

Periprocedural antithrombotic strategies in acute ischemic stroke interventional therapy

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ABSTRACT

In patients undergoing endovascular therapy for acute ischemic stroke, antithrombotic therapies are utilized to prevent distal embolization, arterial reocclusion, or catheter-related embolism. However, this must be weighed against the risk of hemorrhagic complications secondary to existing and ongoing ischemia or silent vessel perforation. In this article, we present an overview of the available literature evaluating antithrombotic therapy in patients undergoing endovascular therapy for acute ischemic stroke and discuss the emerging role of these agents. *Neurology*® 2012;79 (Suppl 1):S174–S181

GLOSSARY

ACT = activated clotting time; **ADP** = adenosine diphosphate; **AIS** = acute ischemic stroke; **CI** = confidence interval; **GP** = glycoprotein; **IA** = intra-arterial; **IAT** = intra-arterial therapy; **IMS** = Interventional Management of Stroke; **IU** = international units; **MCA** = middle cerebral artery; **MERCI** = Mechanical Embolus Removal in Cerebral Ischemia; **OR** = odds ratio; **PCI** = percutaneous coronary intervention; **PROACT** = Prolyse in Acute Cerebral Thromboembolism; **rpro-UK** = recombinant pro-urokinase; **rtPA** = recombinant tissue plasminogen activator; **sICH** = symptomatic intracerebral hemorrhage; **TIMI** = thrombolysis in myocardial ischemia; **UK** = urokinase.

Intra-arterial therapy (IAT) has emerged as an important adjunct to IV thrombolysis in acute ischemic stroke (AIS). Although IAT has many theoretical advantages, including site specificity and high recanalization rates, early reocclusion and distal embolization occur in 18%–22% and 16%, respectively, of the AIS patient population that undergoes endovascular therapy.^{1–3} Periprocedural antithrombotic therapy may be used to reduce these complications, but it must be weighed against the risk of hemorrhagic complications. Here we present an overview of the literature evaluating the utility of antithrombotic therapies for periprocedural support and recanalization in patients undergoing AIS endovascular therapy.

