Current Anticoagulation Options in Percutaneous Intervention: Designing Patient-Specific Strategies

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Anticoagulation during percutaneous coronary intervention is critical to prevent abrupt and subacute closure. Although heparin has been the primary anticoagulant used for this purpose, a number of new drugs are now available. Low molecular weight heparin (LMWH) offers some advantages over unfractionated heparin, and clinical trials have shown its superiority. However, the longer half-life and lack of monitoring of LMWH make its use more difficult. The direct thrombin inhibitors also have been shown to have advantages in the treatment of patients with heparin-induced thrombocytopenia.

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There have been many important advances in coronary intervention, but the development of the coronary stent has been one of the most significant. It has been estimated that more than 70% of patients undergoing coronary intervention now receive a stent. The popularity of stents has grown not only because they significantly reduce restenosis, but also because of their ease of use and their reliable and predictable angiographic results.

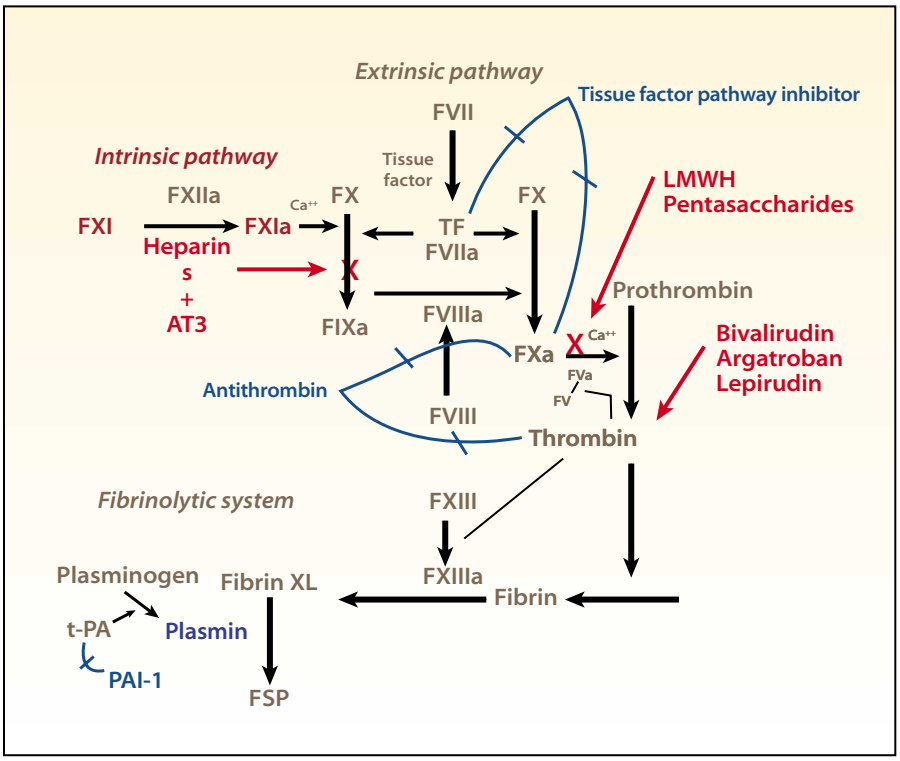

Figure 1. *The coagulation cascade. Heparin uses antithrombin (AT) as a cofactor. Low molecular weight heparin (LMWH) and fondaparinux inhibit factor (F) Xa. Bivalirudin, argatroban, and lepirudin directly inhibit thrombin. PAI, plasmin activator inhibitor; t-PA, tissue plasminogen activator; FSP, fibrin split products.*

