Practical Guidelines for the Use of Anticoagulants in the Catheterization Laboratory

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Optimal treatment of patients during percutaneous coronary interventions (PCIs) is constantly changing as clinical trials provide new and clinically relevant information. Clinicians need to be aware of this information to incorporate these new strategies into clinical practice, leading to improvements in the care of patients. The direct thrombin inhibitor, bivalirudin, will play an increasingly important role as the primary anticoagulant for PCIs because it meets the criteria as a safer, cost-effective, and convenient agent in a spectrum of clinical scenarios. This article will provide practical guidelines to assist the interventional cardiologist to prepare his or her patient for PCI and will focus on some of the more common and more difficult patient cohorts, in particular those patients with chronic kidney disease as well as the elderly, 2 of the fastest growing groups of patients undergoing PCI.
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Optimal treatment of patients in the catheterization laboratory remains a moving target as clinical trials provide new and clinically relevant information. This information then needs to be placed into a format and context that will allow the clinician to incorporate these new strategies into clinical practice leading to improvements in the care of our patients. The early deployment of these data-based enhancements of care will be determined not only by their safety and clinical effectiveness but also by their convenience and cost effectiveness.

Since the early days of coronary stent implantation, there has been a focus on the importance of platelets in the pathophysiology of thrombotic complications. This has led us to become familiar with the mechanisms of action, efficacy, and safety of a host of antiplatelet agents including aspirin, thienopyridines, and intravenous glycoprotein (GP) IIb/IIIa receptor antagonists. However, the stage is now being shared by the anticoagulants as we have recently come to realize that their unique pharmacologic properties may influence safety, efficacy, and ease of use, such as in the platelet-activating effects of unfractionated heparin (UFH) as well as its role in heparin-induced thrombocytopenia (HIT), the pharmacokinetics of low-molecular-weight heparin (LMWH) in patients with chronic kidney disease, and the unique properties of the direct thrombin inhibitor (DTI), bivalirudin. What is clear based on clinical data is that the direct thrombin inhibitor, bivalirudin, will play an increasingly important role as the primary anticoagulant for percutaneous coronary interventions (PCIs) because it meets the criteria as a safer, cost-effective, and convenient agent in a spectrum of clinical scenarios. This article will provide practical guidelines to assist the interventional cardiologist to prepare his or her patient for PCI and will focus on some of the more common and more difficult patient cohorts, in particular those patients with chronic kidney disease as well as the elderly, 2 of the fastest growing groups of patients undergoing PCI.

Pre-Intervention

The preparation of the patient for PCI involves minimizing thrombotic and hemorrhagic complications. From early studies,[1] the use of aspirin has been shown to be effective in reducing acute thrombotic complications after PCI. It has not been determined with a high degree of certainty what dose of aspirin between 81 and 325 mg is optimal; however, pre-treatment with aspirin at least 2 hours in advance of the PCI has been recommended.

With the development and popularization of coronary stent implants, preventing acute, subacute, and late thrombosis has become a high priority. In the Intracoronary Stenting and Antithrombotic Regimen (ISAR) trial,[2] the primary endpoint of cardiac death, myocardial infarction, coronary artery bypass surgery, or repeat angioplasty was reduced 75% with the use of a thienopyridine (ticlopidine) plus aspirin versus aspirin alone. In the STARS (STent Anti-thrombotic Regimen Study) trial,[3] the 30-day primary endpoint of death, target lesion revascularization, and subacute thrombosis or MI was reduced by 85% when ticlopidine was added to aspirin compared to aspirin alone (Figure 1).

Ticlopidine has been replaced by clopidogrel due to its more rapid onset of action as well as a reduced incidence of both neutropenia and thrombocytopenia.[4] The ability of clopidogrel combined with aspirin to provide effective platelet inhibition, particularly when it is used in conjunction with UFH with its associated platelet aggregatory effects, is limited in the acute setting by the interval necessary to achieve clinically relevant platelet inhibitory effects 6 to 24 hours post-bolus[5] and by the more recently recognized phenomenon of clopidogrel resistance.[6] With this in mind, it would seem prudent to reduce reliance on agents such as UFH that have platelet pro-aggregatory effects. The DTIs, including bivalirudin, do not share the platelet aggregatory attributes of UFH.

