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# Advances in Periprocedural Anticoagulation for Percutaneous Coronary Interventions

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## Abstract

Percutaneous coronary intervention (PCI) is commonly used in the surgical treatment of patients with various types of cardiac diseases. Some patients require long-term anticoagulation in the presence of deep vein thrombosis, atrial fibrillation and mechanical heart valves, and inappropriate anticoagulation during the perioperative period may lead to bleeding events or thrombotic events. In this paper, the importance of anticoagulation in the practical application of percutaneous coronary intervention (PCI) is first introduced, and then the various drug regimens used in the perioperative anticoagulation of percutaneous coronary intervention are explored in detail in the light of current research advances, with a view to providing guidance for clinical practice.

## Keywords

Percutaneous Coronary Intervention (PCI), Anticoagulation, Heparin, Warfarin

## 1. Introduction

The incidence of cardiovascular and cerebrovascular diseases has increased year by year, posing a serious risk to people's lives. In the clinical treatment of coronary heart disease, stroke and other cardiovascular diseases, percutaneous coronary intervention (PCI) is commonly used, especially in the clinical treatment of patients with acute coronary syndromes (ACS), which has good therapeutic effects. According to clinical studies, the development of coronary artery disease is associated with stenosis and obstructed blood circulation. In this regard, PCI is performed by placing a catheter with a balloon in the stenosis and keeping the balloon filled to effectively dilate the blood vessels and improve local blood circulation. PCI can significantly improve local stenosis, but it can also lead to other complications, such as damage to the intima after stenting and inflammation,

which can lead to increased thrombosis and recurrence of stenosis. In this regard, patients should be treated with appropriate anticoagulation after PCI to reduce the incidence of thrombosis.

## 2. The Need for Perioperative Anticoagulation in Patients Treated with PCI

The coagulation system and platelets play a very important role in the initiation and development of ACS. If a coronary plaque ruptures, the tissue factor and collagen in the damaged endothelial matrix are fully exposed and the coagulation cascade is activated, with coagulation factor Xa forming a large amount of thrombin, which transforms fibrinogen into fibrin and forms a framework structure during thrombosis. This pathological process can be inhibited and the incidence of thrombosis reduced by the use of anticoagulant therapy and the selection of appropriate anticoagulant drugs [1].

In-stent thrombosis is a serious complication in the treatment of patients undergoing PCI and its causes are complex, including inadequate stent expansion, acquired hypercoagulability and delayed healing resulting in endothelial damage, among others, which can trigger thrombosis. This can lead to increased mortality if safe and effective treatment is not administered in a timely manner. In addition, PCI may cause disruption of the atherosclerotic platelets or endothelial detachment, which may lead to platelet aggregation and activation of the coagulation cascade. Therefore, highly effective anticoagulants and antiplatelet agents should be administered to patients to reduce the incidence of in-stent thrombosis.

## 3. The Current Situation of Perioperative Anticoagulation Therapy for PCI Patients at Home and Abroad

In the perioperative anticoagulation treatment of patients undergoing PCI, the use of common heparin is relatively common, but there is still no uniform standard for the dose of common heparin, especially in terms of the number of cases and the rigour of the studies, and there are relatively few clinical study data, which makes it difficult to ensure the accuracy and reliability of the results. In many developed countries in Europe and the USA, there are two types of doses of common heparin: one is an initial dose of 70 U/kg to 100 U/kg, during the course of administration, ACT monitoring data is collected and adjusted to require a maximum dose of 150 U/kg or less; the other is a single dose of 100 U/kg of common heparin, which does not require monitoring during the course of administration. According to the study, the best efficacy was achieved when the dosage of common heparin was 140,100 U/kg, but patients were prone to the risk of bleeding. Subsequently, experiments were carried out to conduct an in-depth study of the effects achieved and the safety of the dosage of common heparin from 100 U/kg to 140 U/kg. According to the study, it was found that by appropriately reducing the dosage of common heparin, postoperative bleeding