Subacute stent thrombosis was recognized early as a major problem in coronary intervention. Initial trials suggested the need for aggressive antiplatelet and anticoagulant regimens, but with the development of new and effective antiplatelet agents such as clopidogrel, subacute stent thrombosis has been much less of a problem, occurring in only 1%–2% of patients. Current management includes the pretreatment of patients with aspirin, the use of high-dose unfractionated heparin (UFH) during the procedure (activated clotting time [ACT] > 300), and clopidogrel, as well as glycoprotein (GP) IIb/IIIa agents, if a stent is placed or the patient has acute coronary syndromes. The use of GP IIb/IIIa inhibitors has been previously reviewed extensively and will not be the subject of this review.[1]

The results of clinical trials of new anticoagulation regimens have provided many more options for the interventionalist.[2] This is highlighted by the recent American College of Cardiology/American Heart Association (ACC/AHA) unstable angina guidelines, which recommend low molecular weight heparin (LMWH) over traditional UFH in managing patients with acute coronary syndromes (a class IIA recommendation).[3] Although these new drugs offer some advantages, a more effective strategy is to treat individual patients according to the unique properties of the individual drugs, alone or in combination. Just as interventionalists select different stents based on artery and lesion characteristics, anticoagulant regimens should be individualized based on the patient's characteristics and the procedural results. In this review, the clinical trials of new anticoagulants in percutaneous coronary intervention (PCI) will be discussed, and recommendations for their use will be provided.

Heparin versus LMWH in Percutaneous Intervention

Advantages of LMWH

There are a number of potential advantages for the use of LMWH over UFH during interventional procedures. Balloon angioplasty and stenting denude the endothelium and injure the arterial wall, leading to platelet adhesion, aggregation, and thrombus formation. Heparin has been shown to inhibit this process.[4] Heparin binds antithrombin III and causes a conformational change, allowing antithrombin to inhibit factor IIa (thrombin) and factor Xa up to 1000-fold more effectively (see Figure 1). In addition, heparin activates platelets, stimulates antibody formation, and is associated with a prothrombotic rebound phenomenon.[5] There are, however, several important limitations to UFH. Dosing is difficult because of differences in preparation. Moreover, UFH has a narrow therapeutic window, making it difficult to achieve optimal anticoagulation without careful laboratory monitoring.

There was a significant reduction in the need for repeat urgent revascularization (P < .05) in patients who received enoxaparin compared to patients treated with UFH. More importantly, the major hemorrhagic complication rate was similar, at 2%, in both groups.

