

SPECIAL SUPPLEMENT

Pharmacotherapy in Peripheral Vascular Disease

Platelet Inhibition in Critical Limb Ischemia and Peripheral Vascular Interventions

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An Overview of Pharmacotherapy during Percutaneous Peripheral Interventions of Thrombotic Lesions

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Learning Objectives: Upon completion of this educational activity, participants should be able to:

- Discuss the role of platelet inhibition in peripheral vascular disease
- Discuss treatment strategies for patients with critical limb ischemia
- Provide appropriate medical management of patients with vascular disease
- Review current anticoagulants in peripheral percutaneous interventions and why heparin is suboptimal in high-risk patients
- Review algorithms in treating high-risk peripheral intervention patients with a focus on thrombus-containing lesions.

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Platelet Inhibition in Critical Limb Ischemia and Peripheral Vascular Interventions

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Introduction

The peripheral vascular interventional field is changing so quickly that it is difficult for the clinician to develop efficacious Phase III clinical data from large, well controlled trials. Many devices, lasers, balloons and stents are utilized in endovascular treatment; however, less pharmacology or pharmaceutical support exists in treating peripheral disease as exists in percutaneous coronary interventions (PCI). The literature is replete with articles on anticoagulation and how to prepare the PCI patient, but less literature exists for the peripheral vascular disease (PVD) patient. The PVD patient requires an optimal anticoagulation strategy. The subset of patients with critical limb ischemia (CLI) requires an even more superior anticoagulation, antiplatelet, and antithrombin strategy. As part of the disease process, some form of thrombus or clot likely occurs in 100% of peripheral vascular interventional patients.^{1,2} Additionally, peripheral vascular interventional patients are at greater bleeding risk than PCI patients.^{3,4} Since PVD and PCI patients experience a somewhat different disease process, the path to anticoagulation for PVD patients requires much forethought. The basic components of clot are platelets and red blood cells connected via a fibrin strand. To improve outcomes, each component must be manipulated. When a wire, a balloon or a stent is placed in a blood vessel, the endothelium is injured, and thrombogenicity is promoted — the interventional procedure itself promotes thrombogenicity.

In the PVD patient, the diseased vessels, especially those affected by CLI, are very long. The sheaths that are used in PVD patients are much larger, and longer stents are required for these patients than those used in PCI patients. The treated segments are longer; thus, more vessel injury occurs. While complex coronary cases exist, oftentimes, coronary cases can be performed quickly. The peripheral procedure has a long duration, and a low flow state occurs. Many PVD patients have poor runoff. PVD patients have twice the incidence of chronic renal insufficiency than coronary patients, and diabetes is more prevalent in PVD

patients. In PCI patients, the prevalence of diabetes is 20%; in PVD patients, it is 50%–60%. In some PVD patient populations, it is even higher.^{5–7} By nature, PVD patients are hypercoagulable and require a different anticoagulation strategy than PCI patients. To optimize outcomes with less bleeding and improved anticoagulation, the tools of endopharmacotherapy in CLI are just as important as the devices.

Heparin

Heparin has been in use for many years and is inexpensive. Although it has been effective through the years, heparin does not have an indication in PVD, and heparin has limitations: it is unpredictable, it has an indirect effect, and it is bound to proteins. Additionally, heparin has a long half-life. Heparin stimulates platelet activation and aggregation; it is less effective in the presence of an existing clot. It is ineffective in renal patients, and it causes heparin-induced thrombocytopenia (HIT).^{8–10} Antibodies can form with heparin. No science or data for PVD support heparin as the gold standard, though heparin is utilized as the foundation for anticoagulation and platelet activity in peripheral vascular interventions regularly.

Diabetes and Renal Insufficiency

Patients with CLI have a high incidence of diabetes and renal insufficiency. Peripheral vascular patients are more thrombogenic than coronary patients. The PAD patient has a “turned on” platelet; there is increased fibrinogen, and platelets are more likely to aggregate. Additionally, more clotting factors are present, and on the cellular level, peripheral vascular patients have decreased nitric oxide production.

Diabetes. More than 80% of patients with CLI have diabetes, and patients with diabetes are at significant risk for CLI.^{4,11} The patient with diabetes is 7–40 times more likely to suffer an amputation than the patient without diabetes.^{5,11–13} Worldwide, there is an amputation in a patient with diabetes every 30 seconds.^{5,11–14} The diabetic platelet differs from the normal platelet. As known in the surgical literature, diabetic platelets have increased aggregation and reactivity. Platelets are more easily degradable. In other words, the patient with diabetes is also a patient who is hypercoagulable. Inflammation is also heightened in diabetes, and

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patients with diabetes have more thrombus during acute coronary syndromes.

Chronic renal disease. The same platelet dysfunction scenario exists in chronic renal disease. Chronic renal disease affects 20% of PCI patients, 50% of PAD patients and more than 50% of CLI patients.^{15,16} A prothrombotic state also is evident in the renal insufficient patient.

