalizing clotting times. Unfortunately, protamine can be associated with adverse, potentially fatal reactions

including systemic hypotension, anaphylaxis, and pulmonary vasoconstriction.[47] Prior exposure to protamine-containing insulin, vasectomy, and hypersensitivity to fish may be predictors of allergic response and justify steroid and antihistamine pretreatment.[48–50] Initial data from the Mayo Clinic indicate that methylene blue may be beneficial in the treatment of protamine-induced distributive shock, but therapy has otherwise been primarily supportive in nature.[47]

Low-Molecular-Weight Heparin

Reversal of LMWH with protamine is theoretically possible according to guidelines provided in the package insert. An initial dose of 1 mg protamine per 100 anti-Xa units is recommended, followed by a second dose of 0.5 mg per 100 units if blood loss is not controlled. However, compared with reversal of UFH, reversal of the LMWH anti-Xa action is incomplete and difficult to measure, complicating the care of a bleeding patient.[12]

Hirudins

There are currently no reversal agents for these newer, targeted antithrombin agents. This is potentially a major disadvantage, especially in procedures such as cardiopulmonary bypass where rapid reversal of anticoagulation is paramount. The danger of irreversible anticoagulation is theoretically even greater given the ability of the hirudin derivatives to inactivate thrombin even when it is bound to fibrin or endothelial surfaces.

SAFETY

Pregnancy

Unlike warfarin, heparin and LMWH do not cross the placenta and can be safely employed in pregnant women. Anticoagulants are often required in this hypercoagulable subpopulation, which is at an increased risk for deep venous thrombosis (DVT) and pulmonary embolism (PE). With comorbidities such as the antiphospholipid syndromes, administration of heparin is necessary to maintain a viable gestation. The proven safety of heparin in pregnancy, as well as limited opportunities to test new agents in this population of patients, means that its replacement by LMWH or other anticoagulants will be gradual if it occurs at all.[51,52]

Hemorrhage

HEPARIN

Because of difficulty in correlating dose with antithrombotic effect, clinicians run the risk of both undertreatment with resulting thromboembolism and overtreatment with consequent hemorrhage. The incidence of bleeding in venous thromboembolism has been extensively reported in randomized trials that have compared continuous IV heparin with intermittent IV heparin, IV heparin with subcutaneous heparin, and continuous IV heparin and oral anticoagulants compared with oral anticoagulants alone. Extensive data from these trials are beyond the scope of this article, but the rates of major bleeding with IV use of UFH range from 0 to 7% with fatal bleeding in 0 to 2%. For LMWH, the corresponding numbers are 0 to 3% and fatal bleeding in 0 to 0.8%.[53] Results of meta-analyses support the inference that compared with UFH, LMWH does not result in an increased risk of major bleeding. Similarly, the International Stroke Trial, which randomly assigned patients to aspirin, subcutaneous heparin, both, or neither, demonstrated that heparin was associated with a dose-dependent increase of both intracranial and extracranial bleeding that at higher doses offset any potential antithrombotic benefit.[54] Risk of heparin-associated bleeding correlates not only with dose[55] but also with adjunctive administration of additional thrombolytic or antiplatelet agents. Downward adjustment of previously established dosing regimens has proved necessary with the introduction of GP IIb/IIIa inhibitors to coronary angioplasty protocols.[56,57] Bleeding complications and transfusions still remain among the most costly adverse consequences of coronary interventions.[58] However, modified vascular access site management strategies in conjunction with reduced heparin dosing have led to reduced bleeding complication rates in successive coronary intervention trials.[59]

Avoidance of local bleeding complications previously relied upon delayed catheter removal and close monitoring of aPTT and ACT. The development of a variety of wound closure devices now permits more rapid arterial sheath removal than slower manual compressive techniques.[60]

LOW-MOLECULAR-WEIGHT HEPARIN

The growing number of patients receiving chronic subcutaneous LMWH at prophylactic or therapeutic doses complicates interventional radiology care. Interventionalists are faced with a population of patients in whom rapid reversal of anticoagulation is difficult if not impossible. Because of the challenge of measuring the degree of anticoagulation, current practice is based on the pharmacokinetics of these agents. In a patient who has just received prophylactic subcutaneous LMWH, a minimum delay of up to 8 hours prior to procedure initiation may be necessary to avoid increased bleeding risk.[36] Special caution should be taken in patients with epidural catheters given the risk of an epidural hematoma. LMWH should not be administered within 8 hours of epidural catheter insertion or removal.[61,62] A study of patients with acute coronary syndrome going for angioplasty found that preprocedure omission of

the therapeutic morning LMWH, enoxaparin sodium (Lovenox®, Aventis Pharmaceuticals, Bridgewater, NJ), dose led to a vascular complication rate equivalent to that with UFH use without the risk of rebound ischemia.[12] Failure to omit the morning enoxaparin dose led to a higher bleeding rate.[63] In a separate study, patients undergoing percutaneous coronary interventions while taking standard therapeutic dose enoxaparin were found to be at risk for access site hemorrhagic complications.[64] However, as discussed previously, the risk of major bleeding complications was otherwise similar to that with UFH.