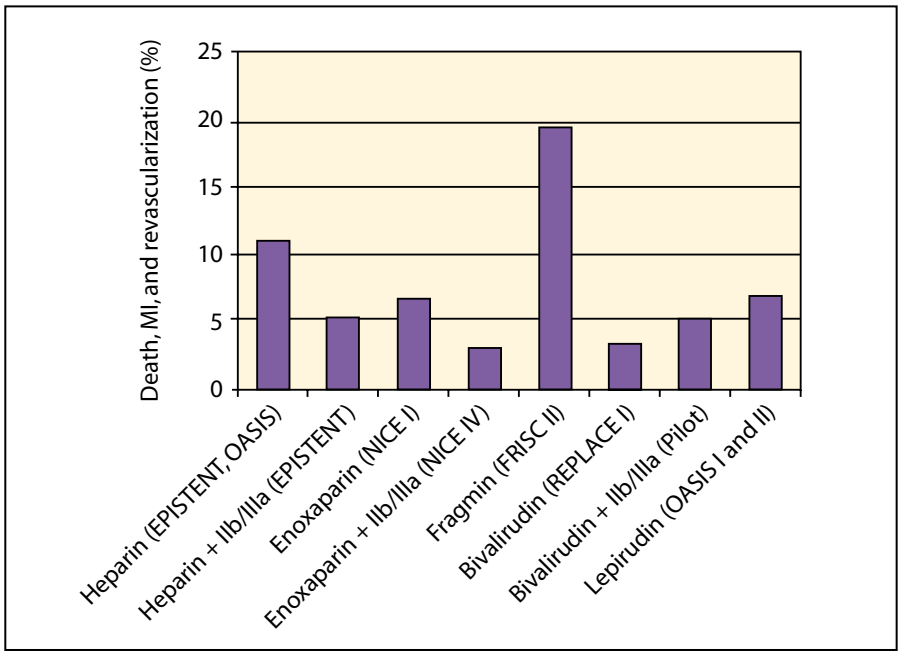

Figure 2. *Composite results of trials of anticoagulants with and without IIb/IIIa inhibitors in percutaneous coronary intervention. Data show comparisons of the major adverse cardiac events of death, myocardial infarction (MI), and revascularization at 30 days. EPISTENT, Evaluation of Platelet IIb/IIIa Inhibition in Stenting; OASIS, Organization to Assess Strategies for Ischemic Syndromes; NICE, National Investigators Collaborating on Enoxaparin; FRISC, Fragmin and Fast Revascularisation during InStability in Coronary artery disease; REPLACE, Randomized Evaluation in Percutaneous Coronary Intervention Linking Angiomax to reduced clinical events.*

LMWH has a molecular weight in the 4000–6500 dalton range, as opposed to UFH's average of 15,000 daltons. The lower molecular weight allows LMWH to bind factor Xa more effectively and more potently, with an anti-Xa:anti-IIa ratio of 2:1 to 4:1.[6] Also, the bioavailability of LMWH for subcutaneous injection is 90%, as opposed to 30% for UFH.[7] Because LMWH binds factor Xa more than factor IIa, monitoring partial thromboplastin time (PTT) is not helpful in dosing; however, LMWH's lower cellular and protein binding and longer half-life result in a predictable response, which eliminates the need for laboratory monitoring. Compared to UFH, LMWH is less inhibited by platelet factor-4 that is released by activated platelets, and it has a greater capacity to release the coagulation inhibitor, tissue factor pathway inhibitor. One recent study also showed that LMWH releases lower amounts of von Willebrand factor than does UFH.[8] LMWH also reduced the incidence of heparin-induced antibodies and thrombocytopenia.[5-6]

Clinical Trials

A number of clinical trials have shown the superiority of LMWH in managing acute coronary syndromes, and the recent ACC/AHA guidelines support its use in high-risk individuals (see Figure 2).[3] However, its safety and efficacy during PCI is less well established.[7,9] The Efficacy and Safety of Subcutaneous Enoxaparin in Non-Q wave Coronary Events (ESSENCE) trial showed that the LMWH enoxaparin (1 mg/kg given subcutaneously every 12 hours), is superior to UFH in the management of unstable angina.[10] In this trial, 142 patients underwent urgent PCI. There was a significant reduction in the need for repeat urgent revascularization ($P < .05$) in patients who received enoxaparin compared to patients treated with UFH. More importantly, the major hemorrhagic complication rate was similar, at 2%, in both groups. There were no episodes of abrupt vessel closure in the enoxaparin group. The anti-factor Xa ratio was reproducibly greater than 1.0 IU/mL up to 8 hours after the last subcutaneous injection, which is consistent with adequate anticoagulation. For those patients who received the last dose between 8 and 12 hours, a booster dose of 0.3 mg/kg intravenously (IV) can be used to ensure adequate anticoagulant efficacy.[7]

The Enoxaparin and Ticlopidine after Elective Stenting (ENTICES) trial compared aspirin and warfarin with enoxaparin and ticlopidine following elective stenting. Not surprisingly, the ticlopidine and enoxaparin regimen was superior.[11]

The National Investigators Collaborating on Enoxaparin (NICE) performed two important studies investigating the safety and efficacy of enoxaparin with and without the platelet GP IIb/IIIa inhibitor abcximab. The NICE I trial was a nonrandomized study examining 827 patients undergoing PCI who were given enoxaparin 1 mg/kg IV immediately prior to an intervention.[12] The results showed that enoxaparin yielded similar outcomes compared to the Evaluation of Platelet IIb/IIIa Inhibition in Stenting (EPISTENT) stent-placebo cohort. The NICE IV