Interventional Endopharmacotherapy

What can be done from a pharmaceutical standpoint during these cases to improve outcomes? Anticoagulation strategies must be optimized. With some of these strategies, bleeding risk can be decreased. Direct thrombin inhibition is important. This aspect of treatment allows for optimal anticoagulation with fewer bleeding complications as illustrated by several large studies in the PCI literature.^{9,16,17} Presently, little data in the periphery exist, but the Randomized Evaluation of PCI Linking Angiomax to Reduced Clinical Events-2 (REPLACE-2) trial was a large coronary trial looking at bivalirudin (Angiomax, The Medicines Company, Parsippany, NJ) as a heparin replacement.^{18,19} Patients experienced fewer overall bleeding complications in REPLACE-2. In PCI, these bleeding complications, even minor bleeding complications, resulted in poorer outcomes. Patients who had minor bleeds, even those who had blood transfusions after PCI, had poorer 1-year outcomes and had more adverse events. If we optimize the bleeding risk for PCI and PVD patients, they likely will experience improved outcomes. The risk of peripheral vascular access complications in PVD cases is 15%–20%.²⁰

Each year, more peripheral procedures are performed. These PVD patients are more challenging for access management. Our high incidence of bleeding complications with heparin resulted in our adoption of bivalirudin. In the first publication of our experience using bivalirudin in renals and iliaes, we reported fewer complications in the bivalirudin group versus the heparin group. This experience, along with the PCI literature, convinced us to anticoagulate our peripheral patients with bivalirudin. This led to the Angiomax Peripheral Procedure Registry of Vascular Events (APPROVE) trial, which was a multicenter trial that examined bivalirudin in peripherals. The APPROVE trial was a 26-site safety and feasibility study in more than 500 patients.^{15,21} The incidence of bleeding was extremely low, and safety and feasibility were proven. This strategy to use bivalirudin as our anticoagulation foundation allows us to have fewer bleeding complications in PVD cases. There are occasions in which we will use heparin, but in general, we strongly consider the limitations of heparin in peripherals and utilize direct thrombin inhibition in PVD. Additionally, in the APPROVE trial, the overall thrombotic complication rate was less than 1%.

Iib/IIIa Inhibition

Direct thrombin inhibition assists with anticoagulation, but what is the role of direct platelet inhibition during the procedure? Why are intravenous control and maximum antiplatelet therapy necessary during the procedure? There is still a patient population in whom Iib/IIIa inhibitors are warranted during PCI. These are the same patients who experience CLI: patients with small vessels and thrombus and patients with diabetes and acute-chronic syndromes. Acute CLI is analogous to acute coronary syndrome (ACS); thus, the same antiplatelet strategy should be utilized in CLI. PCI data show that Iib/IIIa inhibitors may help with thrombolysis, and CLI patients may derive benefit.²² We cannot be confident that Iib/IIIa inhibitors will decrease in-stent restenosis, and longer term patency always will be questionable; however, in 2002, the ACC and the AHA developed a guideline that recommended Iib/IIIa inhibitor use in patients with diabetes and ACS patients undergoing PCI.²³ Iib/IIIa inhibition has been most effective in these patients, and it is reasonable to postulate that the CLI patient would derive benefit. For this reason, we treat the critically ischemic toe like the critically ischemic left anterior descending (LAD) artery. The clinician is alerted by the patient who presents with a LAD thrombosis or a patient who presents with ACS but not CLI.

Data showing our results with Iib/IIIa inhibitors and bivalirudin in 149 patients with CLI are forthcoming.^{13,22,24} We treated vessels from groin to toe, and approximately 75% of these vessels were infrapopliteal. We looked at multiple variables to evaluate safety and feasibility. The limitations of this study included its nonrandomized, retrospective, single-center design. The main findings were the bivalirudin-Iib/IIIa CLI treatment group was found to have fewer bleeding complications and improved immediate and 6-month limb salvage rates as apposed to the heparin group. Although all endpoints did not reach statistical significance due to the small numbers, a strong trend toward significance was demonstrated. Statistical significance was shown with the parameters related to early sheath removal, ambulation and length of hospital stay primarily due to better vascular access management versus heparin. Hopefully, this work will stimulate industry to sponsor large scale, prospective, randomized trials to validate efficacy utilizing direct thrombin and Iib/IIIa inhibition in treating CLI patients.

Conclusion

Simultaneous Iib/IIIa inhibition and direct thrombin inhibition is safe, feasible and a better alternative to heparin alone in treating patients with CLI. The patient with CLI is the highest risk for bleeding and thrombotic complications with poor outcomes and most difficult

patient to treat. A need for randomized data remains. Peripheral disease, especially CLI, is a clinical opportunity for endopharmacotherapy.

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An Overview of Pharmacotherapy during Percutaneous Peripheral Interventions of Thrombotic Lesions

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Introduction

Over the past decade, there has been an exponential rise in lower-extremity peripheral percutaneous interventions (PPI) with a concomitant drop in surgical interventions.¹ Despite this pattern, the rate of limb amputations continued to rise during the same period of time. Lower-extremity amputations account for 97% of vascular amputations and are predominantly seen in patients with chronic² or acute³⁻⁵ limb ischemia. Lower-extremity amputations are a major public health problem — less than 50% of patients achieve mobility or even are alive at 3–4 years, and the 30-day perioperative mortality ranges from 8% to 17%.⁶⁻⁸

The reasons for the continued rise in amputation rates are unclear. Although it could reflect on a sicker population with increasing rates of diabetes, obesity and the metabolic syndrome, it is also likely to be related to our practice of medicine. It has been estimated that approximately 50% of primary amputations occur in the United States without a single ankle-brachial index (ABI) to evaluate for limb ischemia.⁹ Furthermore, amputation rates appear to increase in patients with lower-extremity vascular thrombus, such as in patients with acute and chronic limb ischemia when compared to patients with claudication. Finally, the approach to treating thrombus in the periphery also has a bearing on limb salvage. For instance, surgery or thrombolysis alone in patients with acute limb ischemia carries a high rate of amputation — up to 18% — as shown in multiple clinical trials.³⁻⁵

The objective of this manuscript is to review the literature and propose an approach to treating patients with thrombotic lower-extremity arterial disease with a particular focus on patients with acute limb ischemia, subacute limb ischemia and recent chronic total occlusions.

