Antiplatelet therapy for tibial balloon angioplasty: A clinical perspective

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Abstract
Percutaneous transluminal tibial balloon angioplasty has an important role in the therapeutic approach of critical limb ischaemia. Despite a growing number of patients with critical limb ischaemia, there are no trials to guide the pharmacologic approach post intervention. Guidelines pertaining to the antiplatelet therapy post percutaneous transluminal tibial balloon angioplasty have not been developed. In addition, critical limb ischaemia patients have multiple comorbidities and a higher risk of bleeding. To examine the shortest duration of antiplatelet therapy post percutaneous transluminal tibial balloon angioplasty, we reviewed the preclinical data used to develop the standards for the current angioplasty technique.

Keywords
Peripheral vascular disease, critical limb ischaemia, balloon angioplasty, tibial angioplasty, antiplatelet therapy

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Introduction
Peripheral arterial disease (PAD) is becoming increasingly recognized as a major contributor to public health burden. It is estimated that 8.5 million people in the United States and 202 million people worldwide are affected by PAD.\(^1\) Since the disease prevalence increases with age, obesity, and diabetes, the number of patients affected is expected to increase.\(^2,3\) The advanced form of PAD is critical limb ischaemia (CLI), which affects 1%–2% of the PAD population\(^4\) and has an enormous economic burden, regardless of whether the therapy is primary amputation, surgical bypass, or endovascular revascularization.\(^5,6\)

Therapy for CLI requires revascularization, either surgical or endovascular, aiming to re-establish flow to the foot. Due to multiple factors affecting both approaches, there has been a shift in the management of CLI with a substantial increase in the number of endovascular procedures.\(^1,7,8\) Patients with CLI have significant critical and subcritical stenosis in multiple areas, however with a majority in the popliteal and tibial distribution.\(^9\) In addition, infrapopliteal disease in CLI is characterized by very long areas of stenosis or occlusions.\(^10\) Despite technological improvements, as opposed to the iliac and femoral territories, the primary therapy for the tibial arterial disease, either stenosis or occlusion, remains balloon angioplasty.\(^11-13\) A decade later, Lyden’s\(^14\) description of tibial angioplasty in 2009 remains at the core of tibial interventions:

[…\] angioplasty is performed with long balloons (10–22 cm length) sized less than or equal to the diameter of the native vessel, typically starting with 0.014″ compatible balloons due to better crossability […]. Three minute inflations with the minimal amount of pressure in atmospheres are used to allow the lesion to dilate. Even for short lesions, long balloons (≥10 cm), reduce the incidence of flow limiting dissection.

