Antithrombotics in Vascular Surgery: Current Practice Guidelines

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Abstract

Pre- or post-intervention, vascular surgical patients are expected to be on one or more antithrombotic agents. Antithrombotics have played a key role in reducing cardiovascular mortality in vascular patients. There are wide variations in the practice of prescribing antithrombotic agents in vascular services. Evidence-based current practice guidelines are often not strictly followed which puts some of these patients at increased risk of bleeding complications. This paper looks at the current practice guidelines on antithrombotics.

Keywords: Antithrombotics, aspirin, clopidogrel, current practice guidelines, heparin, vascular surgery, warfarin

Introduction

Vascular surgical patients are often on one or more antithrombotic agents. Antithrombotics include both antiplatelets and anticoagulants and are among the most extensively prescribed drugs worldwide. They have played a major role in reducing cardiovascular morbidity and mortality in vascular patients. Their use is, however, also associated with increased risk of major hemorrhagic complications. The introduction of newer antithrombotic agents into clinical practice in the last decade has reinforced the need for evidence-based prescribing of these life and limb saving drugs.

Aspirin is the most common prescribed antiplatelet agent and has been in use in this capacity since the 1970s when Sir John Vane demonstrated the inhibition of prostaglandin synthesis as its main mechanism of action. The current antiplatelet drugs are categorized into several classes and include irreversible cyclooxygenase inhibitors (Aspirin), adenosine diphosphate receptor inhibitors (Clopidogrel, Ticagrelor), phosphodiesterase inhibitors (Cilostazol), protease-activated receptor-1 antagonists (Vorapaxar), glycoprotein IIB/IIA inhibitors (Abciximab, Eptifibatide, Tirofiban), adenosine reuptake inhibitors (Dipyridamole), and thromboxane receptor antagonists (Terutroban).

Anticoagulant use in medicine dates back to the 1920s when heparin was discovered by Jay McLean and William Henry Howell at Johns Hopkins University. Heparin is a naturally occurring anticoagulant which acts in combination with antithrombin III to inhibit clotting factors. Multiple derivatives of heparin have been developed (Enoxaparin, Tinzaparin) with modification of therapeutic efficacy and side effect profiles.

Clinical practice guidelines of antiplatelet and anticoagulants in vascular surgery have often been based on extrapolation of outcomes of clinical trials in the field of cardiology. The selection of an appropriate agent is based on a number of characteristics including duration of action, predictability, need for monitoring, and the side effect profile.

Antithrombotics in Peripheral Arterial Disease

Patients with lower limb arterial disease may present with claudication, rest pain, or tissue loss. Symptomatic patients have a higher risk of myocardial infarction (MI) and stroke when compared to the normal population. Antithrombotics...
are used for secondary prophylaxis against cardiac and cerebrovascular events in these patients. In a meta-analysis done by the Antithrombotic Trialists Collaboration, aspirin significantly reduced total mortality, nonfatal MI, and nonfatal stroke but increased nonfatal extracranial bleeding events. However, the reduction in the number of vascular events and total deaths far outweighed the number of bleeding events.[6]

After the benefit of aspirin was established, studies were carried out to determine whether other antiplatelet agents or dual antiplatelet regimes would further reduce Cardiovascular events. The clopidogrel versus aspirin in patients at risk for ischemic events study showed statistically significant relative risk reduction of ischemic stroke, MI, or vascular death in favor of clopidogrel compared with aspirin.[7] The clopidogrel for high atherothrombotic risk and ischemic stabilization, management, and avoidance trial demonstrated that dual antiplatelet therapy (DAPT) (clopidogrel plus aspirin) was not more effective than aspirin alone in reducing the rate of MI, stroke, or death in patients with stable cardiovascular disease.[8]

The American College of Cardiology (ACC) and American Heart Association (AHA) task force on clinical practice guidelines on the management of peripheral arterial disease (PAD) (2016) recommend single antiplatelet agent therapy with either aspirin (range 75–325 mg/day) or clopidogrel (75 mg/day) to reduce MI, stroke, and vascular death in patients with symptomatic PAD.[9]