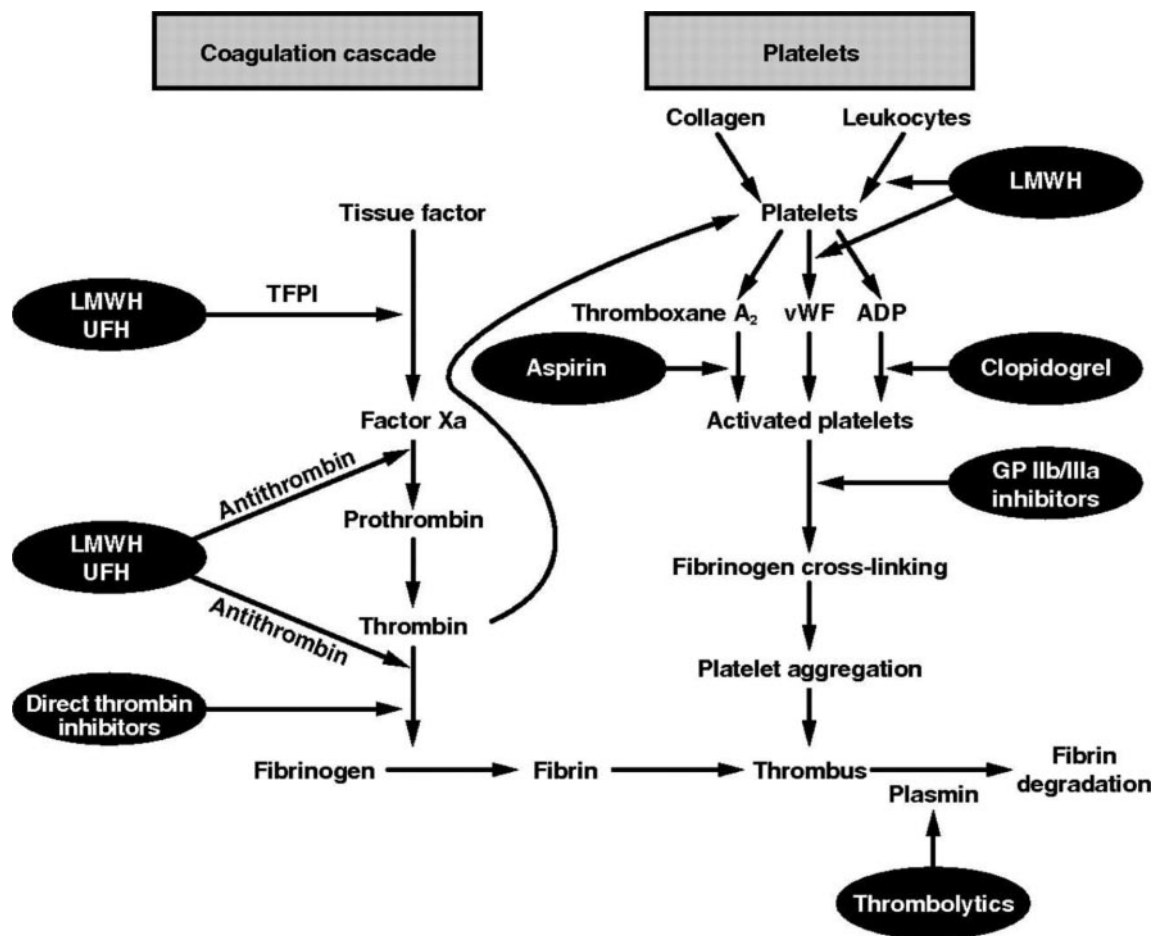
ANTITHROMBOTIC AGENTS FOR PERIPROCEDURAL SUPPORT **Anticoagulation therapy.** Since the development of percutaneous coronary intervention (PCI), IV unfractionated heparin has remained the primary antithrombotic agent for prevention of periprocedural ischemic complications as a result of its immediate anticoagulation effect, its short half-life, its ability to be monitored with point-of-care testing, and the availability of IV protamine sulfate to rapidly reverse its anticoagulation effect.^{4,5} Unfractionated heparin–mediated inactivation of coagulation proteases (thrombin, factors IXa, Xa, XIa, and XIIa) occurs via its binding to and subsequent activation of antithrombin III (figure 1).⁶ Optimal periprocedural activated clotting time (ACT) in PCI has been empirically determined to range from 250 to 350 seconds (normal, 81–125 seconds),⁷ based on the American College of Cardiology level of evidence C (consensus opinion of experts, case studies, standard of care).⁸ Similarly, there are limited data on the safety of periprocedural heparin in AIS endovascular therapy.

The Prolyse in Acute Cerebral Thromboembolism (PROACT) trial was the first double-blind, randomized, placebo-controlled study of recombinant pro-urokinase (rpro-UK) delivered intra-arterially by microcatheter in acute middle cerebral artery (MCA) ischemic stroke.⁹ The initial 16 patients received a 100-IU (international units)/kg IV bolus of heparin, followed by continuous infusion at a rate of 1,000 IU/hour for 4 hours. At the end of the rpro-UK infusion, 81.8% of patients treated with this “high-dose heparin” demonstrated recanalization (thrombolysis in myocardial ischemia score [TIMI], 2 + 3), with an associated symptomatic intracerebral hemorrhage (sICH) rate of 27.3%. The heparin regimen was modified for the remaining patients on the recommendation

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Figure 1 Platelet and coagulation cascade



Graphic of coagulation cascade shows main sites of action of antithrombin therapies. ADP = adenosine diphosphate; GP = glycoprotein; LMWH = low-molecular-weight heparin; TFPI = tissue factor pathway inhibitor; UFH = unfractionated heparin; vWF = von Willebrand factor. Reprinted with permission by Elsevier, from: Selwyn AP. Prothrombotic and antithrombotic pathways in acute coronary syndromes. *Am J Cardiol* 2003;91:3H-11H.

of the External Safety Committee and Drs. Jack Hirsh, Gregory del Zoppo, and Anthony Furlan. The bolus dose and infusion rates were lowered to 2,000 IU and 500 IU/hour, respectively. In patients treated with rpro-UK, the “low-dose heparin” regimen effectively cut the sICH and MCA recanalization rates to 6.7% and 40%, respectively (personal communication, A. Furlan, January 2010).