Bleeding risk and peripheral arterial disease
Patients with PAD have multiple comorbidities,\(^15,16\) usually on complex medical regimens, many on anticoagulation therapy, some with prior significant bleeding history. Just the diagnosis of PAD is known to be associated with an increased risk of bleeding.\(^17\) A retrospective analysis found higher HAS-BLED risk scores in PAD patients compared to matching control without PAD and higher HAS-BLED score in patients with Rutherford class 5 and 6 compared to class 2, 3, and 4.\(^18\) A recent large analysis in the United Kingdom identified dual antiplatelet therapy (DAPT) in symptomatic PAD
patients as risk for gastrointestinal bleeding (GIB). Despite this known heightened risk of bleeding, there have been no studies specifically addressing the pharmacotherapy post tibial angioplasty (TAP). Both the American College of Cardiology/American Heart Association (ACC/AHA) and the TASC II (Inter-Society Consensus for the Management of Peripheral Arterial Disease) guidelines do not provide guidance in therapy. A recent TASC initiative reviewed all evidence and again noted the lack of data for DAPT, despite its use, in the treatment of patients with PAD post revascularization. In addition, guidelines published in 2018 from the European Society of Cardiology and Vascular Surgery did not specify any pharmacotherapy after below-knee intervention. Despite a heightened risk of bleeding, the number of patients treated with DAPT post TAP has been on the rise. In a large analysis of 57,000 patients from the Vascular Quality Initiative (VQI) database, DAPT compared to aspirin was associated with prolonged survival post revascularization, especially in CLI patients, and a recent meta-analysis of randomized controlled trials (RCTs) revealed improved outcomes with DAPT compared to mono-antiplatelet therapy (MAPT) after revascularization with respect to major adverse cardiac events (MACE) and mortality. The MIRROR study is the only completed study addressing the antiplatelet therapy after percutaneous revascularization of PAD patients, which included patients with femoral and popliteal disease. In total, 80 patients were randomly assigned to clopidogrel 75 mg and aspirin 100 mg daily versus placebo and aspirin 100 mg daily after a loading dose of aspirin 500 mg for both groups and 300 mg clopidogrel for the active medication group. The primary outcome was local concentration of platelet activation markers. At 6-month follow-up, there was a statistically significant difference between the secondary endpoints of target lesion revascularization (2 vs 8, p=0.040). Despite different embryologic origins, due to the similar vessel calibre of coronary and tibial vessels and the extensive research on balloon angioplasty in the coronaries, we reviewed the steps and highlight the articles which noted endothelial denudation, enlargement of the arterial lumen, intimal tears, but no medial dissection with abundant recruitment of platelets. In a landmark study of platelet involvement in PTA, Fuster team used a pig model to study the kinetics of platelet deposition at the PTA site. Using an 8-mm balloon, they performed PTA on the normal carotid artery in pigs with an artery diameter of 5–6 mm. Animals were sacrificed starting at 1 h up to 60 days. There was significant platelet deposition and mural thrombus with medial tear injury starting at 1 h, and changes were not observed without a medial tear. At 4 days, the mural thrombus has significantly reduced and no significant platelet deposition was noted after 7 days. In 11% of pigs, the mural thrombus progressed to complete occlusion. The intimal proliferation began after 7 days and developed until 14 days without further changes noted thereafter until the end of the 60-day experiment. The authors concluded that, in their pig model, antiplatelet therapy should be started before the procedure and continued for 4–7 days. Platelet accumulation at the site of angioplasty of injured iliac arteries was also monitored in atherosclerotic rabbits. Radioactively labelled platelets were injected 30 min before the procedure. Animals were sacrificed at 30 min, 2 h, 4 h, 6 h, 24 h, 1 week, and 4 weeks. Platelet accumulation was highest in the first 2 h post angioplasty and reached baseline at 4 h. In addition, platelet accumulation was directly proportional to the degree of injury, with the highest density of platelets at the sites with the highest degree of injury.

**Types of injury post balloon angioplasty**

Animal model findings, confirmed by in vivo human studies, revealed two major types of vessel response to PTA. In case of mild injury, there was endothelial denudation with only minimal disruption of the internal elastic lamina and intimal hyperplasia is the main mechanism of late lumen loss. In case of a deep injury with disruption of the internal elastic lamina and media tear, negative remodelling occurred with neoadventitial formation and vessel shrinkage. Late lumen loss in this case was 30% due to neointimal thickening and 70% due to change in vessel diameter. Interestingly, when a deep injury was created, the vessel diameter was smaller immediately post compared to pre angioplasty.

The degree of injury to the vessel was associated to the technical aspects of the procedure. In an effort to understand the balloon size and inflation pressure necessary to achieve optimal angioplasty results, Sarembock et al. studied the response of femoral artery injury in rabbits. After injury to the femoral artery with nitrous gas, animals were fed a high-cholesterol diet for 30 days. Balloon angioplasty was performed with an oversized (3.0 mm) or an appropriate-sized balloon (2.5 mm) with high (10 atm) or low (5 atm) pressure. Acute histologic changes of thrombus formation, dissection, inflammation, and medial necrosis were more frequent in high-pressure balloon groups and lowest in the appropriate-size balloon at low pressure. Using a similar animal model, a higher number of inflations (6 vs 2) of an appropriate-size...
balloon at 6 atm appear to induce a greater proliferative response.\textsuperscript{35} In humans, Gruentzig conducted a randomized trial to assess the need for a bigger balloon size to reduce restenosis. Apart from the increased number of complications, the bigger size balloons were not associated with any benefit.\textsuperscript{36} Restenosis post balloon angioplasty is the primary method of failure due to elastic recoil, neointimal hyperplasia, and negative remodelling\textsuperscript{37,38} However, these processes appear to have different impacts in the final restenosis based on the vascular bed. In a study on pigs, simultaneous balloon angioplasty was performed in the coronary and iliac arteries. The response to injury was significantly different. The response to injury in the coronary arteries was intimal hyperplasia, while in the iliac vessels there was more negative remodelling and 10 times less intimal hyperplasia. The different response to injury could stem from the difference in vessel structure. The coronary arteries have a fenestrated and incomplete internal lamina and a thin external lamina resulting in a more extensive lamina disruption and less elastic resistance during balloon inflation.\textsuperscript{39} In an effort to understand the pathophysiology of percutaneous transluminal tibial balloon angioplasty (PTTA), angiographic evaluation of pre and post PTTA in humans revealed that tibial arteries' elastic recoil accounts for 30% acute reduction 15 min post angioplasty.\textsuperscript{40} Since blood flow is correlated with the 4th power of the vessel radius, a 30% decrease in diameter will result in a decrease in flow of more than 100%. As such, the choice of balloon size, the inflation pressure, and the number of inflations will impact the degree of injury and subsequently the density of platelets at the PTTA site. In the tibial vessels where the PTA is most of the times the only treatment applied to the vessel, the choice of balloon size and inflation pressure becomes extremely important in achieving the best outcome.