In asymptomatic patients with PAD, (ankle brachial index [ABI] ≤ 0.90), the AHA/ACC 2016 guidelines state that, antiplatelet therapy is reasonable to reduce the risk of MI, stroke, or vascular death.[9] Low ABI (< 0.90) is an independent predictor of MI, stroke, and vascular mortality independent of other cardiovascular risk factors.[10]

The National Institute for Health and Care Excellence guideline TA210 and CG147 on PAD recommends clopidogrel as the first line and aspirin as a second-line antiplatelet agent to prevent occlusive vascular events in patients who have peripheral arterial or multivascular disease.[11]

Symptomatic patients with PAD may need endovascular interventions or open surgery, in the form of angioplasty, stenting, or bypass procedures. It has been suggested that this group of patients have more advanced disease than patients with claudication and may benefit with dual antiplatelets to reduce major adverse cardiovascular events (MACEs) and major adverse limb events. Armstrong et al. reported that dual antiplatelets were associated with a lower risk of MACEs (adjusted hazard ratio [HR], 0.65; 95% confidence interval [CI], 0.44–0.96), overall mortality (adjusted HR, 0.55; 95% CI, 0.34–0.84), and amputation-free survival (adjusted HR, 0.53; 95% CI 0.34–0.80). No association was found between their use and target vessel revascularization over time.[12]

The MIRROR study in 2012 compared dual antiplatelets (aspirin and clopidogrel) with single (aspirin and placebo) agent in patients undergoing femoropopliteal segment angioplasty ± stenting.[13] Patients on dual antiplatelets had lower rates of target lesion revascularization (TLR) at 6 months (5% vs. 20%, P = 0.04). Dual antiplatelets were also found to reduce periprocedural platelet activation.[13] The advantage offered by DAPT did not persist after stopping clopidogrel at 6 months. There was no significant difference in TLR at 12 months (25% vs. 32.4% placebo, P = 0.35).[14]

Prolonged dual therapy (>6 months) is recommended in patients who are at high risk for restenosis.[14]

Recommendations by academic societies on antithrombotics in lower limb angioplasty have evolved over the past decade. In 2012, the American College of Chest Physicians (ACCP) evidence-based clinical practice guidelines had recommended single antiplatelet agent (long-term aspirin [75–100 mg/day] or clopidogrel [75 mg/day]) rather than DAPT for patients undergoing peripheral artery percutaneous transluminal angioplasty with stenting.[15]

The 2016 AHA/ACC guidelines now state that DAPT with aspirin and clopidogrel may be reasonable to reduce the risk of limb-related events in patients with symptomatic PAD after lower extremity revascularization.[9]

Antithrombotics are also widely used following lower limb bypass procedures. In a meta-analysis by the antithrombotic trialists collaboration, antiplatelets (aspirin or aspirin with dipyridamole) were shown to significantly reduce graft occlusion (P < 0.00001).[16] The CASPAR trial compared aspirin with dual antiplatelets (aspirin and clopidogrel) in patients with infrainguinal bypasses. A significant reduction in occlusion and amputation rates was seen in below knee prosthetic grafts, but no significant difference was seen with vein grafts.[17]

The effects of anticoagulation on outcomes of bypass grafts have also been studied. The Dutch bypass oral anticoagulants or aspirin study randomized postbypass patients to oral anticoagulants (with a target international normalized ratio [INR] range of 3–4.5) or aspirin. Oral anticoagulants were shown to be better in prevention of infrainguinal vein graft occlusion but were associated with a higher risk of major bleeds (HR 1.96 [1.42–2.71]).[18] The 2016 ACC guidelines state that the usefulness of anticoagulation to improve patency after lower extremity autogenous vein or prosthetic graft is uncertain.[9]

In patients undergoing lower extremity bypasses, the ACCP guidelines in 2012 recommended single over dual antiplatelets except in below knee prosthetic grafts.[19] In this subgroup, dual antiplatelets were recommended for 1 year. The 2016 ACC guidelines state that there is sparse data on dual antiplatelets after lower extremity revascularization, but it may be reasonable to prescribe dual antiplatelets to reduce limb-related events.[9] [Table 1].