in patients could be effectively reduced The incidence of postoperative haemorrhage was found to be reduced by reducing the amount of normal heparin. Some patients have been treated with sodium fondaparinux prior to surgery and should be treated with ACT to regulate the dose of heparin during surgery [2]. In addition, an analysis of current research findings suggests that oral warfarin can also be instructed in the perioperative anticoagulation of patients undergoing PCI, particularly in patients at high risk of thromboembolism, where the anticoagulant effect of warfarin is significant and some patients are at high risk of vascular perforation and can be bridged with plain heparin when undergoing PCI. In the clinical management of patients with STEMI, the use of intravenous enoxaparin compared to plain heparin during PCI has not been shown to be effective in reducing the incidence of bleeding events, but it has been shown to improve ischaemic symptoms in patients. The use of argatroban in the anticoagulation of patients with acute coronary syndrome (ACS) in the presence of HIT has been shown to be advantageous, but its safety in the clinical management of patients with ACS treated with percutaneous coronary intervention remains to be proven. The use of rivaroxaban in patients can have a good preventive effect and ensure a balanced "bleeding" and "antithrombotic" effect [3].

In 2014, an analysis of the AHA/ACC guidelines indicated that in the clinical management of patients with non-ST-segment elevation acute coronary syndrome (NSTE-ACS), anticoagulants should be administered to patients to reduce the incidence of intracatheter as well as intracoronary thrombosis if a percutaneous coronary intervention protocol is used. The guidelines state that before the patient is treated, heparin should be administered by intravenous drip at a dosage of 85 U/kg, or if an inhibitor is used, the activated clotting time should be monitored and the dosage of heparin should be adjusted. In the clinical management of patients with NSTE-ACS, patients can be treated with percutaneous coronary intervention, which can be administered by intravenous drip, and the patient can be treated with plain heparin, which can have a good anticoagulant effect. In some patients, enoxaparin has been applied 12 h before the surgical treatment, and it is also necessary to apply enoxaparin by intravenous drip administration at a dosage of 0.3 mg/kg before the operation [4].

The ACCF/AHA guidelines indicate that in the clinical management of patients with NSTE-ACS who are treated with percutaneous coronary intervention, a wide range of drugs are available for perioperative anticoagulation, including plain heparin, enoxaparin, bivalirudin, etc. The ESC guidelines state that in patients with NSTE-ACS who are treated with percutaneous coronary intervention In the perioperative period, the use of sodium fondaparinux is promoted and, in some patients, UFH can be used in combination to help reduce the incidence of intra-catheter thrombosis. In some patients there are no postoperative complications and anticoagulants should be discontinued promptly. In addition to this, the Chinese guidelines for percutaneous coronary intervention state that anticoagulants should be discontinued after percutaneous coronary intervention if

the patient is affected by high risk factors for thrombosis.

## 4. Indirect Thrombin Inhibitors

In the practical application of indirect thrombin inhibitors, indirect thrombin inhibitors can effectively bind to antithrombin, which can form thrombin inactivation or inhibition of thrombin, significantly improving the affinity of antithrombin III to thrombin, resulting in inactivation of thrombin. For indirect thrombin inhibitors, there are two types, unfractionated heparin (UFH) and low molecular weight heparin (LMWH) [5].

**1) Common heparin**

UFH can be combined with antithrombin III (AT-III) to catalyse the inactivation of coagulation factors IIa, Xa, IXa, XIa and XIIa, enabling it to perform better as an anticoagulant. UFH anticoagulants are relatively low cost and are early anticoagulants used in clinical practice, and are generally used as controls in the development of new anticoagulants and in clinical trials. In Europe and the US, as well as in China, guidelines suggest that UFH anticoagulants can be used in patients with STEMI in the acute phase and in patients with STEMI treated with PCI, and is also a common anticoagulant in patients with NSTEMI treated with PIC. However, there are some limitations in the practical application of UFH, mainly in the following areas: a) The high variability in the chain weight and manufacturing characteristics of UFH makes it difficult to determine the optimal dose of UFH for clinical use, and in addition, the activated clotting time can easily exceed the therapeutic range, making it difficult to ensure the safety and efficacy of UFH application. b) Thrombosis is likely to occur after the patient has discontinued the drug. c) When patients are treated with heparin, the incidence of thrombocytopenia in patients is relatively high and may pose a risk to their lives. Therefore, in clinical terms, patients should be instructed to stop the drug immediately if they are found to be thrombocytopenic. New anticoagulant drugs are being developed at an accelerated rate and many have been promoted for use in clinical practice, with a gradual increase in the number of types of anticoagulant drugs [6].