Despite the potentially higher risk of minor hemorrhage with LMWH over UFH seen in earlier studies, the use of LMWH in an aggressive interventional practice may be cost saving because of ease of administration and elimination of frequent monitoring.[65] Work from the Coronary Revascularization Using Integrilin and Single bolus Enoxaparin Study found an equivalent bleeding rate in patients receiving enoxaparin and UFH in conjunction with GP IIb/IIIa inhibitors, even when vascular closure devices were used.[66] A similar safety profile was also found in a study that included noncardiac peripheral interventional procedures using enoxaparin and GP IIb/IIIa inhibitors.[67]

HIRUDINS

The availability of dosing optimization data and the stable dose-response curve of the hirudins have led to low bleeding rates, especially for bivalirudin. Most current data come from investigations in acute coronary syndrome therapy, in which bivalirudin appears to have a better safety profile than UFH.[68] In a pilot study comparing bivalirudin with historical heparin controls for percutaneous renal and iliac intervention, there was improvement in time to sheath removal and time to ambulation in all groups. An additional benefit of reduced length of stay was noted in the renal interventions.[69]

THERAPEUTIC USES

Treatment and Prophylaxis of Venous Thromboembolism

Heparin has been used in the treatment and prevention of venous thromboembolism and PE. A meta-analysis of 11 clinical trials involving treatment with either IV UFH (initial bolus of 5000 U followed by 30,000 to 35,000 U per 24 hours with aPTT monitoring) or subcutaneous LMWH found a mean incidence of recurrent venous thromboembolism of 5.4%, with major bleeding in 1.9%.[70] Heparin in a fixed low dose of 5000 U subcutaneously every 8 hours results in 60 to 70% risk reduction for venous thrombosis and fatal PE in surgical patients with a decrease in mortality to 0.2% compared with the 0.7% in controls.[71] Because of the need for frequent monitoring with UFH, alternative agents are being considered for this purpose. LMWH has been extensively compared with low-dose heparin and warfarin. A meta-analysis of UFH versus LMWH demonstrated no significant difference in efficacy or bleeding complications between the two drugs.[72] For massive PE thrombolysis in one study, the recommended adjunctive heparin regimen was first to achieve a target aPTT of 2 to 2.5 times normal. This aPTT was maintained throughout the procedure and was continued after pulmonary artery catheter removal, improving the outcome after treatment.[73]

Heparin and LMWH have also been used in vascular surgery patients. The value of continued postprocedure therapeutic heparin in patients after vascular surgical procedures is the subject of much debate and awaits the results of randomized clinical trials.[74] In one study, patients receiving postoperative anticoagulation with either IV heparin or subcutaneous enoxaparin as a bridge to warfarin therapy were found to have a lower incidence of graft thrombosis, failing graft, or débridement in the LMWH group.[75] In addition to postoperative states, heparin and in particular LMWH have been used in patients with prosthetic valves, mural thrombus, atrial fibrillation, and vertebral-basilar insufficiency.

Percutaneous Angioplasty and Stenting

HEPARIN AND ANGIOPLASTY

Much information on heparin and its analogs in percutaneous angioplasties and stenting is derived from the coronary literature. The role of heparin during percutaneous coronary angioplasty (PCA) continues to evolve. With most coronary angioplasties, postprocedure antiplatelet agents are superior to UFH or other drugs targeting the coagulation cascade.[8,76,77] When heparin is used, it is in combination with aspirin, thrombolytics, or GP IIb/IIIa inhibitors. Because of a higher risk of bleeding, the heparin dose is lower when other agents are simultaneously employed.[54] Accordingly, the initial bolus dose of heparin is 70 IU/kg, with additional boluses given to achieve a target ACT of >200 seconds and with removal of the arterial sheath after the procedure when the ACT is <150–180 seconds.[57] Bolus dosing trials with initial administration of as little as 2500–5000 IU of heparin have demonstrated a reasonable safety profile.[78,79] Use of weight-adjusted heparin therapy rather than simple bolus treatment has the advantage of more rapid postprocedure patient turnover but is otherwise not significantly different in outcome.[80] Most patients continue on postprocedure adjunctive antiplatelet therapy, and further heparin infusion is unnecessary[8] and may merely increase bleeding risk when used after uncomplicated coronary interventions.[76,77] Extensive data are not available for peripheral interventions and clinical regimens use extrapolated data with widespread use of

intraprocedural heparin, although heparin boluses are more frequently utilized.