**Antithrombotics in Acute Limb Ischemia**

The most common cause of nontraumatic acute limb ischemia is thromboembolism. The source of peripheral emboli is
Irrespective of the cause and level of limb ischemia, therapeutic doses of heparin are widely given to inhibit clot propagation and reduce the risk of further embolism.\(^{15}\) The 2016 ACC guidelines recommend acute administration of heparin (generally unfractionated heparin) unless contraindicated.\(^9\) A direct thrombin inhibitor is recommended in those with heparin-induced thrombocytopenia with thrombosis.

Thrombolysis is one of the main therapeutic options in acute limb ischemia. Current percutaneous treatment includes catheter-directed thrombolysis, pharmacomechanical thrombolysis, thrombus aspiration, or a combination of
the above.[24] The need for heparin administration during thrombolysis remains a subject of debate.[23] The surgery versus thrombolysis for ischemia of the lower extremity trial showed a 1-year sustained benefit for a composite clinical end-point of death, amputation, major morbidity, and recurrent ischemia, following the use of heparin with Alteplase during thrombolysis.[26]

**Antithrombotics in Carotid and Vertebral Artery Disease**

Antiplatelets are recommended to reduce the risk of stroke in patients with previous transient ischemic attack (TIA) and stroke.[19] In patients with asymptomatic carotid disease, aspirin 75–100 mg daily was recommended by 2012 ACCP guidelines.[15]

In patients with symptomatic carotid stenosis and in those after a carotid endarterectomy (CEA), long-term antiplatelet therapy is recommended.[15] Aspirin, the combination of aspirin and extended-release dipyridamole or clopidogrel, is recommended for patients undergoing CEA.[15,18] Aspirin does not need to be stopped perioperatively, and the risk of periprocedural MI rises if it is withdrawn.[19] After CEA aspirin should be continued indefinitely.[19] There is evidence that clopidogrel too can be safely continued perioperatively during a CEA.[27]

Studies have not demonstrated a clear benefit of dual antiplatelet treatment (aspirin and clopidogrel) over single antiplatelets in the prevention of strokes.[28,29] Dual antiplatelets were associated with a higher risk of perioperative bleeding. A recent meta-analysis, however, has shown that DAPT significantly reduced postprocedural TIA and had no significant effects on bleeding or other perioperative complications.[28]

The benefits of DAPT have been more convincing in carotid artery stenting.[29,30,32] In 2007, ACC Foundation Task Force supported by other societies released a clinical expert consensus document on carotid stenting.[31] This stated that dual antiplatelets should be started at least 24 h before the procedure (preferably 4 days if possible). The recommendation was to continue aspirin and clopidogrel for at least 30 days and then aspirin alone lifelong.

**Antithrombotics in Carotid or Vertebral Artery Dissections**

Carotid artery injuries can lead to cerebral malperfusion, therefore, the role of antithrombosis has been investigated in reducing neurological sequel. A classification for blunt carotid injury has been proposed by Biffi et al.[33] Management with antithrombosis is recommended for class I (intimal irregularity with <25% narrowing) and class II injuries (dissection or intramural hematoma) by the blunt cerebrovascular injury practice management guidelines.[34] Antiplatelets or anticoagulation are equally efficacious. If anticoagulation is used an INR of 2–3 is maintained for 6 months.

Trauma to the vertebral artery may be associated with posterior circulation strokes though most patients are asymptomatic. Even in symptomatic cases, neurological deficits probably occur at the time of injury.[35] Aspirin should be considered in blunt vertebral artery injuries to reduce strokes, if there are no contraindications for treatment.[33] Anticoagulation in vertebral artery injuries has not been shown to be superior to aspirin in preventing strokes.[35] Anticoagulants may be associated with increased bleeding when compared to aspirin. The decision for anticoagulation, antiplatelet treatment, or no treatment should be made on a case to case basis after assessment of all other injuries.

Antithromboses are also used in the management of nontraumatic carotid or vertebral artery dissection. The 2011 guidelines recommend anticoagulation for the first 3–6 months.[19] Intervention is needed if symptoms worsen despite anticoagulation. Unfractionated or low-molecular-weight heparin (LMWH) followed by warfarin (to maintain a target INR of 2.0–3.0) can be used. This should be followed by antiplatelet therapy with aspirin or clopidogrel.[19]

**Antithrombotics in Aortic Disease**

The use of antithrombosis has been proposed in aneurysms, complex plaques, and mobile thrombi of the aorta to prevent embolic complications and to reduce progression.[20]

The effects of antiplatelet therapy on aortic aneurysms have been studied with conflicting results. A secondary analysis of the UK small aneurysm trial did not find any difference in aneurysm growth rates between aspirin users and nonusers.[37] In contrast, a Swedish study showed reduced rates of expansion with combined aspirin and stain therapy.[38] Despite the conflicting evidence on aneurysm expansion, the use of aspirin may be considered for secondary prevention of nonaneurysm-related cardiovascular events and death.