Peripheral arterial disease (PAD) is thrombogenic and affects a large percentage of patients with conditions associated with endothelial dysfunction and a

hypercoagulable state, including those with diabetes and hyperlipidemia and those who smoke.¹⁰ Patients with PAD have a heightened inflammatory state similar to patients with unstable angina¹¹ and have a high incidence of coexisting arrhythmias, congestive heart failure and coronary artery disease — conditions associated with thromboembolism. In addition, PAD, particularly in the limb ischemia patients, has a high prevalence of chronic occlusions,¹² which predictably contain atherothrombus usually dynamic and multilayered with coexisting acute, subacute and organized thrombus. Furthermore, the PPI itself is thrombogenic and induces a heightened inflammatory reaction. Data from the Eptifibatide does not Reduce Inflammatory Markers in Patients Undergoing Peripheral Vascular Interventions (INFLAME) trial¹³ have shown that high sensitivity-C reactive protein (hs-CRP) peaks 48–72 hours following PPI and remains elevated at the 7-day follow-up period. In addition, the INFLAME trial demonstrated a significant increase in fragment 1,2, a thrombin generation marker that peaks at about 18 hours post intervention despite a high dose of unfractionated heparin (UFH) or a low dose of UFH with eptifibatide. Finally, INFLAME demonstrated a rapid rise in fibrinogen post intervention that remained elevated at 7 days post intervention. Platelet activation is also a significant problem during PPI and allows the formation of micro and macro platelet aggregates contributing to thrombosis and distal embolization.¹⁴ The length of the lesion, slow flow and poor runoff in the lower extremity make the peripheral vascular bed thrombogenic during PPI because of the extent of iatrogenic injury to the vessel wall and exposure of a larger amount of the subendothelial layers to circulating inflammatory and thrombotic cells and coagulation factors that activate the coagulation pathways.

The clinical presentation of peripheral vascular disease and, in particular, the onset of symptoms can provide an insight into whether thrombus will be encountered in these patients.¹⁵ Similarly to the symptomatic coronary patients, the symptomatic peripheral patient also can be classified into 1) acute limb ischemia or ALI (analogous to acute ST segment elevation myocardial infarction [MI]), 2) subacute limb ischemia or SALI (analogous to non ST elevation MI or unstable angina) that includes patients with a recent onset of accelerat-

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ed limb pain with minimal activity or chronic critical limb ischemia (CLI) patients with advanced rest limb pain or ulceration (typically of several weeks duration) or 3) patients with stable claudication (analogous to patients with stable angina), including patients with relatively stable exertional symptoms.

Typically, thrombus is visible in 100% of the patients with ALI. Thrombus is also prevalent in patients with SALI. In a small study of PPI, visible angiographic thrombus was reported in 16.7% of all patients, a third of which had a subacute presentation (< 1 month), and 11% had ulcerations.¹⁶ On the other hand, in a cohort of low-risk patients (renals and claudicants predominantly with long occlusions excluded), visible thrombus was seen in only 3% of patients.¹⁷ Angiography underestimates the presence of thrombus, particularly in the setting of total occlusions. Total occlusions have been reported in almost 90% of patients with CLI.¹² The presence of angiographic thrombus is associated with higher rates of complications, including amputation and death, higher re-occlusion rate post successful revascularization, emergent revascularization post intervention, prolonged hospitalization, thromboembolization and longer procedure times, which mean longer radiation exposure to the patient and a larger amount of contrast dye. Data from our laboratory show that the median amount of time to treat a patient with angiographic thrombus is approximately 150 minutes versus 80 minutes if thrombus is not present.¹⁵

Approaching the patient with symptomatic peripheral vascular disease requires an understanding of the acuity of the clinical presentation, the techniques available to treat these patients and the choice of anticoagulant(s). The selected techniques should be able to minimize procedure length, effectively restore blood flow, assist in dissolving any associated thrombus and reduce both thrombotic and atherosclerotic embolization. The anticoagulant of choice should be able to prevent further platelet and thrombin reactivation, dissolve existing thrombus, lower reocclusion rate, have low bleeding complication rates and be predictable. A combination of anticoagulants and techniques is necessary to achieve optimal results when treating the patient with peripheral vascular disease.

Base Anticoagulant Choice in PPI

Unfractionated heparin has been the anticoagulant of choice for the past several decades in PPI. The ideal dosing of UFH is unknown in PPI, and this drug has not been scientifically tested during complex interventions, such as in patients with limb ischemia or thrombotic occlusions. Despite this, UFH had gone unchallenged for many years until recently when data from the coronary literature demonstrated that other anticoagulants, such as enoxaparin¹⁸ or bivalirudin,¹⁹⁻²² can

provide superior outcomes to UFH.

