Review Paper

SAGE Open Medicine

SAGE Open Medicine
Volume 7: 1–7

DOI: 10.1177/2050312119854579
journals.sagepub.com/home/smo
SAGE

Antiplatelet therapy for tibial balloon angioplasty: A clinical perspective

Costin N Ionescu, Sophia E Altin and Carlos Mena-Hurtado

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

Date received: 5 April 2019; accepted: 13 May 2019

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

Cardiovascular Disease Section, Department of Internal Medicine, Yale School of Medicine, New Haven, CT, USA

Corresponding author:
Costin N Ionescu, Cardiovascular Disease Section, Department of Internal Medicine, Yale School of Medicine, New Haven, CT 06511, USA.
Email: costin.ionescu@yale.edu

patients as risk for gastrointestinal bleeding (GIB).[19] 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)[20] and the TASC II (Inter-Society Consensus for the Management of Peripheral Arterial Disease) guidelines do not provide guidance in therapy.[21] 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.[22] In addition, guidelines published in 2018 from the European Society of Cardiology and Vascular Surgery did not specify any pharmacotherapy after below-knee intervention.[23] 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,[24] 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.[25] 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, $p = 0.040$).[26] 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 shaped the current use of DAPT in clinical practice.

For the initial peripheral percutaneous interventions, Dotter and Judkins[27] did not employ antiplatelet therapy but only heparin, while Libow et al.[28] added aspirin 650 mg for balloon angioplasty of the coronary arteries. Due to the explosive growth of the number of coronary interventions, intensive basic and animal research ensued.

Platelet involvement in the response to balloon angioplasty

Percutaneous transluminal balloon angioplasty (PTA) results in an injury to the arterial vessel wall. Platelets play a central role in the injury caused by PTA. One of the initial studies of post-PTA injury, performed in healthy canine coronary arteries, noted endothelial denudation, enlargement of the arterial lumen, intimal tears, but no medial dissection with abundant recruitment of platelets.[29] In a landmark study of platelet involvement in PTA,[30] 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.[31]

Types of injury post balloon angioplasty

Animal model findings, confirmed by in vivo human studies, revealed two major types of vessel response to PTA.[32] 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.[33]

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.[34] 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.[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.[36] Restenosis post balloon angioplasty is the primary method of failure due to elastic recoil, neointimal hyperplasia, and negative remodelling.[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.[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.[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[41] and restenosis.[42] Supporting the idea of platelet involvement in restenosis, in a rabbit model of atherosclerosis, sulfinpyrazone and aspirin with dipyridamole treatments were associated with decreased thrombus and decreased intimal thickening after iliac artery angioplasty.[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,[44–46] but no difference was noted between the high-dose 900–1000 mg/day versus low-dose 50–300 mg/day aspirin therapy.[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.[50–52]

To decrease the complications of coronary PTA, stent technology was introduced and gained acceptance.[53,54] However, the stent came with another set of complications, especially acute stent thrombosis.[55] Investigation of the platelet IIb/IIIa receptor[56] prompted large randomized trials which showed the superiority of DAPT over aspirin plus anticoagulation in preventing acute stent thrombosis.[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.[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.[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.[61] Clopidogrel was shown to perform marginally better than aspirin in CAPRIE (clopidogrel versus aspirin in patients at risk of ischaemic events).[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.[63] The more potent P2Y12 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).[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.[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.[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.[67] 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.[68]

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.[69] However, two randomized trials (ARTIC[70] and GRAVITAS)[71] 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.[72] 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.[73] Based on the animal studies and data from other vascular beds, one could speculate that antiplatelet therapy after PTTA could be modulated 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[74–76] (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.[23,24]

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.[77] Similarly, a high prevalence of CAD was reported in CLI patients.[78] Lee et al.[79] 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.[80] The 2016 AHA/ACC guidelines do not recommend screening for CAD in asymptomatic patients with PAD.[81]

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 sufficient from a technical standpoint. Recent data on the pathophysiology of CLI[82] and the results of trials with vorapaxar[83] and rivaroxaban[84] 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.

Declaration of conflicting interests

The author(s) declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: C.M.-H. is consultant for Medtronic, Boston Scientific, Bard, Cook, Abbott, Cardinal Health, and Gore.

Funding

The author(s) received no financial support for the research, authorship, and/or publication of this article.