Subsequently, multiple IAT trials evaluating endovascular therapy in AIS have relied on a low-dose heparin regimen similar to that of the PROACT trial. The previously effective low-dose heparin protocol was also shown to be effective in eliciting a recanalization and sICH rate of 66% and 10%, respectively, in PROACT II, a phase III trial designed to assess the clinical efficacy and safety of intra-arterial (IA) rpro-UK in acute MCA ischemic stroke of less than 6-hour duration.¹⁰ Moreover, a low-dose IV regimen (2,000 IU bolus followed by 450 IU/hour), in addition to a heparin flush (40 IU/hour, administered via access sheath and guide catheter),

was used in the Interventional Management of Stroke (IMS) I and II trials.^{11,12} These trials, designed to assess whether a combined IV/IAT approach to recanalization was superior to standard IV rtPA alone in AIS, found that recanalization rates (TIMI 2 + 3) were similar (IMS I: 56%; IMS II: 60%), with rates of sICH comparable to those in other endovascular acute stroke studies (IMS I: 6.3%; IMS II: 9.9%).^{11,12} The ongoing IMS III study uses the same heparin regimen used in IMS I and IMS II.¹³

Recently, the safety of low-dose heparin, when combining mechanical devices with IV or IA thrombolytic therapy, has been further demonstrated in multiple prospective, multicenter single-arm mechanical embolectomy trials. In the Mechanical Embolus Removal in Cerebral Ischemia (MERCII) trial, 164 patients with large-vessel stroke underwent thrombectomy with the Merci retriever device within 8 hours of symptom onset, including 48 patients (29.3%) who received IV rtPA before intervention.¹⁴ Peri-procedural heparin was given at the

Table 1 Doses of periprocedural heparin used in acute ischemic stroke endovascular trials

Trial name	Heparin IV bolus dose	Heparin IV infusion dose	Heparin IA
Prolyse in Acute Cerebral Thromboembolism (PROACT I) ⁹	First 16 patients: 100 IU/kg	First 16 patients: 1,000-IU/h infusion for 4 h	None
	Remaining patients: 2,000 IU	Remaining patients: 500-IU/h infusion for 4 h	
Prolyse in Acute Cerebral Thromboembolism (PROACT II) ¹⁰	2,000 IU	500-IU/h infusion for 4 h	None
Interventional Management of Stroke (IMS I, II, and III) ¹¹⁻¹³	2,000 IU	450-IU/h infusion for the time of the procedure	40-IU/h infusion for the time of the procedure
Mechanical Embolus Removal in Cerebral Ischemia (MERC I) ⁴²	Allowed at the discretion of the investigator	Allowed at the discretion of the investigator	None
Multi Mechanical Embolus Removal in Cerebral Ischemia (Multi-MERC I) ¹⁵	Allowed at the discretion of the investigator	Allowed at the discretion of the investigator	None
Study of the Penumbra System ¹⁶	Subjects without IV thrombolytic treatment: 5,000 IU	Subjects without IV thrombolytic treatment: continuous infusion at 2,000-IU/hour to maintain an ACT \geq 250 seconds	None
	Subjects with IV thrombolytic treatment: 2,000 IU	Subjects with IV thrombolytic therapy: continuous infusion at 1,000-IU/hour	

Abbreviations: ACT = activated clotting time; IA = intra-arterial; IU = international units.

discretion of the treating interventionalist, and data on periprocedural heparin use was collected on consecutive patients enrolled in the final 6 months of the study. Of the 51 patients enrolled during this study period, 24 (47%) received periprocedural IV heparin, with a median dose of 3,000 IU, including 8 patients who received IV rtPA. In a post hoc analysis, there was no significant difference in rates of revascularization success, hemorrhage, procedural complications, or 90-day mortality between patients receiving heparin and those not receiving heparin. In multivariable analysis, a 90-day good outcome (modified Rankin Scale score, 0–2) was associated with periprocedural heparin use (odds ratio [OR] 5.89; 95% confidence interval [CI] 1.34–25.92; $p = 0.0189$).¹⁵

In the phase I study of the Penumbra System, 20 patients received treatment with mechanical embolectomy, including 6 patients who received IV rtPA and 9 patients who received postdevice IA rtPA.¹⁶ Heparin (2,000-IU bolus, followed by 1,000-IU/hour continuous infusion) was administered systemically to patients who received thrombolytic therapy. Patients who did not receive thrombolytic therapy were administered a higher bolus dose (5,000 IU) and infusion rate (continuous infusion of 2,000 IU/hour) to maintain ACT of at least 250 seconds. Recanalization (TIMI 2–3) before IA lysis was achieved in all treated cases, and 2 patients (10%) developed sICH.¹⁶

Table 1 summarizes the doses of periprocedural heparin used in AIS endovascular trials.