**Antiplatelet agents and restenosis post balloon angioplasty**

Platelets play an important role in the development of the major complications after coronary balloon angioplasty acute occlusion\textsuperscript{41} and restenosis.\textsuperscript{42} Supporting the idea of platelet involvement in restenosis, in a rabbit model of atherosclerosis, sulfipyrazone and aspirin with dipyridamole treatments were associated with decreased thrombus and decreased intimal thickening after iliac artery angioplasty.\textsuperscript{43} As such, several trials were performed to address the effect of antiplatelet drugs on restenosis in the peripheral arteries. There was a difference in restenosis between placebo and aspirin/dipyridamole,\textsuperscript{44-46} but no difference was noted between the high-dose 900–1000 mg/day versus low-dose 50–300 mg/day aspirin therapy.\textsuperscript{47-49} These trials have been the topic of review in several articles, but suffice it to say that there were no patients treated with PTTA.\textsuperscript{50-52}

To decrease the complications of coronary PTA, stent technology was introduced and gained acceptance.\textsuperscript{53,54} However, the stent came with another set of complications, especially acute stent thrombosis.\textsuperscript{55} Investigation of the platelet IIb/IIIa receptor\textsuperscript{56} prompted large randomized trials which showed the superiority of DAPT over aspirin plus anticoagulation in preventing acute stent thrombosis.\textsuperscript{57,58} The use of DAPT after coronary stenting has been extended, without clinical trials, to any percutaneous intervention, regardless of the utilization of stent or balloon. There have been no studies to date on DAPT in PTA in any vascular territory.

**Trials of antiplatelet agents in peripheral arterial disease**

There have been numerous studies conducted in patients with peripheral artery disease involving the lower extremity. Aspirin, clopidogrel, ticagrelor, and vorapaxar have been studied. Monotherapy with aspirin versus placebo was found to have a significant decrease in cardiovascular (CV) events in a meta-analysis of more than 6000 patients, but only in patients with symptomatic disease.\textsuperscript{59} The CLIPS study revealed a significant reduction of vascular events with low-dose aspirin; however, the randomized trial had numerous problems, including slow enrollment with premature termination, the final number of patients being far less than the initial calculated sample.\textsuperscript{60} In asymptomatic patients, despite the presence of diabetes, the prevention of progression of arterial disease and diabetes (POPADAD) trial did not show any benefit of aspirin therapy in decreasing CV events or major amputation for CLI.\textsuperscript{61} Clopidogrel was shown to perform marginally better than aspirin in CAPRIE (clopidogrel versus aspirin in patients at risk of ischaemic events).\textsuperscript{62} A subgroup analysis of the CHARISMA trial showed a benefit of the DAPT with clopidogrel and aspirin versus aspirin alone in patients with peripheral vascular disease; however, the overall trial was neutral as pertains to the primary composite endpoint of CV death, MI, and stroke.\textsuperscript{63} The more potent P2Y\textsubscript{12} inhibitor ticagrelor was studied in the two large RCTs. In the EUCLID (Examining Use of Ticagrelor in Peripheral Artery Disease), which enrolled 13,885 patients, ticagrelor was not superior to clopidogrel with a similar primary efficacy endpoint (CV death, MI, and stroke) and secondary endpoint (acute limb ischaemia and revascularization).\textsuperscript{64} In the PEGASUS-TIMI 54 trial, which compared ticagrelor + aspirin versus aspirin, a post hoc analysis of 1145 patients with lower extremity PAD demonstrated a 4.1% absolute risk reduction in the primary endpoint of CV death, MI, and stroke with DAPT.\textsuperscript{65}