Unfractionated heparin has several limitations. It has an unpredictable anticoagulation response and can activate platelets at higher doses. Additionally, UFH does not inhibit clot-bound thrombin and can potentially lead to heparin-induced antibodies and heparin-induced thrombotic syndrome. Data from PPI show that UFH provides a similar unpredictable response, and higher doses of UFH are associated with higher bleeding complications and serious adverse events.¹⁶

Bivalirudin has been shown to be safe and effective as a base anticoagulant in PPI (off-label application).²³⁻²⁶ Bivalirudin provides a predictable anticoagulant response, can inhibit clot-bound and soluble thrombin and does not activate platelets. The drawback of using bivalirudin is the lack of an antidote to this drug, which is offset by its short half-life (25 minutes) in patients with normal renal function.²⁷ Data on the use of this drug in PPI are now widely published, although no randomized data between UFH and bivalirudin exist at this time. The APPROVE (Angiomax Peripheral Procedure Registry of Vascular Events) prospective registry is the largest source of published data on bivalirudin in the periphery showing the feasibility and safety of this drug in low-risk PPI patients with overall low complication rates including major bleeding.^{17,28} An overview of published data on bivalirudin in PPI also was published recently showing an acute success rate with bivalirudin of 97% and low complication rates (limb loss of 0.11%, major bleeding 1.8% and acute thrombosis almost 0.21%).²⁶ Again, the majority of included patients had low-risk interventions, predominantly in renals and claudicants. A recent retrospective study of high-risk patients (CLI) comparing UFH, enoxaparin and bivalirudin (groups matched to various demographic and angiographic variables) has shown that a complication-free procedure was achieved more often with bivalirudin or enoxaparin when compared to UFH and despite a high use of GP IIb/IIIa inhibitors and/or fibrinolytics in the bivalirudin group.²⁹ Although statistical significance was not achieved in this small study among the 3 groups, the data is likely to be clinically significant. A randomized trial in high-risk PPI patients that compares UFH and bivalirudin is warranted at this time to scientifically validate bivalirudin as a base anticoagulant in these patients.

Approaching the Patient with ALI

Patients with ALI present with resting foot pain, a cold foot and an acute lower-extremity arterial occlusion typically occurring over a range of mild to severe atherosclerotic lesions. Collaterals are typically minimal in those patients, and the thrombus itself either has formed in situ secondary to plaque rupture or turbulent flow in diseased arterial segments or has embolized from a proximal vascular bed or the heart. The presen-

tation is similar to a patient with an acute ST elevation myocardial infarction, where a sudden interruption of blood flow occurs and an emergent intervention is needed to save the myocardium. In ALI, emergent intervention is needed to save the limb.

Treatment of ALI patients with thrombolysis or surgery alone carries a high rate of mortality and amputation. In 3 randomized trials of surgery versus thrombolysis, the range of mortality rates was 6.5%–20% and 8.5%–42% with thrombolysis and surgery, respectively. Also, amputation rates were as high as 18% with both treatment modalities.^{3–5} In an attempt to improve on these outcomes, in 2001 Duda et al³⁰ published a randomized trial attempting the addition of GP IIb/IIIa inhibitor to a fibrinolytic treatment in patients with ALI. In this study, 70 patients were randomized to abciximab and urokinase versus urokinase alone. The primary outcome of the study was the combined endpoints of surgical revascularization and limb amputation. Patients receiving the combined therapy had a significantly better outcome than urokinase alone. In addition, the RELAX trial,³¹ published in 2004, was a randomized trial of 75 patients receiving varied dosing of reteplase versus reteplase plus abciximab with a 90-day follow-up. The addition of abciximab reduced the rate of distal embolization significantly (5% vs. 31%). Reteplase at 0.2 units per hour was effective in dissolving the thrombus and restoring vessel patency with no clear dose-response relationship. Furthermore, data from 16 patients with acute limb thrombosis enrolled in a small registry³² of tenecteplase and eptifibatide showed a technical success rate of 91% and a clinical success rate (defined as no death, intracranial hemorrhage or remote sites of bleeding or minor bleeding complications) of 82% of the arterial occlusions treated. There was 1 major bleeding reported related to a femoral artery access that resolved after therapy. Finally, the combination of tenecteplase and tirofiban was tested in 48 ALI patients with iliofemoral arterial thrombosis.³³ All patients who received low-dose UFH showed a success rate of 95.8%. Complete lysis (defined as more than 95% lysis) was achieved in about 73% of those patients. The 30-day and 14-month limb salvage rates were 95.8% and 89.6%, respectively, which compare favorably to the historic patients receiving thrombolysis or surgery alone. Despite higher success rates with the addition of GP IIb/IIIa inhibitor to a fibrinolytic agent, a prolonged infusion of thrombolysis continues to lead to higher complication rates proportional to the length of the infusion and the amount of thrombolytic administered as well as an increase in costs.

A new strategy that minimizes the amount and duration of thrombolysis used has been tested recently by investigators from the Cardiovascular Institute of the South. Although rheolytic thrombectomy in ALI

patients recently has been used in a multicenter, prospective study using the AngioJet device (Possis Medical, Inc., Minneapolis, Minnesota) and with low amputation and mortality rates at 30 days (7.1% and 4%, respectively), 37.4% of these patients still required the infusion of a thrombolytic agent.³⁴ By using the same AngioJet device and closing its outflow port, the device reverses flow and become a pulsing infusion catheter. This technique, called the power-pulse spray (P-PS), is capable of infusing a thrombolytic agent directly into the thrombus, which is then aspirated after a wait period of 15–20 minutes. The majority of patients are then treated without the need for a prolonged thrombolysis and with the use of only a small amount of thrombolytic agent, leading to shorter procedure times and less complication rates. In a small study of 49 patients with ALI and iliofemoral thrombotic occlusions, procedural success was reported in 92% and 91% of patients receiving tenecteplase or urokinase, respectively.³⁵ Furthermore, the duration of the procedure was approximately 72–75 minutes, a short time compared to historic controls. Limb salvage was also high, exceeding 90% in these patients.