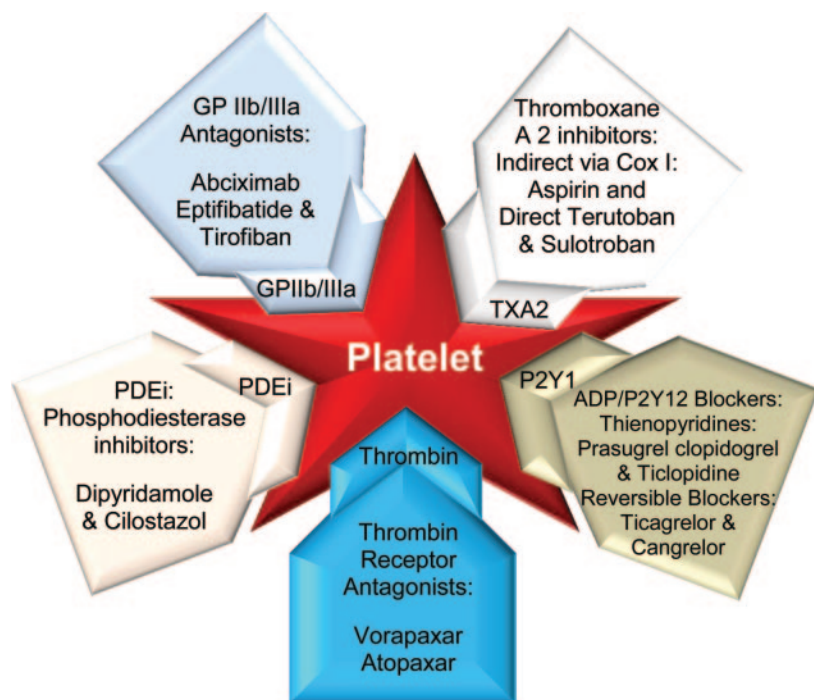
Antiplatelet therapy. Platelet adhesion and aggregation are central features of arterial thrombosis and arterial reocclusion.² The inhibitory effect of conven-

tional antiplatelet drugs, including aspirin and adenosine diphosphate (ADP) analogues (clopidogrel or ticlopidine), are dependent on inhibition of prostaglandin synthesis or signal transduction pathways induced by activated ADP receptors (figure 2).

The evolution of intracranial stenting for AIS highlights the importance of adequate platelet inhibition for periprocedural support to prevent stent thrombosis. In the first US Food and Drug Administration–approved prospective study on primary intracranial stenting for AIS,¹⁷ preprocedural oral antiplatelet therapy included clopidogrel, 600 mg, and aspirin, 650 mg (oral or rectal), combined with intraprocedural heparin to achieve an ACT between 250 and 300 seconds. Recanalization (TIMI 2 or 3) was achieved in all 20 patients, with 1 (5%) symptomatic and 2 (10%) asymptomatic hemorrhages. No stent thrombosis occurred in the study.

Rapid onset of the full antiplatelet effect of aspirin and clopidogrel is essential when performing urgent intracranial stenting to reduce the risk of stent thrombosis. Studies on the optimal dosing of aspirin and clopidogrel have been extrapolated from PCI data. For patients not already on chronic aspirin therapy, 300 to 325 mg of aspirin at least 2 hours before PCI is recommended¹⁸; for patients not on chronic clopidogrel therapy, loading with 600 mg has been shown to achieve the full antiplatelet effect within 2 hours of administration, to result in higher plasma concentrations of the active metabolite, and to significantly lower ADP-induced platelet aggregation in comparison with a loading dose of 300 mg; loading doses of 900 mg have not been shown to result in significantly more antiplatelet effects.^{19–22}

Figure 2 Antiplatelet therapies and their interactions with platelet receptors



ADP = adenosine diphosphate; GP = glycoprotein; PDEi = phosphodiesterase inhibitor; TXA2 = thromboxane A2.