Peri-Intervention

Unfractionated Heparin

Although the use of UFH has been part of the catheterization landscape for many years, newer agents, such as bivalirudin, are becoming increasingly used due to their enhanced safety and maintained efficacy. Intravenous UFH prevents clot formation at the site of arterial injury[7] and on coronary guidewires and catheters used for coronary angioplasty.[8] The 2005 ACC/AHA/SCAI practice guidelines give the use of UFH a class I indication, which stipulates that there is "general agreement that a given procedure or treatment is beneficial, useful, and effective"

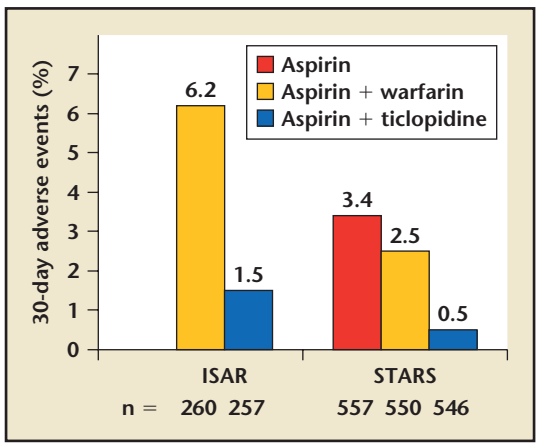


Figure 1. *Randomized trials with stents. Comparison of results of ISAR and STARS trials regarding adverse events with use of aspirin, aspirin plus warfarin, and aspirin plus ticlopidine. In the ISAR trial, the primary endpoint of cardiac death, myocardial infarction, coronary artery bypass surgery, or repeat angioplasty was reduced 75% with the use of the thienopyridine (ticlopidine) plus aspirin versus aspirin alone. In the STARS trial, the 30-day primary endpoint of death, target lesion revascularization, and subacute thrombosis or myocardial infarction was reduced by 85% when ticlopidine was added to aspirin compared to aspirin alone. ISAR, Intracoronary Stenting and Antithrombotic Regimen; STARS, STent Anti-thrombotic Regimen Study. Data from Schömig A et al[2] and Leon MB et al.[3]*

despite a level of evidence C that is consistent with "only consensus opinion of experts, case studies, or standard of care" and therefore not derived from randomized trial data.[9] Shortcomings of UFH include direct platelet activation[10,11] and inability to inactivate clot-bound thrombin.[12]

Empiric recommendations regarding heparin dosage during coronary angioplasty have been proposed,[13,14] but activated clotting time (ACT) levels after a fixed dose of UFH may vary substantially due to differences in body size,[15] concomitant use of other medications, including intravenous nitroglycerin,[16,17] and the presence of acute coronary syndromes that increase heparin resistance. This certainly does not allow for a consistent dose-response effect, leading to an unpredictable therapeutic response. The relationship between the level of the ACT and development of ischemic complications during coronary angioplasty has been controversial. Whereas some studies have identified an inverse relationship between the initial ACT and the risk of ischemic events,[18,19] others found either no relationship or a direct relationship between the degree of anticoagulation and occurrence of complications.[20] It is generally believed that very high levels (ACTs greater than 400 to 600 seconds) of periprocedural anticoagulation with UFH are associated with an increased risk for bleeding complications.

In those patients who do not receive GP IIb/IIIa inhibitors, sufficient UFH should be given during coronary angioplasty to achieve an ACT of 250 to 300 seconds with the HemoTec device and 300 to 350 seconds with the Hemochron device. A weight-adjusted bolus of heparin (70 to 100 IU per kg) can be used to avoid excess anticoagulation. If the target values for ACT are not achieved after a bolus of UFH, additional boluses (2000 to 5000 IU) can be given. Early sheath removal should be performed when the ACT falls to less than 150 to 180 seconds. The UFH heparin bolus should be reduced to 50 to 70 IU/kg when GP IIb/IIIa inhibitors are given to achieve a target ACT of 200 seconds with either the HemoTec or Hemochron device.