LOW-MOLECULAR-WEIGHT HEPARIN

Dosing regimens are being developed for LMWH during PCA. An IV route is employed rather than subcutaneous administration. This route provides an earlier, higher peak anticoagulant activity during the procedure and a more rapid postintervention drop in anti-Xa activity, reducing bleeding risk.[12] Head-to-head trials comparing LMWH with UFH have been favorable to LMWH. The National Investigators Collaborating on Enoxaparin (NICE 1) study revealed equivalent or better outcomes of coronary interventions including stenting using 1 mg/kg enoxaparin IV compared with UFH historical controls.[81] The follow-up NICE 4 study involving enoxaparin at a reduced dose of 0.75 mg/kg in conjunction with the GP IIb/IIIa inhibitor abciximab again showed results at least as good as historic UFH + GP IIb/IIIa controls.[81] Less data are available for the other commercially available LMWHs. The REDUCE trial demonstrated equivalent efficacy and complication rate for bolus dosing with 7000 IU reviparin IV and UFH.[82] Dose-finding trials for dalteparin have been promising, with a dose of 60 IU/kg providing a balance between therapeutic peak anti-Xa activity and duration of action.[12]

HIRUDINS

Similarly, hirudin has been compared with UFH for the prevention of restenosis after PCA in a large European trial. Although hirudin use led to significantly lower early cardiac events, there was no difference in event-free survival at 7 months or in the incidence of restenosis.[83] The Bivalirudin Angioplasty Study showed that bivalirudin has a superior side effect profile when compared with UFH with equivalent therapeutic efficacy. Furthermore, in a subset of patients with unstable angina there were fewer adverse clinical events.[84,85] A multicenter trial that undertook sequential dose escalation to determine the appropriate dose demonstrated that at doses of 1.8–2.2 mg/kg it was possible to perform coronary angioplasty with an anticoagulant other than heparin in aspirin-pretreated patients.[86] Bivalirudin use in PCA is associated not only with fewer bleeding complications than with heparin but also with significant reductions in the cost of therapy.[58] A growing body of evidence supports the use of bivalirudin in acute coronary syndrome and in percutaneous coronary interventions for patients with unstable angina.[68,87] Although bivalirudin is presently not used in noncardiac interventions, its potential should be kept in mind.

HEPARIN AND STENTING

Anticoagulation is playing a particularly vital role in vascular stenting. Stenting in coronary and peripheral interventions is increasingly prevalent because of its proven clinical benefit,[88–90] with 60–80% of percutaneous coronary interventions now resulting in placement of one or more stents.[91] Acute management of stented vessels has evolved to the point that the majority of thrombotic complications do not occur until the subacute phase or later.[27] Although periprocedural use of heparin reduces early ischemic complications,[92,93] subacute complications in stented patients are much better controlled with antiplatelet agents than with heparin.[94] Of the antiplatelet agents, aspirin demonstrably reduces baseline adverse cardiovascular events, but only clopidogrel and ticlopidine have a proven role in reducing stent thrombosis.[95–97] There is no proven role for UFH or LMWH in reducing subacute restenosis on the basis of current data.[77,96]

The problem of late stent restenosis is now being addressed through the use of coated stents. The heparans and heparin are appealing candidates for this purpose given their antithrombotic properties and their ability to modulate inflammation and cellular proliferation. Initial results using heparin-coated Jostents in patients after acute myocardial infarction (AMI) appear promising,[98] although the data are limited and presently not widely accepted.