**Platelet reactivity in critical limb ischemia**

In a small study of 20 patients with CLI (11 treated with aspirin), platelet activity was measured before and after activation. As compared to healthy controls, CLI patients not on aspirin therapy had an increased baseline P-selectin expression and fibrinogen binding capacity suggesting an overall increase in baseline platelet activation.\textsuperscript{66} Clavijo
et al. studied 100 patients with CLI on aspirin and clopidogrel, performing vasodilator-stimulated phosphoprotein (VASP) and VerifyNow P2Y12 assays. They found an overall prevalence of non-responders of 35% for aspirin or clopidogrel and 8% for both. A more potent P2Y12 inhibitor was studied by the same investigators in the STT-CLIPS trial. Platelet activity in patients with CLI was tested with VerifyNow assay. Patients were treated with clopidogrel and then switched to ticagrelor therapy. Patients with high platelet reactivity while on clopidogrel showed improved platelet inhibition with the more potent P2Y12 inhibitor ticagrelor.

Assuming that a high proportion of CLI patients have a high platelet activity on aspirin and/or clopidogrel, tailoring therapy of antiplatelet drugs based on platelet testing seems appealing. However, two randomized trials (ARTIC and GRAVITAS) totalling 4654 patients undergoing coronary stenting in the setting of stable coronary artery disease (CAD) or non-ST elevation myocardial infarction did not show any benefit of the tailored approach with respect to CV death, ST and non-ST myocardial infarction, and bleeding complications.

How should we integrate the available data into daily practice without trials designed to address this patient population? How should we use antiplatelet therapy in CLI after PTTA? The answer to this question is especially important for patients already on anticoagulants, since triple therapy should be avoided if possible due to high bleeding risk. Crucial to the therapy is the outcome of the angioplasty procedure. If stents have been implanted, trials performed in the coronary arteries strongly favour DAPT. The latest coronary stents would require 1 month of triple therapy. Based on the animal studies and data from other vascular beds, one could speculate that antiplatelet therapy after PTTA could be modified based on the angiographic result of angioplasty: 7 days of monotherapy with an antiplatelet agent for uncomplicated PTTA or 2 weeks for a complicated PTTA (i.e. dissection not requiring stenting). This approach could be used in patients at high risk of bleeding, as determined by the available scores (indeed derived from a different population) or in patients already on anticoagulant therapy. However, if bleeding risk is low, DAPT should be considered to decrease adverse CV events.

Concomitant critical limb ischemia and coronary artery disease
The complications related to undiagnosed CAD in patients with PAD prior to intervention have been the source of a continuing debate. There have been several case series reporting on screening for CAD before intervention to the lower extremities. A review of the published literature in 2012 reported a 55% concomitant CAD in patients with PAD. The authors found a different prevalence of CAD depending on the peripheral territory affected, with the highest prevalence in patients with carotid disease. Similarly, a high prevalence of CAD was reported in CLI patients. Lee et al. published a series of 252 patients with CLI intervention investigated with coronary angiography. They found CAD, defined at >50% stenosis, in 167 patients and 114 (45.2%) patients required coronary intervention prior to endovascular intervention for CLI. At 1 year, there was no difference in MACE between the CAD and no-CAD patients. The authors suggested that revascularization might have improved outcomes in patients with severe CAD to explain the similar outcome. However, in the only randomized trial of CAD revascularization prior to PAD intervention, 510 patients were randomized to revascularization or no revascularization prior to vascular surgery. There were 27% of patients with CLI (rest pain and tissue loss). After a median follow-up of 2.7 years, there was no difference in the primary outcome of long-term mortality between the two groups. The 2016 AHA/ACC guidelines do not recommend screening for CAD in asymptomatic patients with PAD.

Limitations
There are several limitations to this review. In the absence of a prospective, randomized trial, the conclusions should be interpreted with caution. The animal data presented might not apply to intervention in humans. The majority of trials discussed are subgroup analyses of larger trials which have known limitations.

Conclusion
Our literature review did not find data to suggest that DAPT would improve acute closure rates or decrease restenosis post angioplasty in the tibial vessels. A short antiplatelet course in patients with high bleeding risk or on anticoagulants might be insufficient from a technical standpoint. Recent data on the pathophysiology of CLI and the results of trials with vorapaxar and rivaroxaban might shift the treatment into a new direction. However, the ongoing tug of war between the prevention of adverse events and bleeding is far from over. Further research is needed in the area of pharmacotherapy to improve our understanding and care of patients with CLI.

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