Low-molecular-weight heparins demonstrate less platelet activation and protein binding than unfractionated heparin.

Low-Molecular-Weight Heparin

There has been interest in replacing UFH with LMWH as an anticoagulant during PCI. LMWHs demonstrate less platelet activation and protein binding than UFH.[21] But like UFH, the LMWHs cannot inhibit clot-bound thrombin or platelet-bound factor Xa within the prothrombinase complex.[22,23] It was hoped that the more consistent dose-response effect of LMWH would provide clinical benefit over UFH in patients undergoing PCI. Unfortunately, clinical trials have not shown a superiority of LMWH compared to UFH in patients undergoing PCI. In the Superior Yield of the New strategy of Enoxaparin, Revascularization, and Glycoprotein IIb/IIIa Inhibitors study (SYNERGY), a large, multicenter, randomized trial comparing enoxaparin to UFH in patients with acute coronary syndromes undergoing PCI, there was no difference in the 30-day rates of death and myocardial infarction with slight excess bleeding in the enoxaparin group.[24]

In patients who have received subcutaneous enoxaparin (1 mg/kg twice daily) for the treatment of non–ST-segment elevation MI and are to undergo PCI within 8 hours of the last subcutaneous dose, no additional anticoagulant should be administered. In those who undergo PCI 8 to 12 hours after the last subcutaneous dose, an additional intravenous dose of 0.3 mg/kg should be administered immediately before device activation. LWMHs have little effect on measurements of ACT and should not be used as a guide to anticoagulation therapy in these patients. Sheath removal followed by manual groin compression may be performed 4 hours after the last intravenous dose of enoxaparin or 6 to 8 hours after the last subcutaneous dose of enoxaparin.[25,26]

There was no clear explanation for the increased bleeding complication rate when there was a crossover from either unfractionated heparin or low-molecular-weight heparin prerandomization to the other heparin in the SYNERGY trial.

An observation of some concern and with no clear explanation was the increased bleeding complication rate when there was a crossover from either UFH or LMWH prerandomization to the other heparin in the SYNERGY trial (Figure 2). In addition, the SYNERGY trial excluded patients with creatinine clearance (CrCl) less than 30 mL/min; therefore, it was not able to provide guidance for use in patients with severe and endstage chronic kidney disease.

Because there does not seem to be any significant benefit in terms of safety and efficacy despite increased

	Enoxaparin	Unfractionated Heparin	Hazard Ratio (95% CI)
Prerandomization Antithrombin Therapy			
No prerandomization antithrombin therapy, No.	1212	1228	
Death or MI at 30 days, No. (%)	152 (12.6)	181 (14.8)	0.84 (0.68–1.06)
Any transfusion, No. (%)	205 (16.9)	212 (17.3)	
Prerandomization enoxaparin only, No.	2186	2108	
Death or MI at 30 days, No. (%)	298 (13.6)	276 (13.1)	1.4 (0.88–1.23)
Any transfusion, No. (%)	369 (16.9)	309 (14.7)	
Prerandomization unfractionated heparin only, No.	1428	1512	
Death or MI at 30 days, No. (%)	216 (15.2)	252 (16.7)	0.89 (0.74–1.08)
Any transfusion, No. (%)	253 (17.7)	253 (16.7)	
Both agents, No.	167	137	
Death or MI at 30 days, No. (%)	30 (18.1)	13 (9.5)	2.0 (1.03–3.90)
Any transfusion, No. (%)	23 (13.8)	22 (16.1)	
No Prerandomization Antithrombin Therapy or Postrandomization Therapy Same as Prerandomization Therapy			
No.	3398	2740	
Death or MI at 30 days, No. (%)	450 (13.3)	433 (15.9)	0.82 (0.72–0.94)
Any transfusion, No. (%)	574 (16.9)	465 (17.0)	
Postrandomization Crossovers*			
No crossover			
No.	4400	4780	
Death or MI at 30 days, No. (%)	593 (13.5)	677 (14.2)	
Crossover			
No.	593	205	
Death or MI at 30 days, No. (%)	103 (17.4)	45 (22.0)	
Any transfusion, No. (%)			
No crossover	671 (15.3)	724 (15.1)	
Crossover	179 (30.2)	72 (35.1)	