Aortic plaques are known to be associated with cerebral and peripheral arterial embolic events.[20] The stroke prevention in atrial fibrillation study showed that complex aortic plaques (over 4 mm) caused a four-fold increase in stroke.[39] Similar results were seen in the French study of aortic plaques in stroke, where lesions over 4 mm were independent predictors of recurrent brain infarction and any vascular event.[40]

An observational study by Ferrari et al. comparing Vitamin K agonists (VKA) and antiplatelets in patients with complex aortic plaques showed lower vascular events in patients on VKAs.[41] Contrasting results were seen in a study by Tunick et al. where there was no significant benefit of warfarin or antiplatelet drugs on the incidence of stroke and other embolic events.[42] Due to lack of conclusive evidence, guidelines of the European Society of Cardiology (2014) state that more data are needed to make firm recommendations.[20]

Mobile thrombi without evidence of atherosclerosis are known to occur in the aorta, with a predilection for the arch region. The etiology is often unexplained and probable causes include...
thrombophilic states or paradoxical embolization through a patent foramen ovale.\textsuperscript{[20]} Anticoagulation has been suggested to lower embolic risk, but no conclusive evidence is available.

A role for antithrombotic therapy has been proposed in the management of aortic dissections. Partial thrombosis of the false lumen is associated with a poor prognosis,\textsuperscript{[45]} and it has been suggested that anticoagulation may reduce malperfusion and improve outcomes.\textsuperscript{[144]} However, most intersocietal guidelines do not include recommendations for antithrombotic use in acute aortic syndromes. The 2017 European Society of Vascular Surgery (ESVS) guidelines on management of thoracic aorta disease recommend antiplatelets as apart of ongoing medical therapy to reduce the incidence of late cardiovascular death.\textsuperscript{[21]}

**Antithrombotics in Mesenteric Vascular Disease**

Antithrombotics are used in a number of mesenteric vascular disorders including acute mesenteric artery occlusion, chronic mesenteric ischemia, mesenteric artery dissection, and mesenteric vein thrombosis. The indications for their use have recently been updated in the ESVS Guidelines on the Management of the Diseases of Mesenteric Arteries and Veins.\textsuperscript{[22]}

Symptomatic acute mesenteric ischemia most often occurs due to thromboembolic occlusion of the superior mesenteric artery (SMA). Bowel ischemia or infarction are uncommon due to isolated occlusion of the celiac axis or inferior mesenteric artery due to collateral circulation. Most patients with symptomatic SMA occlusion require laparoscopic or open revascularization. Anticoagulation with heparin has been successfully used to manage residual thrombi in the distal circulation.\textsuperscript{[22]} For patients who recover, the ESVS guidelines recommend antiplatelets or anticoagulation for secondary prevention.

In chronic mesenteric ischemia, open and endovascular options are available to restore blood flow and provide symptomatic relief. Following revascularization, antiplatelet therapy is indicated. The ESVS guidelines state that DAPT may be considered for 3–12 months after endovascular revascularization.

Isolated dissections of the mesenteric arteries are uncommon, and their etiology is poorly understood. Most patients can be managed conservatively. The ESVS guidelines recommend antiplatelet therapy for asymptomatic patients and initial treatment with antiplatelets or anticoagulation for symptomatic patients.

Mesenteric ischemia also occurs due thrombosis in the portal venous system and is known to occur in association with prothrombotic states, intraabdominal tumors, and cirrhosis. Anticoagulation is the main therapeutic option for these patients and has been shown to achieve recanalization in over 80% of patients.\textsuperscript{[45,46]} Recommended agents include heparin or LMWH during the initial period which may need to be withheld if bowel resection is needed. These can be converted to VKAs or directly acting oral anticoagulants later. Anticoagulation has been shown to reduce recurrence and improve survival in these patients.\textsuperscript{[22]}

**Periprocedural Use of Antithrombotic Agents**

Periprocedural heparin use dates back to the 1940s.\textsuperscript{[47]} It was understood that injury to the endothelium by introduction of foreign materials into the vessels during vascular surgical or interventional procedures poses a risk of thrombosis, necessitating antithrombotic therapy.