**2) Low molecular heparin**

Low molecular weight heparin (LMWH) is a mixture of heparin, which can be chemically or enzymatically depolymerised to produce a fragment of amino dextran sulphate based on ordinary heparin, which is only 1/3 of the length of ordinary heparin and has an average molecular weight of 3000 KD - 5000 KD. There are many types of low molecular heparin, including enoxaparin, nadroparin, dalteparin and bemiparin, etc. Among them, enoxaparin is more commonly used and is the only low molecular heparin that can be used for anticoagulation in the perioperative period of PCI in both domestic and international guidelines.

Enoxaparin is a low molecular heparin that inhibits FXa, however, it is less able to inhibit coagulation factor IIa than UFH. In contrast to UFH, anticoagulant effects can be predicted in the clinical use of enoxaparin and no testing is

required. After discontinuation of the drug, rebound of coagulant activity does not usually occur and is safer, with a lower incidence of complications such as thrombocytopenia (HIT) and osteoporosis in patients [7].

The anticoagulant effect of enoxaparin in the treatment of STEMI patients with PCI has been shown to be significant, particularly in the ATOLL trial. In the ATOLL trial, 910 patients with STEMI were selected for the study and all patients were treated with PCI. Patients in the enoxaparin group had a significantly lower 30-d mortality and myocardial infarction complication rate than the UFH group. However, the results of the ATOLL trial could not be directly applied to clinical studies, mainly because all patients were treated with clopidogrel in this trial and not with the more common drugs used in clinical work today, such as tigretol and the new P2Y12 receptor antagonist.

The delayed onset of action of tegretol in the prophylactic treatment of patients with opioids may result in a significant increase in the incidence of acute in-stent thrombosis, which requires scientifically effective antithrombotic treatment to avoid the risk of delayed onset of action of tegretol. The results of the PENNY PCI study, in which enoxaparin was administered at a dosage of 0.75 mg/kg at 6 h intervals, were analysed and anti-FXa levels were measured before, during and after the PCI procedure. During the infusion, the anti-Xa level was at a certain value and the patient did not experience any type of complications. Therefore, enoxaparin can be used as an alternative to UFH and also as an alternative to GPI to avoid delayed absorption after the administration of P2Y12 inhibitors. However, during the PENNYPCI study, only 19 patients were selected for the study, therefore, the study was also extended in order to validate the results of the trial [8].

## 5. Direct Thrombin Inhibitors

**1) Bivalirudin**

Bivalirudin is a peptide that accurately identifies the fibrinogen binding site of thrombin and also inhibits the active site of thrombin. Bivalirudin has the advantage of being less dependent on the patient's renal function, has a lower incidence of allergic reactions and inhibits thrombin.

Clinical medicine researchers in many countries around the world are actively conducting clinical trials related to bivalirudin. The REPLACE-2 trial was the first of its kind to combine bivalirudin with UFH as a glycoprotein platelet inhibitor in a pilot study of perioperative anticoagulation for PCI. In the pilot study, all study participants were divided into a bivalirudin group and a UFH + GPI group, in which patients in the bivalirudin group had less 30-d bleeding, however, patients had a higher incidence of thrombosis. In addition, the BRIGHT trial led by Academician Han Yaling chose to study 2400 patients and divided all patients into three groups, one of which was the bivalirudin group, the second was the single application heparin group and the third was the heparin plus tirofiban group. Therefore, patients had a lower incidence of thrombosis [9].

The HEAT-PPCI trial was conducted in 2014 and according to this trial study, the incidence of NACE was lower with UFH compared to bivalirudin. In this trial, 1800 patients were selected for the study and for all patients, all patients were divided into two groups and treated with bivalirudin as well as UFH. According to the analysis of the trial study, after applying bivalirudin to the patients for the incidence of thrombosis was higher in patients after anticoagulation. In the MATRIX trial, 7213 patients with ACS were divided into two groups, one with UFH and the other with bivalirudin, and it was found that the rate of bleeding and mortality was lower when bivalirudin was administered. In the VALIDATE-SWEDEHEART trial, which compared the use, efficacy and safety of bivalirudin with UFH in the anticoagulation of patients with acute myocardial infarction, it was found that there was less difference in the amount of bleeding between patients treated with bivalirudin or with heparin alone.