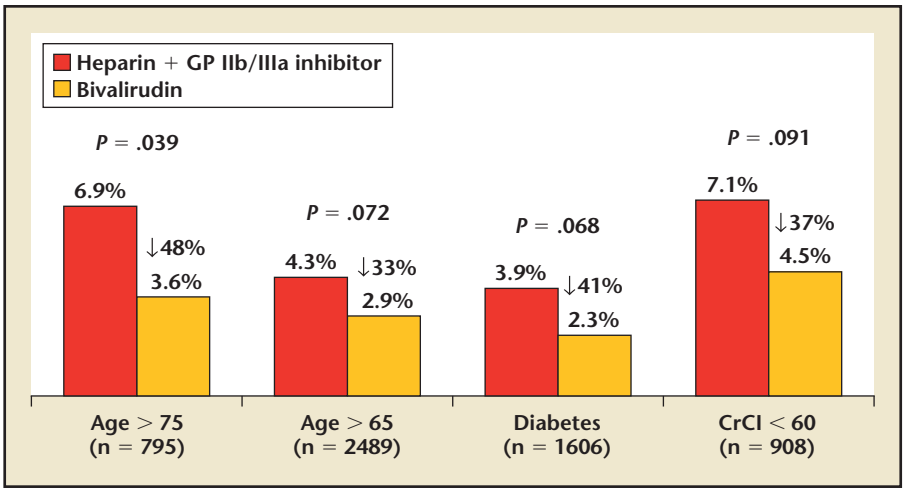
Figure 2. *SYNERGY trial. Outcomes by pretreatment antithrombin therapy and postrandomization crossover. An observation of some concern and with no clear explanation was the increased bleeding complication rate when there was a crossover from either UFH or LMWH prerandomization to the other heparin in the SYNERGY trial. *For enoxaparin, crossover/no crossover hazard ratio (95% CI) is 0.95 (0.85-1.06). For unfractionated heparin, no crossover/crossover hazard ratio (95% CI) is 0.76 (0.53-1.09). MI, myocardial infarction; SYNERGY, Superior Yield of the New strategy of Enoxaparin, Revascularization, and Glycoprotein IIb/IIIa Inhibitors. Reproduced with permission from Ferguson JJ et al.[24]*

cost, the possibility of an increased risk of bleeding in patients who crossover from UFH to LMWH and visa versa, and lack of clinical data in patients with significant chronic kidney disease, it would not be anticipated that the use of currently approved LMWHs will replace UFH for use in most patients undergoing PCI.

Direct Thrombin Inhibitor: Bivalirudin

Bivalirudin is a direct thrombin inhibitor with a short half-life (25 minutes) providing "fast-on, fast-off" activity. It neutralizes both circulating (free) and clot-bound thrombin, which limits the explosive burst of thrombin generation, and it inhibits thrombin-mediated platelet activation; therefore it does not promote coagulation. Because bivalirudin does not generate heparin antibodies, it poses no risk of heparin-induced thrombocytopenia or thrombosis syndrome, and it offers a predictable dose response, thus requiring no continuous ACT monitoring. It has also been shown to be safe in a variety of high-risk populations, including patients with chronic kidney disease (CKD) or diabetes mellitus and the elderly. The Randomized Evaluation of PCI Linking Angiomax to Reduced Clinical Events (REPLACE)-2 study, a randomized, double-blind, multi-center trial, involved 6010 patients undergoing elective and urgent stenting, angioplasty, or atherectomy between October 2001 and August 2002.[27] Patients were randomized to receive bivalirudin plus provisional GP IIb/IIIa inhibitor or heparin plus routine GP IIb/IIIa inhibitor. There was a significant reduction in the rate of major bleeding in the bivalirudin arm of the study (4.1% vs 2.4%, $P < .001$) despite no significant difference in ischemic complications at the 30-day endpoint, and a trend to a significant reduction in mortality at the 1-year endpoint from 2.5% to 1.9%. In addition, the primary endpoint of