Based on the aforementioned data, the algorithm in Figure 1 is proposed for the treatment of patients with ALI.¹⁵ First, an angiogram is performed emergently in all patients with ALI. Second, bivalirudin is administered as a base anticoagulant, and all patients are treated with a loading clopidogrel dose and aspirin. A wire is then used to cross the acutely occluded vessel. Once this is achieved, a GP IIb/IIIa inhibitor is then administered. Rheolytic thrombectomy is then performed with the AngioJet device. If the thrombus persists, the P-PS is then used with the administration of a lytic agent. Rheolytic thrombectomy is then repeated after a 15–20 minute waiting period. At this time, most thrombus is expected to have resolved. If not and the vessel is patent with slow flow, a prolonged infusion of a thrombolytic is then applied at a low rate along with a continued infusion of the GP IIb/IIIa inhibitor. A more definitive treatment of the lesion is then performed.

Approaching the Patient with SALI

Patients with lower limb thrombotic occlusions can present subacutely over several weeks. Typically, limb pain is accelerated with minimal activity or at rest (CLI). The underlying lesions are usually severe narrowings to total occlusions. In these patients, collaterals are usually present but not very well developed. There is a high likelihood that a recent thrombus is present, usually organized but most likely multilayered, subacute and acute. This presentation is similar to the unstable coronary syndromes. Patients can present with severe accelerated claudication or rest limb pain. In these patients, dethrombosing of the vessel is an important first step to reduce thrombotic embolization

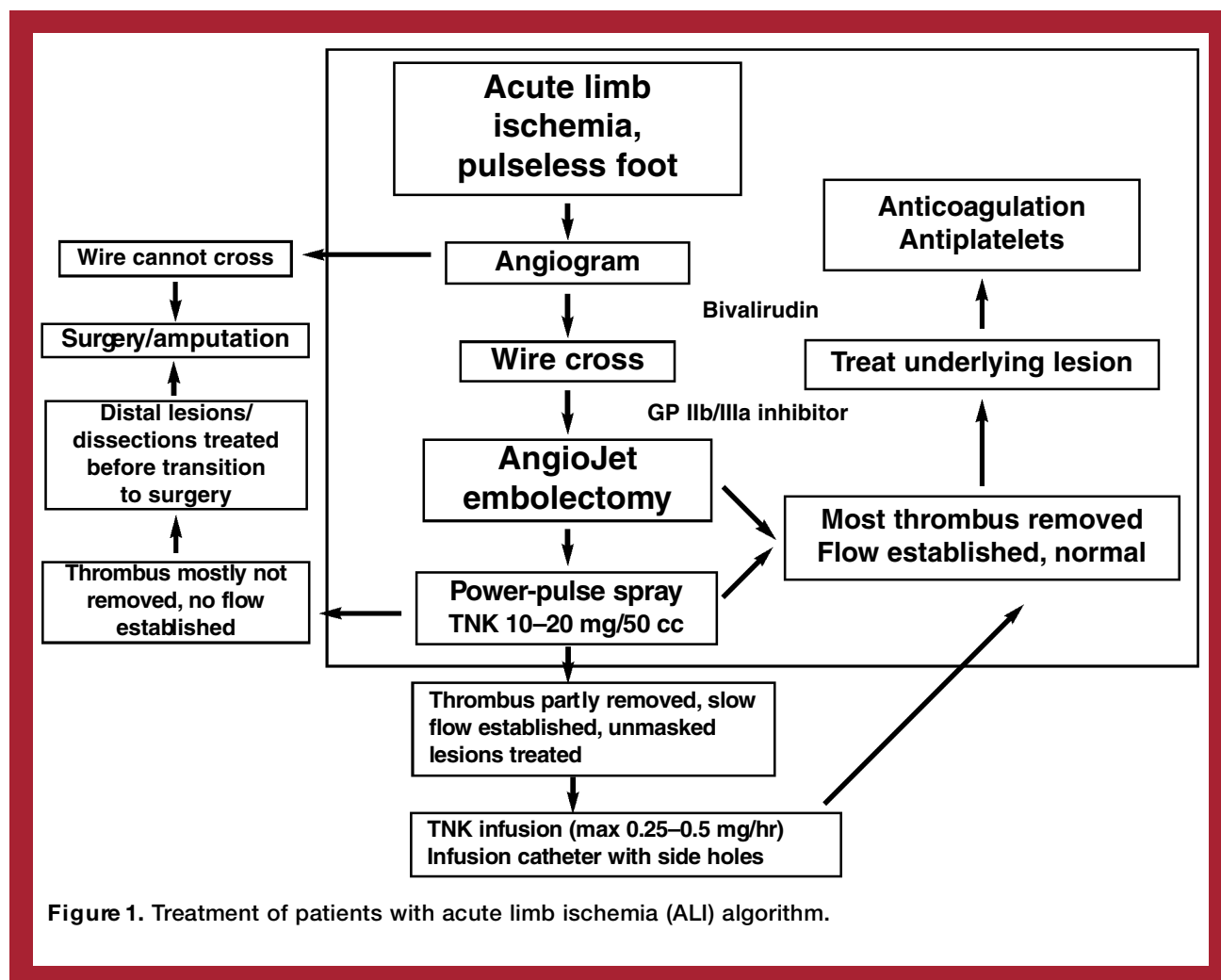


Figure 1. Treatment of patients with acute limb ischemia (ALI) algorithm.

and reduce reocclusion rates and complications post treatment. Traditionally, patients with critical limb ischemia have been classified as ALI or CLI. However, we believe that CLI is part of a larger syndrome of SALI, a clinical entity that also includes patients with severe claudication of recent symptom onset of several weeks and characterized by advanced limb ischemia with high prevalence of thrombotic occlusions.