Data on the safety of a clopidogrel bolus in AIS is limited to a single case series of 20 patients, in which a loading dose of 600 mg of clopidogrel prior to initiating a regular dose of 75 mg/day was not associated with hemorrhagic transformation in any of the patients.²³

It has been recognized that the response to clopidogrel varies among patients.^{24,25} Clopidogrel is a prodrug that requires oxidation by hepatic CYP450 enzymes to generate the active metabolite that inhibits the platelet for its lifespan. The majority of clopidogrel is inactivated by carboxylesterases, such that only 15% of the active metabolite reaches the platelet receptor after undergoing 2 steps of oxidative biotransformation. As a result, loss-of-function alleles in the gene encoding CYP450 2C19 can significantly lower levels of the active metabolite of clopidogrel, and patients with these loss-of-function alleles who undergo PCI have been shown to have increased cardiovascular events, including stent thrombosis, in comparison with extensive metabolizers.^{26–28} The impact of clopidogrel resistance in AIS endovascular therapy remains largely unstudied.

The use of platelet function testing has been considered one potential approach to identify patients with clopidogrel resistance and to individualize therapy. This concept was evaluated in the Gauging Responsiveness with a VerifyNow (Accumetrics, Inc., Corporation, San Diego, CA) assay—Impact on

Thrombosis And Safety (GRAVITAS) trial evaluating patients undergoing elective PCI.²⁹ Patients identified by the VerifyNow assay as nonresponders to clopidogrel were randomly assigned to high-dose (repeat 600-mg load, followed by 150 mg daily) or standard-dose (75 mg daily) clopidogrel 1 day after PCI. There was no difference between the 2 treatment arms in cardiovascular outcomes, including death and stent thrombosis, at 30 days and 6 months. Although individualizing antiplatelet therapy on the basis of platelet function testing is appealing, routine platelet function testing is not currently recommended in PCI^{30,31} and requires study in AIS endovascular therapy.

Newer oral antiplatelet agents such as prasugrel, which requires only 1 hepatic CYP450 oxidation step to generate its active metabolite, and ticagrelor, which is rapidly absorbed as an active metabolite without requiring any hepatic or intestinal oxidative biotransformation, may be more effective in patients who have loss-of-function alleles.³¹ However, prasugrel is currently contraindicated in patients with a history of stroke or TIA, after a post hoc analysis in acute coronary syndrome patients identified a higher rate of the combined endpoint of death from any cause, nonfatal myocardial infarction, nonfatal stroke, or nonfatal major bleeding in comparison with clopidogrel (hazard ratio 1.54; 95% CI 1.02–2.32; $p = 0.04$),^{32,33} and ticagrelor has not been evaluated in stroke patients.

ANTITHROMBOTIC AGENTS FOR RECANALIZATION

IV antiplatelet agents. Because the final common event in platelet aggregation requires binding of fibrinogen to the glycoprotein (GP) IIb/IIIa complex, agonist pathways activating the GP IIb/IIIa complex that are not affected by aspirin or ADP analogues are still able to potentiate platelet aggregation.³⁴ Although the GP IIb/IIIa inhibitors abciximab, eptifibatide, and tirofiban have undergone large clinical trials in PCI to establish their safety and effectiveness, data on their role in patients with AIS undergoing IAT is limited to only 4 case series that have included ≥ 10 patients and 2 prospective studies of patients treated with combination thrombolysis and abciximab.^{35–40}

In one AIS study, a total of 26 patients were treated with IA urokinase (UK), with or without IV abciximab (0.25-mg/kg bolus, then 0.125- μ g/kg/min periprocedural infusion).³⁵ Patients who received both treatments had significantly higher recanalization rates (TIMI 2 + 3) than patients treated with IA UK alone (UK + abciximab 90% vs UK 43.8%; $p = 0.037$), with no significant difference in sICH (UK + abciximab, 16%, vs UK, 30%;