Figure 3. *1-year mortality—high-risk patients: death rates among elderly, diabetic, renally impaired patients. Patients were randomized to receive bivalirudin plus provisional GP IIb/IIIa inhibitor or heparin plus routine GP IIb/IIIa inhibitor; there was a significant reduction in the rate of major bleeding in the bivalirudin arm of the study (4.1% vs 2.4%, P < .001) despite no significant difference in ischemic complications at the 30-day endpoint, and a reduction in mortality at the 1-year endpoint from 2.5% to 1.9%. GP, glycoprotein; CrCl, creatinine clearance. Data from Lincoff A et al,[27] Stone GW,[28] and The Medicines Company, Data on file.*



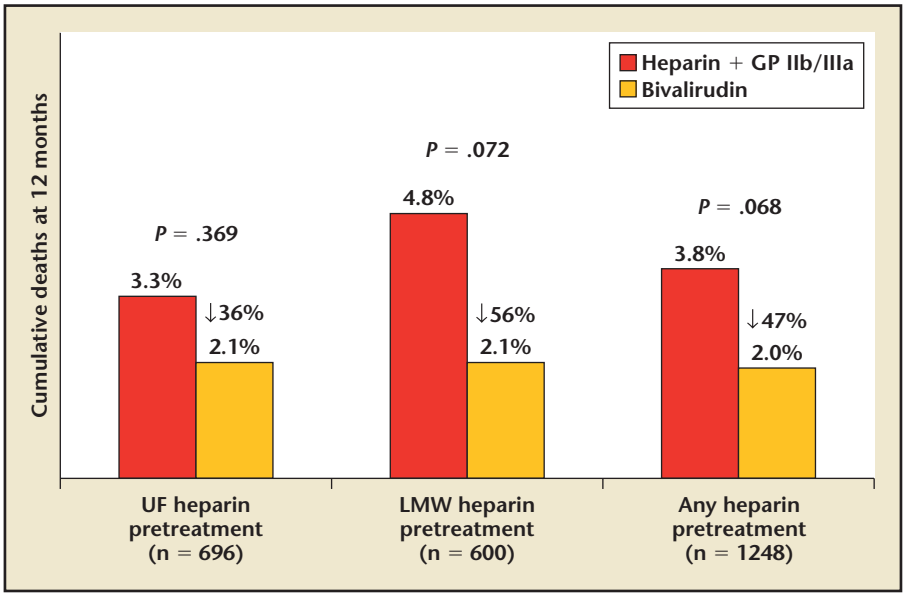


Figure 4. *1-year mortality—prior heparin: death rates in patients treated with "upstream" heparin or LMWH. In contradistinction to the observations of the SYNERGY trial with LMWH, the safety of bivalirudin use during PCI was not affected by the "crossover" effect. GP, glycoprotein; UF, unfractionated; LMW, low-molecular-weight; SYNERGY, Superior Yield of the New strategy of Enoxaparin, Revascularization, and Glycoprotein IIb/IIIa Inhibitors; PCI, percutaneous coronary intervention. Adapted from Stone GW.*[28]

death, myocardial infarction, urgent revascularization, or major bleeding trended to benefit those patients who presented with an acute coronary syndrome. The 1-year mortality endpoint showing the benefit of bivalirudin was observed across a variety of high-risk patient subgroups (Figure 3).

In addition, in contradistinction to the observations of the SYNERGY trial with LMWH, the safety of bivalirudin use during PCI was not affected by the "crossover" effect (Figure 4). This allows the interventional cardiologist added flexibility to switch the anticoagulant from either UFH or LMWH to bivalirudin in the catheterization laboratory without sacrificing the safety benefit.