The ideal anticoagulant in treating SALI is unknown. In the Circulate Pilot trial,³⁶ 85 patients with severe claudication or CLI were treated with eptifibatid in addition to conventional UFH. The procedure was technically successful in 98.8% of those patients. Of these patients, 1.2% required target vessel revascularization within 30 days. Low rates of major bleeding and thrombocytopenia were reported. In a recent study by Allie et al,³⁷ 149 patients with CLI received tirofiban and bivalirudin and were matched to 149 patients that received UFH with no GP IIb/IIIa inhibitors. There was a trend toward lower reintervention and higher limb salvage at 6 months in the bivalirudin-tirofiban group. Also, shorter time to sheath removal and lower

embolization rates were seen in the bivalirudin-tirofiban group. Furthermore, the same group recently published its experience with eptifibatid-bivalirudin combination (n = 162) in treating CLI matched to a historic control of patients with CLI and treated with UFH without a GP IIb/IIIa inhibitor.³⁸ In this study, the eptifibatid-bivalirudin group showed a statistically significant improvement ($p < 0.0001$) in sheath removal time < 2 hours and length of hospital stay < 72 hours. There were also trends toward fewer major access site complications, secondary reinterventions and 6-month limb salvage.

Based on these data, the algorithm in Figure 2 is proposed to treat SALI patients.¹⁵ First, an angiogram is performed on all patients with SALI after pretreating each with a loading dose of clopidogrel and aspirin 24 hours prior to the procedure when feasible. Second, bivalirudin is administered as a base anticoagulant during the procedure. A wire is then used to cross the acutely occluded vessel. Once this is achieved, a GP IIb/IIIa inhibitor is then administered. Conventional treatment is then performed with angioplasty, stenting

