Antithrombotic Therapy in Percutaneous Coronary Intervention

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KEYWORDS

• Antithrombotics • Anticoagulation • Percutaneous coronary intervention • Acute coronary syndrome • Stable coronary artery disease

KEY POINTS

- Despite lack of randomized data compared with placebo, unfractionated heparin is the most commonly used antithrombotic agent in percutaneous coronary intervention. Dose adjustment based on activated clotting time and use of antiplatelet therapy are crucial when using unfractionated heparin.
- Low-molecular-weight heparin is more difficult to monitor than unfractionated heparin in percutaneous coronary intervention. Bleeding rates are higher when switching between low-molecular-weight heparin and unfractionated heparin.
- Fondaparinux is useful among patients being medically managed for acute coronary syndromes. Use of fondaparinux during percutaneous coronary intervention is limited by the occurrence of catheter-related thrombosis.
- Bivalirudin is associated with similar ischemic outcomes compared with heparin and glycoprotein IIb/IIIa receptor inhibitors as well as fewer bleeding complications. It is likely associated with higher rates of acute stent thrombosis.

INTRODUCTION

Antithrombotic therapy is a crucial component in the management of patients undergoing percutaneous coronary intervention (PCI). These drugs target various points in the coagulation cascade to ultimately prevent thrombin activation, which converts fibrinogen to fibrin, activates platelets, stimulates platelet aggregation, and may lead to catastrophic clot formation. Antithrombotic and antiplatelet therapies for PCI have undergone considerable evolution since the early days of balloon angioplasty. The ideal combination of agents minimizes ischemic complications while limiting bleeding risk.

The main goal of antithrombotic therapy during PCI is to avoid the adverse consequences related to thrombus formation from vascular injury and intravascular foreign bodies, including catheters, wires, and stents. Vascular injury exposes tissue factor, which activates the coagulation cascade. In addition, plaque rupture from balloon inflation or stent deployment exposes the thrombogenic lipid core, inciting an influx of coagulation factors causing thrombosis.

A large body of evidence supports the use of a variety of agents in the setting of stable

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coronary artery disease (CAD), non-ST elevation acute coronary syndrome (NSTE-ACS), and ST-elevation myocardial infarction (STEMI). This review describes antithrombotic therapies used in PCI, including unfractionated heparin (UFH), low-molecular-weight heparin (LMWH), factor Xa inhibitors, and direct thrombin inhibitors, and summarizes their pharmacokinetics and evidence supporting their clinical use.

ANTITHROMBOTIC AGENTS

Unfractionated Heparin

UFH is the most commonly used antithrombotic agent for PCI. UFH is easy to administer and has a rapid onset when used with initial bolus, and the degree of anticoagulation is easily monitored with activated partial thromboplastin time or activated clotting time (ACT). In the absence of randomized data compared with placebo, the first antithrombotic agent used for PCI, UFH, became the standard of care. Therefore, current dosing regimens are empiric and based on clinical experience. In a pooled analysis of data from the UFH control arms of 6 randomized clinical trials, ischemic events with relationship to ACT followed a U-shaped curve. An ACT of 350 to 375 seconds yielded the lowest 7-day composite ischemic event rate, although bleeding rates were the lowest with ACT of 300 to 325 seconds.[1] A substudy of the STEEPLE trial[2] noted the ACT range with the lowest ischemic outcome, and major bleeding was 300 to 350 seconds, with bleeding increasing significantly with ACT greater than 325 seconds, but ischemic events increasing with ACT less than 325 seconds. Available data do not support the use of prolonged heparin infusions after PCI whereby excess bleeding events and length of stay are not offset by a reduction in ischemic events.[3]

Anticoagulation using UFH alone appears insufficient to optimally protect against ischemic events in patients undergoing PCI. Aggressive antiplatelet therapy is necessary to further prevent platelet activation and/or aggregation. The use of ^{P2Y}12 platelet inhibitors and/or glycoprotein IIb/IIIa receptor inhibitors (GPI) along with UFH reduces periprocedural ischemic complications.[4–6] The high ACTs used in early studies are no longer necessary when UFH is given with antiplatelet agents. A meta-analysis of 4 large clinical trials with high use of clopidrogrel or GPI showed that ACT in the lowest quartile (<256 seconds) group was associated with the lowest bleeding rates without an increased ischemic rate.[7] Current guidelines recommend using a 50 to 70 U/kg bolus for goal ACT of 200 to 250 seconds when GPI is used and a bolus of 70 to 100 U/kg for goal ACT of 250 to 300 seconds when UFH is used alone[8] (Table 1).

During PCI, major limitations of UFH include its narrow therapeutic window, unpredictable individual response, and a risk for heparin-induced thrombocytopenia (HIT).[9] In addition, clot-bound thrombin is resistant to inhibition by the heparin-antithrombin complex and can continue to serve as a nidus to propagate thrombus upon discontinuation of heparin. To address these limitations, other agents have been developed.

Low-Molecular-Weight Heparin

Low-molecular-weight heparin (LMWH) is produced by depolymerization of UFH, resulting in fragments with a low mean molecular weight. These agents have a greater activity against factor Xa than against thrombin and a lower incidence of HIT. They have more predictable and consistent anticoagulation because there is less plasma protein binding. LMWHs are cleared renally and have a longer half-life than UFH. LMWH dosing cannot be reliably adjusted using the ACT (see Table 1).

Enoxaparin is the most studied LMWH. An observational study of 803 patients with ACS treated with 1 mg/kg twice daily enoxaparin subcutaneously showed that 30-day mortality was closely linked with anti-Xa levels,[10] and anti-Xa levels greater than 0.5 U/mL are considered therapeutic for enoxaparin.[11] However, because of logistical challenges, anti-Xa levels are not commonly measured during PCI, although they are occasionally measured in medically treated patients.

The CRUISE[12] trial randomized 261 patients undergoing elective or urgent PCI to intravenous (IV) enoxaparin 1 mg/kg or UFH, with all patients also receiving eptifibatide. There was no difference in the primary endpoint of bleeding as well as vascular access site complications, angiographic complications, or ischemic endpoints, although the study was underpowered to detect these differences. The STEEPLE[11] trial evaluated 3528 elective PCI patients who were randomized to IV enoxaparin (0.5 or 0.75 mg/kg) or UFH and stratified according to the use of GPI. GPI and P2Y12 inhibitors were used in 40% and 95% of patients, respectively. Compared with UFH, the 0.5 mg/kg enoxaparin arm had a lower bleeding rate at 48 hours (5.9% vs 8.5%; $P = .01$), and the 0.75 mg/kg enoxaparin arm had a nonsignificantly lower bleeding rate (6.5% vs 8.5%, $P = .051$). The trial was not