The dosing of bivalirudin is simple to calculate and provides an excellent dose-response effect. With the exception of patients with significant renal insufficiency (CrCl < 30 mL/min), it is dosed as a 0.75 mg/kg bolus followed by 1.75 mg/kg per hour. In patients with CrCl less than 30 mL/min and for those on dialysis, the bolus remains the same but the intravenous infusion of bivalirudin is reduced to 1.0 mg/kg per hour and 0.25 mg/kg per hour, respectively (Table 1).

This type of dosing strategy virtually assures that all patients will have therapeutic ACTs greater than 300 seconds. There is no need to check the ACT during the PCI with the exception of patients with CrCl less than 30 mL/min (Figure 5). There has been no relationship observed between the ACT in patients treated with bivalirudin and either thrombotic or hemorrhagic complications.[29] Upon completion of the coronary intervention, the bivalirudin infusion is terminated with either immediate placement of an arterial closure device or hand compression of the femoral artery access site 1 to 2 hours later. Coagulation times return to normal approximately 1 hour following the cessation of the intravenous infusion. There is no need to make any dose adjustments when using bivalirudin with the glycoprotein IIb/IIIa inhibitors.

With CKD, one of the most potent predictors of both thrombotic and hemorrhagic complications associated with PCI and with the high prevalence of renal insufficiency in patients undergoing PCI, it is imperative that actions be taken to minimize risk in this population. In REPLACE-2, a CrCl of 30 to 60 mL/min and less than 30 mL/min were associated with a 6-month mortality risk odds ratio of 4.56 and 10.65, respectively, compared to those with normal renal function (data on file, The Medicines Company). The thrombotic and hemorrhagic risk associated with bivalirudin compares favorably to UFH across all spectrums of severity of

Table 1
Dosage and Administration With Renal Impairment*

Creatinine Clearance	Bivalirudin Bolus	Bivalirudin Infusion
> 90 mL/min	0.75 mg/kg	1.75 mg/kg/h
60-89 mL/min	0.75 mg/kg	1.75 mg/kg/h
30-59 mL/min	0.75 mg/kg	1.75 mg/kg/h
< 30 mL/min	0.75 mg/kg	1.0 mg/kg/h
Dialysis	0.75 mg/kg	0.25 mg/kg/h

*With the exception of patients with significant renal insufficiency (CrCl < 30 mL/min), bivalirudin is dosed as a 0.75 mg/kg bolus followed by 1.75 mg/kg per hour. In patients with CrCl less than 30 mL/min and for those on dialysis, the bolus remains the same but the intravenous infusion of bivalirudin is reduced to 1.0 mg/kg per hour and 0.25 mg/kg per hour, respectively. CrCl, creatinine clearance. Data taken from Angiomax [package insert]. Parsippany, NJ: The Medicines Company, 2005.