$p = 1.0$).³⁵ Patients who received abciximab also required significantly lower amounts of UK to achieve recanalization than patients treated with UK alone (418,000 IU vs 828,000 IU; $p < 0.005$). In another series, 12 AIS patients refractory to IV or IA thrombolysis, were given an IV or IA abciximab bolus (mean, 11.8 ± 5.8 mg) in addition to angioplasty, mechanical embolectomy, or stenting; 11 patients (92%) had successful recanalization (TIMI 2 + 3), with 1 instance (8.3%) of sICH.³⁶ GP IIb/IIIa inhibitors were also evaluated as adjunctive therapy for patients with large-vessel occlusion and AIS refractory to pharmacologic thrombolysis with rtPA and mechanical disruption, balloon angioplasty, or both. Twenty-one patients with large-vessel occlusion refractory to IAT were treated with IV or IA GP IIa/IIIb inhibitors, with recanalization (TIMI 2 + 3) achieved in 17 (81%) and no cases of sICH.³⁷ IV tirofiban has also been evaluated in combination with heparin and followed by IA urokinase in 21 AIS patients³⁸; recanalization (TIMI 2 + 3) was achieved in 17 patients (81%), although sICH occurred in 5 patients (24%) and included 3 fatal hemorrhages. Although these case series suggested high recanalization rates associated with the use of GP IIb/IIIa inhibitors in IAT, the risk of sICH associated with their use remained a concern.

The Combined Local Fibrinolysis and IV Abciximab in Acute Vertebrobasilar Stroke Treatment (FAST) multicenter study prospectively evaluated IV abciximab (0.25 mg/kg) followed by a 12-hour infusion (0.125 $\mu\text{g}/\text{kg}/\text{min}$) and low-dose IA rtPA (median dose, 20 mg) in patients with acute vertebrobasilar occlusion; additional angioplasty/stenting was allowed if there was severe residual stenosis.³⁹ Of 47 patients, 34 (72%) achieved recanalization (TIMI 2 + 3), though 14 patients required angioplasty/stenting; sICH occurred in 6 patients (13%), all of whom died. In another prospective study, the combination of IV abciximab (0.25-mg/kg bolus, followed by 0.125 $\mu\text{g}/\text{kg}/\text{min}$) with escalating doses of IA reteplase (0.5, 1, 1.5, 2 units) was evaluated in AIS patients 3 to 6 hours after symptom onset as part of an open-label, dose-ranging, phase I study.⁴⁰ Twenty patients were recruited; 18 successfully received IV abciximab with escalating doses of IA reteplase, and 2 patients had premature discontinuations due to sICH or pseudothrombocytopenia. Recanalization (defined as an improvement by 1 or more grades from baseline) was achieved in 13 patients (65%), and 1 patient had sICH (5%). The safety stopping rule was not activated in any of the tiers.⁴⁰ Together these prospective studies demonstrated high recanalization rates associated with the use of GP IIb/IIIa inhibitors in IAT with a moderate risk of sICH.

Although other case series also suggest that IV abciximab may be effective in the treatment of arterial reocclusion after initial recanalization in AIS,^{2,3,41} data from the Multi-MERCI Trial, part 1, suggest caution is warranted in the use of abciximab to complement AIS endovascular therapy. Major protocol violations in this study included 9 patients who were treated with IV abciximab, and its use was associated with asymptomatic subarachnoid hemorrhage (OR 19.2; 95% CI 3.68 to >100).⁴² Additionally, a recent multicenter series including 12 AIS patients undergoing IAT with adjunctive IV or IA abciximab resulted in sICH in 3 (25%).⁴³ The use of GP IIb/IIIa inhibitors in AIS patients undergoing IAT remains investigational and of uncertain benefit.

Oral antiplatelet agents. Although pooled analyses from 2 large, randomized, placebo-controlled trials have shown a modest but statistically significant benefit from aspirin in the prevention of recurrent stroke events when initiated within 48 hours of ischemic stroke,⁴⁴ aspirin administration is contraindicated for 24 hours after IV thrombolysis.^{45,46} The optimal timing to initiate oral antiplatelets in AIS patients who do not receive IV thrombolysis and undergo endovascular therapy has yet to be systematically evaluated. The majority of endovascular trials in AIS have prohibited the administration of antiplatelet agents or anticoagulants for 24 hours posttreatment.^{9–13} The MERCI and Multi-MERCI studies allowed 325 mg of aspirin to be given orally or rectally at the end of the embolectomy procedure, with no oral/IV anticoagulation administered in the first 24 hours posttreatment.

DISCUSSION Optimal doses of heparin and antiplatelet therapies for periprocedural support during AIS endovascular therapy have not been established. However, these data suggest that a low-dose heparin regimen (2,000-IU bolus followed by a 500-IU/hour continuous infusion) may be safe in cases where IV rtPA has been administered. In cases where mechanical embolectomy is performed, without prior IV rtPA administration, a higher-dose heparin regimen (5,000-IU bolus followed by a 2,000-IU/hour continuous infusion, to maintain ACT ≥ 250 seconds) may be considered. Periprocedural support for intracranial stenting in AIS requires adequate platelet inhibition to reduce the risk of stent thrombosis and can be achieved with loading doses of aspirin, 300 to 650 mg, and clopidogrel, 600 mg. The role of platelet function testing in AIS endovascular therapy requires further study before its routine use can be recommended.