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Table 1
Comparison of Properties of Heparin and Anti-Xa Agents

	UFH	Enoxaparin	Dalteparin	Nadroparin	Fondaparinux
Trade name	—	Lovenox*	Fragmin†	Fraxiparine‡	—
Molecular weight (daltons)	15,000	4500	6000	4500	1700
Binds AT III	Yes	Yes	Yes	Yes	Yes
Anti-Xa:anti-IIa ratio	1.0	3.3	2.0	3.0	1000
Bioavailability (%)	30	91	87	98	100
Half-life (hours)	0.15	4.00–6.00	4.00	2.00–4.00	15.18
HIT (%)	1.0–2.0	0.1	0.1	0.1	0.0

UFH, unfractionated heparin; AT III, antithrombin III; HIT, heparin-induced thrombocytopenia.
* Aventis Pharmaceuticals, Inc., Bridgewater, NJ
† Pharmacia Corporation, Peapack, NJ
‡ Sanofi-Synthelabo, Paris, France

trial examined 817 patients receiving enoxaparin at 0.75 mg/kg IV combined with standard-dose abciximab.[13] There were no discernible increases in bleeding, and an additional benefit was observed when abciximab was added to enoxaparin.

More prospective, randomized data will be obtained from the ongoing Superior Yield of the New Strategy of Enoxaparin, Revascularization and Glycoprotein IIb/IIIa Inhibitors (SYNERGY) trial, which is evaluating the efficacy of LMWH versus UFH combined with GP IIb/IIIa inhibitors in high-risk patients.[14] The patients will be given 1.0 mg/kg of enoxaparin every 12 hours or dalteparin 120 IU/kg every 12 hours. If PCI is performed within 8 hours of the last dose of LMWH, then no further enoxaparin or dalteparin will be given. If the procedure is performed between 8 and 12 hours, then a 0.3 mg/kg "booster" dose of enoxaparin or a 40 IU/kg dose of dalteparin will be given IV at the time of PCI. Conversely, patients in the 8–12 hour range may be switched over to UFH at 50 U/kg with IIb/IIIa inhibition and 60 U/kg without inhibition. The primary endpoint will be major adverse cardiac events (MACE), which will be measured at 30 days, 6 months, and 1 year.[7]

Separate But Not Equal

The two currently available LMWHs, enoxaparin and dalteparin, are pharmacologically different from each other and have had differing clinical results in randomized trials. They differ in their molecular weights; dalteparin has a molecular weight of 4000–6000, a lower anti-Xa:IIa ratio, and different pharmacokinetics (Table 1).[15] As mentioned above, the ESSENCE and Thrombolysis in Myocardial Infarction (TIMI)[14] trials both showed superiority of enoxaparin over UFH in patients with acute coronary syndromes. In contrast, the Scandinavian study, Fragmin and Fast Revascularisation during InStability in Coronary artery disease (FRISC) II, comparing dalteparin with UFH in the management of unstable angina and non-Q wave myocardial infarction (MI), showed no difference in effectiveness between dalteparin (Fragmin) for 3 months postprocedure and standard UFH during the angioplasty procedure and placebo.[15] Although both dalteparin and standard UFH significantly reduced death and MI at 6 days, this reduction lost significance at 40 days.[16] The study also evaluated the benefit of an early invasive strategy compared with a conservative strategy and found that after 6 months the early invasive strategy had a composite endpoint of death and MI of 9.4% compared to 12.1% in the conservative arm. These studies would suggest that not all LMWHs are the same.