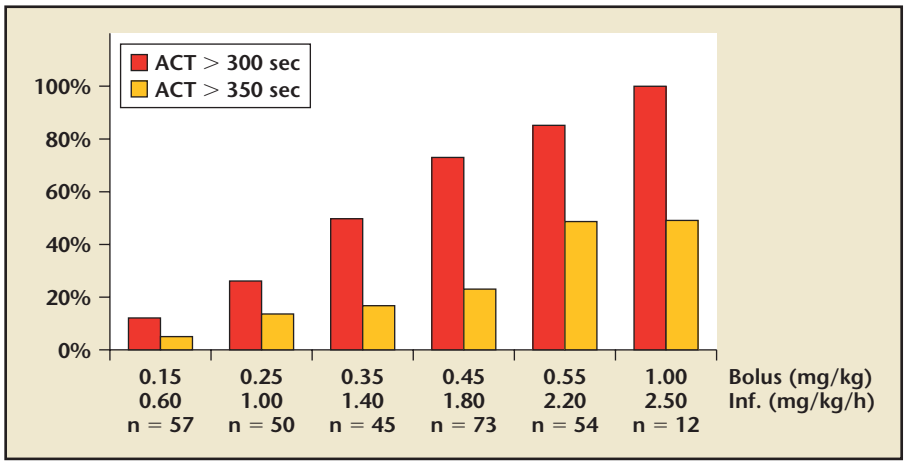


Figure 5. *Bivalirudin dose study and achievement of ACT > 300 seconds. There is no need to check the ACT during the PCI with the exception of patients with CrCl less than 30 mL/min. There has been no relationship observed between the ACT in patients treated with bivalirudin and either thrombotic or hemorrhagic complications. ACT, acute coronary thrombosis; PCI, percutaneous coronary intervention; CrCl, creatinine clearance. Adapted from The Medicines Company, Data on file.*

CKD in a meta-analysis of 3 clinical trials. This analysis has shown that bivalirudin use compared to UFH is associated with a reduced risk of thrombotic and hemorrhagic complications across the entire range of renal function.[30] The use of enoxaparin is contraindicated in patients with a CrCl less than 30 mL/min.

Sheath Removal. In patients not receiving a vascular closure device, the bivalirudin infusion should be discontinued and sheath removal should take place within 1 hour of cessation of therapy in most patients, except in those with CKD. However, in those patients with CKD, ie, creatinine clearance less than 30 mL/min, sheath removal may need to be delayed for 2 hours or more. ACT should be obtained in these patients prior to intravenous sheath removal. This policy is supported by the single-center AFRICA study.[31] Because of the delayed clearance of bivalirudin in patients with chronic kidney disease, it may be reasonable to choose either an activated partial thromboplastin time (< 50 seconds) or ACT (< 175 seconds) strategy for sheath removal.

Heparin-Induced Thrombocytopenia

HIT is defined as a drop in platelet count by more than 30% within 5 to 12 days of initial exposure to heparin. The platelet count is often reduced only to a moderate extent (80-100 $\times$ 10^3) and therefore is often overlooked. With over 12 million patients treated with UFH per year, it occurs in approximately 3% of patients treated for deep venous thrombosis (DVT) and pulmonary emboli (PE) and in approximately 0.5% of those treated with lower doses of UFH. Between 30% and 75% of patients in whom HIT develops suffer from a thromboembolic complication including new or worsening DVT or PE, stroke, myocardial infarction, or arterial thrombosis of an extremity.

With the use of intravenous full-dose UFH, a ubiquitous part of the pre-catheterization medical treatment for patients presenting with acute

Main Points

- Shortcomings of unfractionated heparin (UFH) include direct platelet activation and inability to inactivate clot-bound thrombin.
- Low-molecular-weight heparins (LMWHs) demonstrate less platelet activation and protein binding than UFH. But like UFH, the LMWHs cannot inhibit clot-bound thrombin or platelet-bound factor Xa within the prothrombinase complex.
- In patients undergoing percutaneous coronary intervention (PCI) where this is a predisposition for the occurrence of heparin-induced thrombocytopenia (HIT), approved options for anticoagulation include bivalirudin at a dose of 0.75 mg/kg bolus followed by 1.75 mg/kg per hour or argatroban dosed at 350 μg/kg per minute for the duration of the procedure.
- The in vitro ability to bind to and inhibit both soluble and clot-bound thrombin and not be neutralized by products of platelet granules, the in vivo effect of preventing platelet activation compared to the platelet activating effects of UFH, its consistent dose-response effect, its efficacy and safety in high-risk patient subsets and its indication for use in patients with HIT are some of the positive attributes of bivalirudin.
- The thrombotic and hemorrhagic risk associated with bivalirudin compares favorably to unfractionated heparin across all spectrums of severity of chronic kidney disease in a meta-analysis of 3 clinical trials.
- The direct thrombin inhibitor, bivalirudin, will play an increasingly important role as the primary anticoagulant for PCI, because it meets the criteria as a safer, cost-effective, and convenient agent in a spectrum of clinical scenarios.