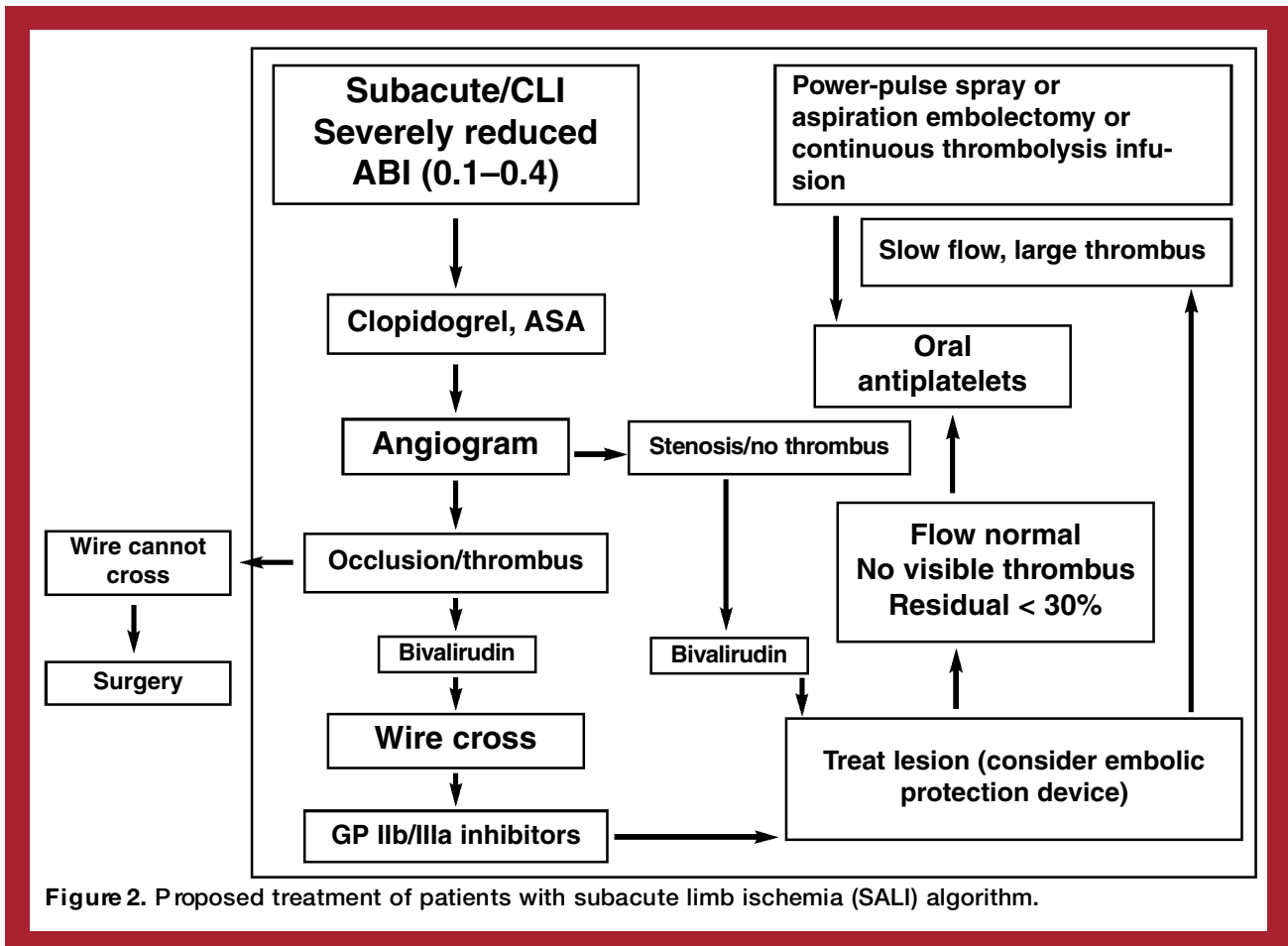


Figure 2. Proposed treatment of patients with subacute limb ischemia (SALI) algorithm.

or atherectomy as selected by the operator. Rheolytic thrombectomy and the P-PS are used only as a bail out in this situation if significant visible thrombus is encountered during the treatment.

As previously noted, SALI patients including CLI patients are likely to have thrombotic occlusions with organized thrombus. In the APART study, Tepe et al³⁹ tested the use of lytic therapy in these patients. In this prospective study, patients with up to 60 days history of limb ischemia were included and randomized to abciximab plus reteplase or to urokinase plus reteplase. The primary endpoint of this study was defined as therapeutic success and survival without open surgery or major amputation at 30 days follow-up. The amputation rate was only 1.7% on follow-up, a favorable number compared to historic control. Currently, the dethrombosis protocol in SALI is evaluating the role of thrombolysis in these patients using the P-PS technique prior to definite treatment following a predefined algorithm. A cohort of 20 consecutive patients will undergo intravascular ultrasound to evaluate for thrombotic occlusions in these patients. In this protocol (Figure 3), an angiogram is performed on all patients with SALI. Second, bivalirudin is administered as a base anticoagulant, and all patients are treated with a loading clopidogrel dose and aspirin. A

wire is then used to cross the acutely occluded vessel. Once this is achieved, rheolytic thrombectomy and P-PS are then performed with the AngioJet device followed by a more definitive treatment to the lower limb. GP IIb/IIIa inhibitors are used as a bail out in this protocol rather than a primary treatment.

Approaching the Patient with Stable Claudication

Patients with stable claudication generally present with several months history of exertional lower-extremity pain or claudication. The underlying lesions are typically severe narrowings or total occlusions and suboptimal collaterals are usually present. The chronic presentation (> 1 month) of these patients does not exclude the presence of a thrombus. Organized thrombus could be encountered in total occlusions. It is unusual, however, to see a thrombus in patent vessels of patients with stable claudication.

Patients with claudication generally can be managed with a single anticoagulant as in the APPROVE trial.¹⁷ However, in this study, long occlusions were excluded. In a prospective, double-blind, placebo-controlled study that evaluated abciximab versus placebo in 98 patients with long femoral popliteal occlusions, the patency with