Thrombolysis

HEPARIN

Literature on thrombolytic therapy in AMI reveals different recommended heparin dosing regimens depending on the fibrinolytic agent selected. Based on the Thrombolysis in Myocardial Infarction (TIMI)-10B and Assessment of the Safety and Efficacy of a New Thrombolytic Regimen (ASSENT)-2 trials and also noted in the TIMI-9 and Global Use of Strategies to Open Occluded Coronary Arteries (GUSTO)-2 studies, lower doses of heparin with thrombolysis are associated with reduced rates of intracranial and major hemorrhage. In addition, guidelines for the management of AMI by the American College of Cardiology/American Heart Association recommend a new, lower dose of heparin with a bolus of 60 U/kg and an initial infusion of 12 U/kg/hr (up to 1000 U/hr).[11] Heparin administration can begin only when the aPTT < 70 seconds with an aPTT target of 50–70 seconds and therapy duration at least 48 hours.[11] A comparison of heparin dosing in multiple alteplase thrombolytic therapy trials for acute coronary syndrome revealed a need for concomitant early IV heparin to improve late infarct-artery patency.[11] Dosing level remains controversial for the variety of thrombolytics in use, and there is no evidence-based standard aPTT range for all thrombolysis protocols. In general, lowered dosing regimens in later trials were associated with a reduced risk of hemorrhage.[11]

LOW-MOLECULAR-WEIGHT HEPARIN

The ASSENT-3 PLUS ST elevation MI trial compared tenecteplase plus either enoxaparin or UFH. The lower early ischemic events in the LMWH group were offset by an increased intracranial complication rate in elderly patients, prompting recommendation of dose reduction in the aged.[99] The AMI-SK study demonstrated that in acute coronary syndrome patients receiving streptokinase, those also treated with enoxaparin rather than UFH had both better early angiographic patency and lower 30-day adverse events.[100] A different enoxaparin versus UFH study found a reduction in the combined adverse events of death, reinfarction, and unstable angina at 90 days with enoxaparin.[101] Multiple studies have demonstrated that enoxaparin is equivalent to UFH as an adjunct to thrombolysis in AMI.[102,103] An animal study of thrombolysis in AMI suggested that adding a GP IIb/IIIa inhibitor to enoxaparin might have additional benefit over LMWH alone, UFH alone, or UFH plus GP IIb/IIIa.[104] The ASSENT PLUS study of alteplase plus either dalteparin or UFH also showed lower early ischemic events with LMWH, but 30-day mortality or MI was identical.[105] Such studies portend an emerging role for LMWHs in all types of thrombolysis.

HIRUDINS

Early studies demonstrated that administration of direct thrombin inhibitors prior to thrombolysis dramatically improved early infarct artery patency.[106] These results are consistent with the unique ability of direct thrombin inhibitors to impair clot-bound thrombin activity. This finding led to optimism that direct thrombin inhibitors might outperform heparin as adjuncts to fibrinolysis. In the TIMI-5 trial a higher rate of reinfarction was observed with heparin than with desirudin (11.9% versus 4.3%). However, the later TIMI-9B trial failed to show any difference in the primary endpoint of death.[107,108] Another recombinant hirudin, lepirudin, also showed no benefit over UFH in the series of Hirudin for Improvement of Thrombolysis studies.[109,110]

Several small-scale studies evaluating streptokinase with bivalirudin versus UFH showed only trends toward greater early flow in the bivalirudin group.[111,112] A larger study, the Hirulog Early Reperfusion/Occlusion-2 trial, was designed to evaluate further the potential benefit of bivalirudin with streptokinase. It demonstrated a reduced rate of early reinfarction during treatment with bivalirudin compared with heparin but no change in 30-day mortality.[68] Use of bivalirudin with other thrombolytic agents awaits the results of further investigation.[87]

Although results for bivalirudin appear promising, substantial improvement in clinical outcomes with use of direct thrombin inhibitors over heparin has not been observed in fibrinolytic therapy for AMI.[11]

HEPARIN-SPECIFIC COMPLICATIONS

Systemic Hypotension

The vasodilatory effects of heparin deserve special emphasis, as clinically relevant hypotension has been reported in association with heparin bolus administration. In a study of patients receiving heparin bolus for coronary bypass, an average fall in mean arterial pressure of 12.5% occurred within 5 minutes of UFH administration. The drop in blood pressure was significant enough to prompt immediate treatment with vasoactive drugs in nearly one third of patients.[113]