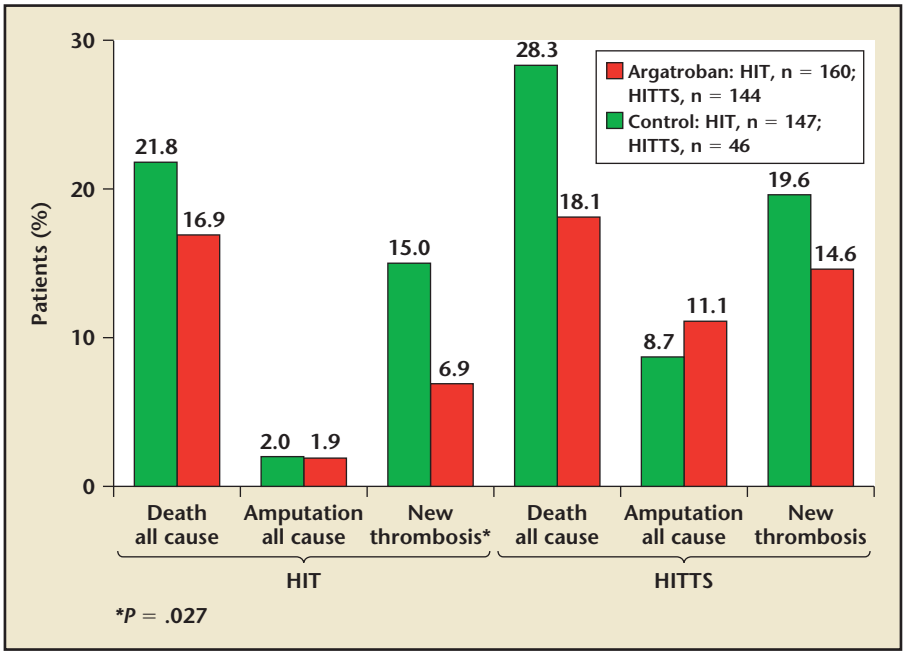


Figure 6. *Efficacy results for argatroban: components of the composite endpoint. HIT, heparin-induced thrombocytopenia; HITTS, HIT with thrombosis syndrome. Adapted with permission from Lewis BE.*[32]

coronary syndromes, cardiologists need to be aware of the sometimes subtle presentation of HIT. This is particularly true in patients at higher risk for developing HIT due to a previous exposure or longer duration of exposure to UFH. In patients undergoing PCI where this is a predisposition for the occurrence of HIT, approved options for anticoagulation include bivalirudin at a dose of 0.75 mg/kg bolus followed by 1.75 mg/kg per hour or argatroban at a dose of 350 μg/kg per minute for the duration of the procedure. The agents approved for use in patients who suffer from HIT and need to undergo a PCI include argatroban and bivalirudin.

Argatroban was evaluated in 2 similarly designed studies that enrolled patients with a current diagnosis or history of HIT, with or without thrombosis.[32] HIT was defined in these studies as a platelet count of <100,000/mcL or a 50% drop in platelet count after initiation of heparin. Clinical outcomes were compared with 193 historical controls. Patients were evaluated at baseline, during treatment, and for 30 days after treatment ended.

Argatroban anticoagulation improved clinical outcomes in patients with heparin-induced thrombocytopenia (Figure 6). No increase in bleeding risk was seen.

Argatroban is contraindicated in patients with significant chronic kidney disease. A dose adjustment is necessary when argatroban is used in patients with hepatic insufficiency.

The in vitro ability to bind to and inhibit both soluble and clot-bound thrombin and not be neutralized by products of platelet granules, the in vivo effect of preventing platelet activation compared to the platelet-activating effects of UFH, its consistent dose-response effect, its efficacy and safety in high-risk patient subsets and its indication for use in patients with HIT are some of the positive attributes of bivalirudin. The Acute Catheterization and Urgent Intervention Triage Strategy (ACUITY) trial will provide guidance on the use of bivalirudin in medium and high-risk ACS patients undergoing PCI. In summary, bivalirudin seems to have the qualities of a very desirable anticoagulant for use in the catheterization laboratory during PCI. ■

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