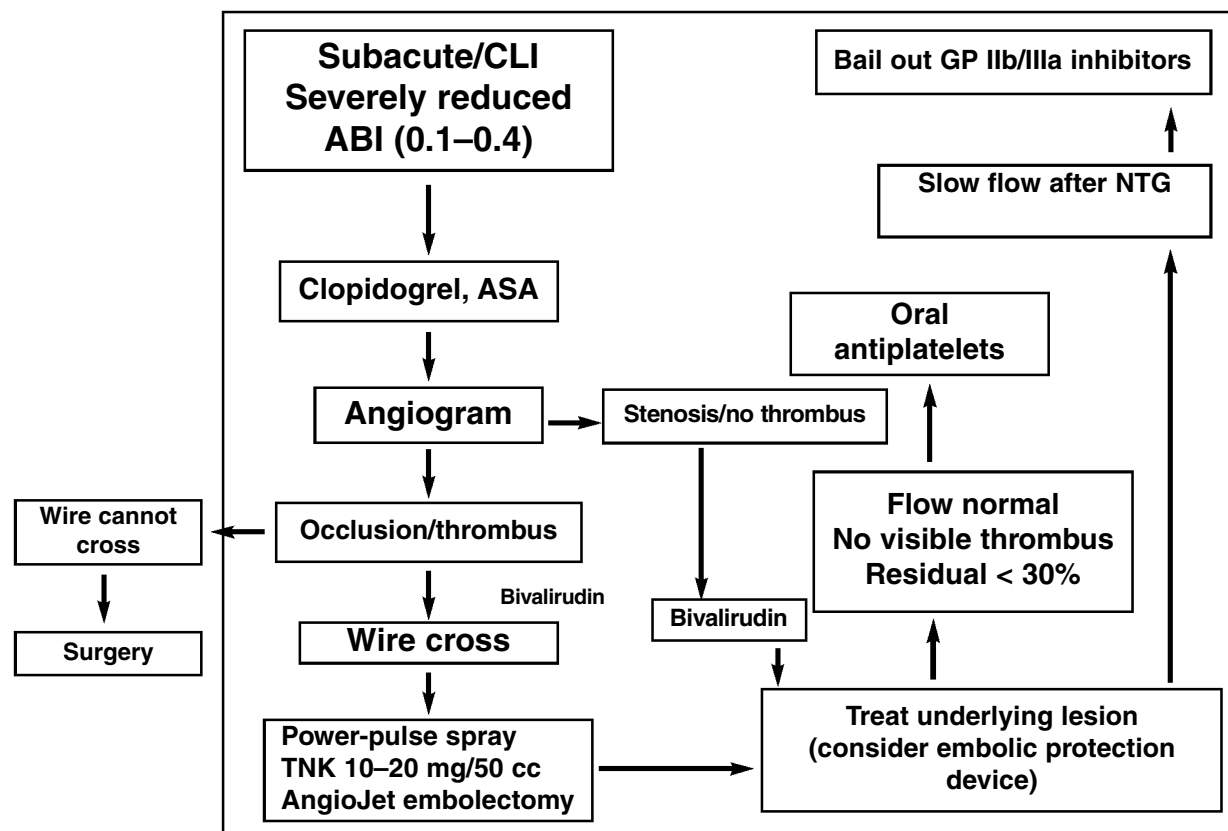


Figure 3. Dethrombosis protocol algorithm using the power-pulse spray to treat patients with subacute limb ischemia (SALI) as an alternate to Figure 2 algorithm. This protocol is currently being tested for feasibility by the Midwest Cardiovascular Research Foundation Investigators.

abciximab was 95.7% versus 80.4% ($p = 0.02$) and 61.7% versus 41.2% ($p = 0.03$) at 30 days and 6 months, respectively.⁴⁰ A better clinical outcome as assessed by the Rutherford-Baker score was noted in the abciximab group. We believe that long occlusions in these patients, particularly those with a recent clinical history of symptoms within 6 months, have a thrombotic element to their occlusion, hence explaining some of the benefit of GP IIb/IIIa inhibitors in these patients.

Conclusion

Thrombus is abundant in patients with ALI, SALI (including CLI) and claudication with recent long total occlusions. Thrombosis is associated with higher complication rates and prolonged procedure times. Early data suggest that in patients with ALI, GP IIb/IIIa inhibitors added to a fibrinolytic agent can result in clinically favorable results in reducing limb amputation and complications. The P-PS technique is emerging to be an important technique in treating these patients, and currently, it is being tested in patients with SALI including those with CLI.

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“Pharmacotherapy in Peripheral Vascular Disease” Post Test

Choose the single best answer to the following questions.

1. **Which of the following statements is true?**
 - A. The incidence of diabetes mellitus is about the same in patients having PCI as in patients having PPI for CLI
 - B. Unfractionated heparin (UFH) is FDA approved and indicated for both PCI and PPI
 - C. UFH has linear kinetics
 - D. All of the above
 - E. None of the above
2. **Which of the following statements is true?**
 - A. UFH stimulates platelet aggregation
 - B. PAD patients show increased platelet activation and aggregation
 - C. PAD patients have increased levels of von Willebrand factor
 - D. All of the above
 - E. None of the above
3. **Which of the following statements is true?**
 - A. GP IIb/IIIa benefits in PCI that may be applicable to PPI include improved outcomes in patients with diabetes, visible thrombus and small vessels
 - B. The 2002 ACC/AHA guidelines recommend GP IIb/IIIa inhibition in patients with diabetes and ACS undergoing PCI
 - C. Retrospective safety and feasibility trials of using GP IIb/IIIa in patients with CLI have been published
 - D. All of the above
 - E. None of the above
4. **Unfractionated heparin:**
 - A. Produces predictable anticoagulation
 - B. Inhibits soluble thrombin
 - C. Has no effect on platelet aggregation
 - D. Inhibits production of fibrinogen following percutaneous intervention
5. **Vascular amputations in the United States:**
 - A. Are on the decline
 - B. Occur quite often without a single ABI
 - C. Are associated with a low rate of 30-day perioperative mortality
 - D. Are not reduced effectively with percutaneous intervention
6. **Patients with CLI and a subacute presentation:**
 - A. Have well developed collaterals
 - B. Have a high frequency of thrombotic occlusions
 - C. Typically present with ulceration
 - D. Are best treated surgically
7. **Bivalirudin:**
 - A. Has predictable anticoagulation
 - B. Dissolves bound and soluble thrombin
 - C. Does not activate platelets
 - D. All the above
8. **The combination of a GP IIb/IIIa inhibitor and bivalirudin appears:**
 - A. Safe with no increase in major bleeding compared to heparin
 - B. To produce clinically important reduction in re-intervention rates at 6 month
 - C. To lead to a clinically higher limb salvage at 6 months compared to heparin
 - D. All the above
9. **Laser atherectomy using the excimer laser:**
 - A. Is very effective in recanalizing occluded vessels in CLI patients
 - B. Has no ability to dissolve thrombus
 - C. Leads to clinically important embolization
 - D. Is superior to angioplasty and stenting
10. **The power-pulse spray:**
 - A. Is effective in dissolving thrombus at a low thrombolytic dose
 - B. Results in high procedural success rates in patients with acute thrombotic occlusions
 - C. Shortens procedure time in thrombus removal
 - D. All the above
11. **The presence of acute intravascular thrombus:**
 - A. Leads to a higher rate of amputations
 - B. Results in higher death rate
 - C. Prolongs the interventional procedure
 - D. All of the above



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