In the ACUITY trial, 13,813 patients with NSTEMI were selected for the study and all patients were divided into three groups, one for the single bivalirudin group, one for the combined bivalirudin and GPI group, and one for the combined UFH and GPI group. According to the study, the incidence of ischaemic outcomes was approximately the same in all three groups, with relatively less bleeding in the bivalirudin group, however, the difference in the incidence of adverse events between the three groups was relatively small. In the latest AHANSTEMI guidelines, it is proposed that for bivalirudin, it can be recommended as a Class IB recommendation as well as a Class IIB recommendation.

When treating patients with ACS with PCI, the prognosis of patients varies depending on the approach, and it is therefore important to choose the appropriate anticoagulant. In a pilot study comparing radial access with femoral access, it was found that patients had a lower mortality rate when radial access was applied, but the role of various anticoagulants in different access routes varies and clinical studies need to be carried out [10].

**2) Argatroban**

Argatroban is an arginine derivative that can reversibly bind to the catalytic site of thrombin. Argatroban can inhibit the catalytic reaction of thrombin, thus exerting an anticoagulant effect. Agatroban has been used in Japan since the 1980s for the treatment of patients with peripheral arterial occlusive disease, and in 1990 for the treatment of patients with arterial thrombosis. 2000 saw the approval of agatroban for the treatment of patients with heparin-induced thrombocytopenia in the US. By comparing the effects of argatroban with those of heparin in anticoagulation therapy, argatroban has a rapid onset of action but a relatively short duration of action.

**3) Dabigatran**

Dabigatran is a new oral prothrombin inhibitor which, when administered as anticoagulation, acts directly on thrombin to reduce the incidence of bleeding in patients. In addition, dabigatranate can be administered orally and is fast-acting and stable with a relatively short half-life. In addition, a comparison of the effects

of favalin with dabigatranate in the anticoagulation of patients with NVAF showed that dabigatranate is safer and has a lower risk of bleeding in patients [11].

## 6. Warfarin

Warfarin is a bicoumarin derivative that inhibits the conversion between vitamin K and 2,3-epoxide. Warfarin has a narrow therapeutic window and the dose of warfarin varies considerably when applied to different patients, which may lead to bleeding symptoms and even embolism and valve thrombosis if not properly controlled. Therefore, in clinical application, the International Normalised Ratio (INR) values need to be closely monitored and the dosage of warfarin should be adjusted appropriately accordingly [12].

## 7. Conclusions

In the practical application of percutaneous coronary intervention protocols, a coronary stent can be inserted into the coronary artery through the femoral or radial artery via transvascular puncture, thereby effectively relieving coronary stenosis or occlusion. The use of anticoagulants in the perioperative period is crucial in the treatment of patients undergoing PCI, not only for the success of the procedure, but also to significantly reduce the incidence of thrombotic events through the use of safe and effective anticoagulants. Today, modern PCI procedures are rapidly evolving, and the combination of anticoagulant drugs, as represented by drug-coated stents, can significantly improve the success rate and safety of PCI procedures.

In this study, a variety of drugs used in the perioperative anticoagulation of patients undergoing PCI are described in detail. Among them, plain heparin is the most commonly used anticoagulant and is the first choice for perioperative anticoagulation in patients undergoing PCI because it is easy to administer, inexpensive, simple to monitor and effective in the event of any complications. Low molecular heparin exerts the same anticoagulant effect as plain heparin, which is beneficial in reducing the incidence of bleeding complications in patients and has a better anticoagulant effect than plain heparin. Some patients are at greater risk of bleeding and the use of bivalirudin can be promoted, but research on bivalirudin in the perioperative anticoagulation of patients undergoing PCI is still in its infancy. Some patients have heparin-induced thrombocytopenia and argatroban can be applied to patients, but its safety is yet to be verified. Dabigatran has not yet been promoted and applied, and there is a lack of clinical experience with its use. With the continuous development of medical technology, the types of anticoagulant drugs will gradually increase, and by choosing safe and reliable anticoagulants, the long-term prognosis of patients can be significantly improved.

## Conflicts of Interest

The author declares no conflicts of interest regarding the publication of this paper.

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