Heparin-Induced Thrombocytopenia

Heparin-induced thrombocytopenia (HIT) occurs in 1–5% of patients treated with heparin and can occur immediately, although onset after several days of treatment is most common. HIT occurs as a consequence of anti-heparin/PF4 antibodies that activate platelets and are intensely thrombogenic. It is a life-threatening condition in which at least half of the patients develop arterial or venous thrombosis that can lead to amputation or death.[114] Diagnosis is based on the presence of HIT antibodies, fall in platelet count of $>50\%$, and cutaneous lesions at injection sites.[115,116] It is important to note that platelet counts may still remain within the normal range. Use of central venous catheters dramatically increases the risk of associated DVT in HIT patients.[117] Given their high risk of clot formation, it is recommended that patients with HIT receive antithrombotic therapy even in the absence of known thrombus. Treatment should continue until the platelet count has rebounded. Despite thrombocytopenia, petechiae and bleeding are not features of HIT, and platelet transfusion is not indicated. Anecdotal reports indicate that platelet transfusions may actually promote thrombosis.[118]

Although the incidence of HIT with LMWH therapy is lower, it can still occur, and LMWH is not recommended in patients with known HIT. Warfarin is contraindicated in these patients because of its early exacerbation of coagulation through inhibition of protein C synthesis. Direct antithrombin agents such as hirudin and its derivatives are useful.[114] The recombinant hirudin lepirudin has demonstrated efficacy for treatment of HIT-induced thrombosis, although bleeding risk is increased with treatment.[119] A loading dose of 0.4 mg/kg is given, followed by an adjustable infusion of $\sim$0.15 mg/kg/hr with an aPTT maintained at 1.5–2.5 times normal. For patients with HIT undergoing thrombolytic therapy with streptokinase or alteplase, this loading dose may be reduced to 0.1 mg/kg lepirudin.[11] Over time, these patients can generate antibodies against lepirudin, and therefore regular monitoring of aPTT is necessary.[120,121]

As an alternative to the hirudin derivatives, danaparoid sodium or argatroban (Novastan®, GlaxoSmithKline, Research Triangle Park, NC) can be employed.[8] Danaparoid sodium is an anti-Xa glycosaminoglycan mixture that is not targeted by HIT antibodies. Argatroban is a direct thrombin inhibitor derived from arginine. Although it is useful in patients with HIT, argatroban does not have proven benefit over heparin in clinical studies.[122]

Several commercially available tests can detect the HIT antibodies, permitting appropriate treatment planning in patients with a clinical history suspicious for HIT.[123,124] The antibody titer often fades over time, and when an undetectable titer is documented, heparin may be acutely employed for interventions in former HIT patients. UFH should be used only when the need for rapid postprocedure reversal with protamine is anticipated.[125] Otherwise, direct thrombin inhibitors remain the safest choice.

Heparin-Induced Osteoporosis

Clinical situations that require long-term use of UFH and LMWH, such as those involving pregnancy, recurrent thromboembolic events, and some immobilized patients, carry a risk of osteoporosis. Reductions in bone density have been observed in ~30% of patients, and symptomatic vertebral fractures occur in 2 to 3%.[8] LMWH seems to carry a lower risk than UFH. LMWH was compared with UFH in 80 patients with DVT. Six of the 40 patients who received UFH developed spinal fractures, compared with 1 patient in the LMWH group. These data as well as other studies reiterate the need to switch patients requiring long-term anticoagulation to oral anticoagulation or LMWH.

CONCLUSION

Heparin remains central to interventional radiology procedures because it is familiar, has a proven track record, and is inexpensive. Its greatest liability is its unpredictable dose response and potentially severe side effects. Interventional cardiologists are gradually replacing it with LMWH and more specifically with enoxaparin sodium. Concerns regarding risk of bleeding and the absence of a proven LMWH reversal agent have been greatly mitigated by encouraging safety data. More LMWH regimens are being developed because of its increasing popularity with both interventional cardiologists and radiologists.

The future for direct thrombin inhibitors is less certain. They remain tempting agents because of their homogeneity and specificity. Their role is well established in patients with HIT but is not yet proved for other applications. The most promising data exist for bivalirudin, but it will be several years before sufficient evidence accumulates to justify potentially the replacement of UFH. Development of a bivalirudin reversal agent would also facilitate this process.

The utility of hirudin and bivalirudin to interventional radiology is likely to be procedure specific. In cases in which there is already established clot, the unique ability of direct antithrombins to inhibit fibrin-bound thrombin may prove critical. However, in the majority of cases when antithrombotic drugs are being given prophylactically, the use of these newer agents is not yet justified. Further data regarding their safe use in conjunction with antiplatelet agents are also necessary before they can be more widely adopted.

To date, there is no perfect antithrombotic agent. Pending future drug development, clinicians will have to make do with their current armamentarium. They should do so in a systematic fashion using evidence-based medicine to optimize care. Unfractionated and low-molecular-weight heparins will remain vital components in their arsenal.

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