Heparin is the most widely used agent and is employed as a prophylactic bolus and also as a flushing solution to prevent clot formation in the vessels and on or within catheters.\textsuperscript{[48]} Most antithrombotic regimes used in vascular interventions are based on evidence gathered from studies done in the field of interventional cardiology.

In 2012 a survey was carried out by Durran et al., among members of the British Society of Interventional Radiology regarding their current practice in periprocedural heparin use.\textsuperscript{[49]} Most interventionalists were in agreement that a 3000 IU bolus should be the standard dose for straightforward therapeutic procedures and 5000 IU for complex, crural, and endovascular aneurysm repair work. A concentration of 1000 IU/L was recommended for heparinized saline used as a flushing concentration in arterial vascular interventions. The TASC II guidelines recommend heparinization in peripheral vascular intervention to achieve a target activated clotting time between 200 and 250 s.\textsuperscript{[50,51]}

Guidelines developed by the Cardiovascular and Interventional Radiological Society of Europe (2014) have outlined anticoagulation during endovascular procedures for aortoiliac disease. While heparin doses of 30–80 U/kg may be used, it is stated that the use of doses below 60 U/kg and maintenance of activated clotting time under 250s are adequate for safety and efficacy.\textsuperscript{[52]}

**Venous Thrombosis**

Anticoagulant therapy for deep vein thrombosis dates back to the 1940s when treatment was not based on clinical evidence. In 1960, a randomized trial by Barritt and Jordan demonstrated the benefits of anticoagulation in deep venous thrombosis (DVT) with pulmonary embolism where 1.5 days of heparin and 14 days of VKA treatment markedly reduced recurrent pulmonary embolism.\textsuperscript{[53,54]}

The aims of anticoagulation in DVT are to prevent propogation and embolization thereby minimizing adverse clinical sequelae, including pulmonary embolism, postthrombotic syndrome, and recurrence of DVT. Several factors are considered to determine the type and duration of anticoagulation. They include the site of DVT, underlying cause, and bleeding risk.

The choice of anticoagulant depends on the underlying cause. For all DVT except those caused by malignancy, the directly
acting anticoagulants (dabigatran, rivaroxaban, apixaban, or edoxaban) are recommended. For cases occurring due to malignancy, LMWHs are considered the standard of care. [55]

Anticoagulation is recommended for a minimum of 3 months. The current ACCP Recommendations for anticoagulation identifies 2 phases of treatment: long-term (3 months) or extended (over 3 months). Treatment for 3 months is recommended if the DVT was provoked by surgery or by a transient nonsurgical risk factor. If no such factor is identified, extended anticoagulation is recommended unless there is a high risk of bleeding. D-dimer levels 1 month after stopping treatment may be useful to determine duration. [55]

In DVT caused by malignancy, extended anticoagulation is recommended. Patients undergoing extended treatment should be reevaluated annually.

Anticoagulation is also recommended in the management of other types of venous thrombosis, including superficial thrombophlebitis, upper limb vein thrombosis, and splanchic vein thrombosis. [34]

**Antithrombotics in Vascular Surgery—The Future**

Advances in the fields of molecular biology and genetic engineering have made it possible to develop new antithrombotic agents and optimize drug selection in patients. Better understanding of the complex molecular mediators in thrombosis and fibrinolysis has led to targeting of specific mediators by “designer” antithrombotic agents.

Genetic variations influencing the pharmacokinetics and pharmacodynamics of antithrombotics are being extensively investigated. Common polymorphisms in VKORC1 and the CYP2C9 genes play an important role in warfarin metabolism leading to variations in therapeutic effects. [56]

Similarly, clopidogrel metabolism is affected by CYP2C19 gene. [56]

Identifying such variations enables clinicians to individualize antithrombotic therapy to optimize therapy and minimize side effects in the management of vascular surgical patients.

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