The safety and efficacy of IV and oral antiplatelets to augment recanalization in AIS endovascular ther-

Table 2 Dosing table for anticoagulant and antiplatelet therapy during endovascular therapy for acute ischemic stroke

Drug	During endovascular therapy	
	Patient received IV thrombolytic	Patient did not receive IV thrombolytic, and IA thrombolytic use anticipated
Parenteral anticoagulants		
Unfractionated heparin	May consider 2,000-IU bolus followed by 500-IU/h continuous infusion throughout procedure ^a	May consider 5,000-IU bolus followed by a 2,000-IU/h continuous infusion throughout the procedure to achieve target ACT \geq 250 seconds ^b
Glycoprotein IIb/IIIa receptor antagonists^c		
Abciximab	Of uncertain benefit	Of uncertain benefit; may consider in patients who have arterial reocclusion after initial recanalization; LD of 0.25 mg/kg IV bolus, MD of 0.125 μ g/kg per minute (maximum 10 μ g/min)
Eptifibatid	Of uncertain benefit	Of uncertain benefit; LD of 100 mcg/kg IV bolus, MD of 0.75 μ g/kg/min; reduce infusion by 50% in patients with estimated creatinine clearance <50 mL/min
Tirofiban	Of uncertain benefit	Of uncertain benefit; LD of 0.4 μ g/kg/min IV bolus, MD of IV infusion of 0.1 μ g/kg/min; reduce rate of infusion by 50% in patients with estimated creatinine clearance <30 mL/min
Oral antiplatelet agents		
	Avoid for 24 h after IV thrombolytic therapy ^c	May consider initiating immediately after endovascular therapy ^d ; LD of aspirin, 300-650 mg, and clopidogrel, 600 mg, for patients undergoing intracranial stenting and not on chronic aspirin and clopidogrel therapy ^e

Abbreviations: ACT = activated clotting time; IU = international units; LD = loading dose; MD = maintenance dose.

^a Based on Prolyse in Acute Cerebral Thromboembolism (PROACT)⁹ and PROACT II trials.¹⁰

^b Based on the prospective study of the Penumbra system.³⁴⁻⁴³

^c Based on the National Institute of Neurological Disorders and Stroke (NINDS) tPA Stroke Study⁴⁵ and the European Cooperative Acute Stroke Study (ECASS) 3 trial.⁴⁶

^d Based on the Mechanical Embolus Removal in Cerebral Ischemia (MERC1) trial⁴² and the Multi-MERC1 trial.¹⁴

^e Based on the Stent-Assisted Recanalization in Acute Ischemic Stroke (SARIS) trial.¹⁷

apy has not been established. Although preliminary studies suggest that IV antiplatelet therapies may augment recanalization in AIS endovascular therapy when combined with IV or IA thrombolytic therapy, the risk of hemorrhagic complications remains a concern and further prospective studies are needed before their use can be recommended. Oral antiplatelet therapies remain contraindicated for 24 hours after IV thrombolytic therapy; however, early initiation may be considered after AIS endovascular therapy, especially in patients who have undergone mechanical embolectomy without IA thrombolysis. Our recommended strategies for periprocedural anticoagulants and antiplatelet therapies in AIS endovascular therapy are summarized in table 2.

CONCLUSION Despite the availability of multiple antithrombotic agents, many questions remain on the optimal use of these agents for AIS endovascular therapy, as evidenced by the lack of uniformity among studies to date. Although periprocedural anti-coagulant and antiplatelet therapies have been demonstrated to reduce periprocedural thrombotic

complications in PCI, further studies are warranted in AIS to define their optimal use and dosing during IAT when balanced against their risk of hemorrhage.

AUTHOR CONTRIBUTIONS

Dr. Nahab: drafting/revising the manuscript, study concept or design, analysis or interpretation of data. Dr. Kass-Hout: drafting/revising the manuscript. Dr. Shaltoni: drafting/ revising the manuscript, acquisition of data.

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DISCLOSURE

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