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A recently published study examined the effects of varying doses of dalteparin with abciximab. The 60 IU/kg plus standard-dose abciximab appeared comparable to the UFH and abciximab group in Evaluation in PTCA to Improve Long-Term Outcome with Abciximab GP IIB/IIIa Blockade (EPILOG), but the 40 IU/kg group had a disturbing 11% periprocedural thrombosis rate.[17]

The Reviparin in a Double-Blind

Unfractionated Heparin Placebo Controlled (REDUCE) trial examined the effect of reviparin, another LMWH, versus that of UFH on restenosis after angioplasty.[18] Although reviparin did not reduce restenosis, major bleeding and major adverse cardiac events (effects that would be expected with such a drug) were similar in both groups, despite the use of reviparin for 28 days after the procedure.

The Role for Direct Thrombin Inhibitors

The U.S. Food and Drug Administration has approved three direct thrombin inhibitors for use in coronary intervention. One possible benefit of these agents over LMWH is that they prolong the ACT, allowing monitoring of the dose as is the case with UFH. Bivalirudin has been approved for high-risk angioplasty, and hirudin and argatroban have been approved for heparin-induced thrombocytopenia.[19] One advantage of the direct thrombin inhibitors is that they inhibit bound as well as free thrombin. Hirudin and bivalirudin are isolated from the salivary glands of the medicinal leech. Hirudin forms a slowly reversible complex with thrombin and is a more powerful inhibitor of thrombin than is bivalirudin. Hirudin has been evaluated in unstable angina and non-Q wave MI. In the Global Use of Strategies to Open Occluded Coronary Arteries (GUSTO) IIB study and Organization to Assess Strategies for Ischemic Syndromes (OASIS) 2 study, the added benefit of hirudin over heparin was not impressive. Hirudin had either a transient or small benefit that was offset by increased bleeding episodes.[20,21] However, in a meta-analysis of 11 randomized trials (35,970 patients), all antithrombins demonstrated a significant reduction in death or MI compared to that for heparin.[22]

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As it is metabolized by the liver, argatroban has an important application in renal patients and in patients with heparin-induced thrombocytopenia. In our experience, the bolus dose should be cut at least in half, as over-anticoagulation is the rule rather than the exception when the standard dose is used in renal failure.

Bivalirudin (hirulog; Angiomax [BenVenue Laboratories, Bedford, OH]) has been evaluated in approximately 8700 patients for a variety of antithrombotic indications.[23] Although this drug was originally thought to carry excessive bleeding risk, the opposite result has been demonstrated. In a recent randomized trial involving 4312 patients undergoing percutaneous intervention, Angiomax reduced the incidence of clinical ischemic events and, surprisingly, decreased the risk of major bleeding.[23] The Comparison of Abciximab Complications with Hirulog for Ischemic Events Trial (CACHET) showed that hirulog (1 mg/kg bolus followed by a 2.5 mg/kg/hr infusion for 4 hours) was safe with full-dose abciximab in 30 patients. The investigators concluded that "bivalirudin with planned or provisional abciximab may be at least as safe and effective as low-

Main Points

- An estimated 70% of patients undergoing percutaneous coronary intervention (PCI) now receive stents. Subacute stent thrombosis was recognized early as a major problem.
- New anticoagulation regimens provide many more options for the interventionalist, allowing anticoagulant regimens to be individualized based on the patient's characteristics and the procedural results.
- A number of clinical trials have shown the superiority of low molecular weight heparin (LMWH) over unfractionated heparin (UFH) in managing acute coronary syndromes, and recent ACC/AHA guidelines support its use in high-risk individuals. However, the safety and efficacy of LMWH during PCI is less well-established.
- The U.S. Food and Drug Administration has approved three direct thrombin inhibitors: bivalirudin for high-risk angioplasty, and hirudin and argatroban for heparin-induced thrombocytopenia.
- A possible benefit of direct thrombin inhibitors over LMWH is that they prolong the activated clotting time, allowing monitoring of the dose.
- Fondaparinux, a synthetic oligosaccharide, has been shown in clinical trials to be more effective than LMWH in patients with deep vein thrombosis.

dose heparin plus abciximab during percutaneous coronary intervention." The Randomized Evaluation in Percutaneous Coronary Intervention Linking Angiomax to reduced clinical events (REPLACE) I study demonstrated that bivalirudin (0.75 mg/kg bolus followed by a 1.75 mg/kg/hr infusion during the procedure) was safe to use in "routine" interventional patients and demonstrated reduced adverse events and major bleeding compared to heparin.[24] The REPLACE II study is underway and will examine whether bivalirudin alone is comparable to heparin plus abciximab. Because of its apparent increased efficacy and safety, bivalirudin should be considered in the high-risk patient.

Pentasaccharides

Fondaparinux, a synthetic oligosaccharide, has recently been introduced. This agent, like other heparins, inhibits Xa, but it has even more specificity for Xa than either LMWH or UFH has and binds irreversibly. It also does not interact with platelet factor-4 and does not promote heparin-induced thrombocytopenia. In four phase III trials randomizing 7344 patients and in the Rembrandt study, fondaparinux has been shown to be more effective than LMWH in patients with deep vein thrombosis.[25] In addition, the early clinical trials STEMI (ST segment Elevation Myocardial Infarction), PENTALYSE (Pentasaccharide as an Adjunct to Fibrinolysis in ST-Elevation Acute Myocardial Infarction),[26] and PENTUA (Pentasaccharide in Unstable Angina)[27] suggested that this agent is at least as effective as enoxaparin in patients with a lower bleeding rate. The PICASSO trial will evaluate the effectiveness and safety of fondaparinux in 16,000 patients with acute MI or acute coronary syndromes. A substudy will also evaluate the benefit in patients undergoing PCI.

Current Recommendations

In addition to the use of aspirin and clopidogrel, the above evidence would suggest the following recommendations for the use of anticoagulants during PCI:

Low Molecular Weight Heparin

1. Use enoxaparin (Lovenox) (1 mg/kg subcutaneous b.i.d.) rather than UFH for unstable angina and non-ST segment elevation myocardial infarction (NSTEMI) patients who are admitted to a monitored unit.
2. When the patient is taken to the catheterization laboratory, check the medication sheet to determine when the last dose of Lovenox was given. If it was given less than 8 hours ago, then proceed with the intervention without a booster dose. If the time frame is greater than 8 hours and less than 12 hours, then use an additional 0.3 mg/kg IV bolus of Lovenox. Alternatively, you can use UFH at 50 U/kg IV. If the last dose was given more than 12 hours ago, then give Lovenox 1 mg/kg IV or use UFH in the standard fashion. Use of the GP IIb/IIIa inhibitor abciximab (ReoPro, Eli Lilly and Company, Indianapolis, IN) should be considered as the clinical situation dictates.
3. If the patient comes into the emergency room with unstable angina or NSTEMI and you want to proceed directly to the catheterization laboratory, then give 1 mg/kg of Lovenox IV with a GP inhibitor and proceed with the intervention. The SYNERGY trial will offer more data concerning this strategy. Alternatively, standard UFH and GP inhibition can be used. We would recommend the use of enoxaparin, as the results with dalteparin have been disappointing. The SYNERGY trial may yield more information about the use of dalteparin in PCI. Alternatively, standard UFH and a GP inhibitor can be used.
4. Wait at least 4 hours after the last dose of LMWH before removing the sheath. If a closure device can be used, then the artery may be closed after the procedure.
5. Discontinue LMWH at least 8 hours prior to performing coronary artery bypass grafting.

Thrombin Inhibitors

1. Consider using bivalirudin (Angiomax) in patients who have high-risk lesions or who are at a high risk of bleeding complications. The REPLACE II results will help to determine if Angiomax is superior to UFH and a GP IIb/IIIa inhibitor.
2. Use argatroban or bivalirudin in the setting of heparin-induced thrombocytopenia. Use argatroban with a reduced bolus in the renal-failure patient. ■

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