ORCID iD

Costin N Ionescu https://orcid.org/0000-0003-2633-5450

References

1. Gerhard-Herman MD, Gornik HL, Barrett C, et al. 2016 AHA/ACC guideline on the management of patients with lower extremity peripheral artery disease: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *Circulation* 2017; 135(12): e726–e779.
2. Criqui MH and Aboyans V. Epidemiology of peripheral artery disease. *Circ Res* 2015; 116(9): 1509–1526.
3. Bommer C, Sagalova V, Heesemann E, et al. Global economic burden of diabetes in adults: projections from 2015 to 2030. *Diabetes Care* 2018; 41(5): 963–970.
4. Farber A and Eberhardt RT. The current state of critical limb ischemia: a systematic review. *JAMA Surg* 2016; 151(11): 1070–1077.
5. Peacock JM, Keo HH, Duval S, et al. The incidence and health economic burden of ischemic amputation in Minnesota, 2005–2008. *Prev Chronic Dis* 2011; 8(6): A141.
6. Mustapha JA, Katzen BT, Neville RF, et al. Determinants of long-term outcomes and costs in the management of critical limb ischemia: a population-based cohort study. *J Am Heart Assoc* 2018; 7(16): e009724.
7. Kudo T, Chandra FA and Ahn SS. The effectiveness of percutaneous transluminal angioplasty for the treatment of critical limb ischemia: a 10-year experience. *J Vasc Surg* 2005; 41(3): 423–435; discussion 435.
8. Agarwal S, Sud K and Shishehbor MH. Nationwide trends of hospital admission and outcomes among critical limb ischemia patients: from 2003–2011. *J Am Coll Cardiol* 2016; 67(16): 1901–1913.
9. Rueda CA, Nehler MR, Perry DJ, et al. Patterns of artery disease in 450 patients undergoing revascularization for critical limb ischemia: implications for clinical trial design. *J Vasc Surg* 2008; 47(5): 995–999; discussion 999.
10. Baumann F, Engelberger RP, Willenberg T, et al. Infrapopliteal lesion morphology in patients with critical limb ischemia: implications for the development of anti-restenosis technologies. *J Endovasc Ther* 2013; 20(2): 149–156.
11. Jens S, Conijn AP, Koelemay MJ, et al. Randomized trials for endovascular treatment of infrainguinal arterial disease: systematic review and meta-analysis (Part 2: below the knee). *Eur J Vasc Endovasc Surg* 2014; 47(5): 536–544.
12. Armstrong EJ, Bishu K and Waldo SW. Endovascular treatment of infrapopliteal peripheral artery disease. *Curr Cardiol Rep* 2016; 18(4): 34.
13. Hammad TA and Prasad A. The contemporary role of stents and angioplasty for the treatment of infrapopliteal disease in critical limb ischemia. *Curr Cardiol Rep* 2017; 19(7): 58.
14. Lyden SP. Techniques and outcomes for endovascular treatment in the tibial arteries. *J Vasc Surg* 2009; 50(5): 1219–1223.
15. Nehler MR, Duval S, Diao L, et al. Epidemiology of peripheral arterial disease and critical limb ischemia in an insured national population. *J Vasc Surg* 2014; 60(3): 686.e2–695.e2.
16. Shishehbor MH and Hammad TA. Treatment of infrapopliteal disease in critical limb ischemia: beyond angioplasty. *Circ Cardiovasc Interv* 2016; 9(5): e003882.
17. Bhatt DL, Peterson ED, Harrington RA, et al. Prior polyvascular disease: risk factor for adverse ischaemic outcomes in acute coronary syndromes. *Eur Heart J* 2009; 30(10): 1195–1202.
18. Baumann F, Husmann M, Benenati JF, et al. Bleeding risk profile in patients with symptomatic peripheral artery disease. *J Endovasc Ther* 2016; 23(3): 468–471.
19. Cea Soriano L, Fowkes FGR, Allum AM, et al. Predictors of bleeding in patients with symptomatic peripheral artery disease: a cohort study using the health improvement network in the United Kingdom. *Thromb Haemost* 2018; 118(6): 1101–1112.
20. Hirsch AT, Haskal ZJ, Hertzer NR, et al. ACC/AHA 2005 guidelines for the management of patients with peripheral arterial disease (lower extremity, renal, mesenteric, and abdominal aortic): executive summary a collaborative report from the American Association for Vascular Surgery/Society for Vascular Surgery, Society for Cardiovascular Angiography and Interventions, Society for Vascular Medicine and Biology, Society of Interventional Radiology, and the ACC/AHA Task Force on Practice Guidelines (Writing Committee to Develop Guidelines for the Management of Patients with Peripheral Arterial Disease). *J Am Coll Cardiol* 2006; 47(6): 1239–1312.
21. Norgren L, Hiatt WR, Dormandy JA, et al. Inter-Society Consensus for the Management of Peripheral Arterial Disease (TASC II). *J Vasc Surg* 2007; 45(Suppl. S): S5–S67.
22. Hess CN, Norgren L, Ansel GM, et al. A structured review of antithrombotic therapy in peripheral artery disease with a focus on revascularization: a TASC (InterSociety Consensus for the Management of Peripheral Artery Disease) initiative. *Circulation* 2017; 135(25): 2534–2555.
23. Aboyans V, Ricco JB, Bartelink MEL, et al. 2017 ESC guidelines on the diagnosis and treatment of peripheral arterial diseases, in collaboration with the European Society for Vascular Surgery (ESVS): document covering atherosclerotic disease of extracranial carotid and vertebral, mesenteric, renal, upper and lower extremity arteries. Endorsed by: the European Stroke Organization (ESO) The Task Force for the Diagnosis and Treatment of Peripheral Arterial Diseases of the European Society of Cardiology (ESC) and of the European Society for Vascular Surgery (ESVS). *Eur Heart J* 2018; 39(9): 763–816.
24. Soden PA, Zettervall SL, Ultee KH, et al. Dual antiplatelet therapy is associated with prolonged survival after lower extremity revascularization. *J Vasc Surg* 2016; 64(6): 1633.e1–1644.e1.
25. Beiswenger AC, Jo A, Harth K, et al. A systematic review of the efficacy of aspirin monotherapy versus other antiplatelet therapy regimens in peripheral arterial disease. *J Vasc Surg* 2018; 67(6): 1922.e6–1932.e6.
26. Tepe G, Bantleon R, Brechtel K, et al. Management of peripheral arterial interventions with mono or dual antiplatelet therapy – the MIRROR study: a randomised and double-blinded clinical trial. *Eur Radiol* 2012; 22(9): 1998–2006.
27. Dotter CT and Judkins MP. Transluminal treatment of arteriosclerotic obstruction. Description of a new technic and a preliminary report of its application. *Circulation* 1964; 30: 654–670.
28. Libow M, Gruentzig AR and Greene L. Percutaneous transluminal coronary angioplasty. *Curr Probl Cardiol* 1985; 10(6): 1–55.

29. Pasternak RC, Baughman KL, Fallon JT, et al. Scanning electron microscopy after coronary transluminal angioplasty of normal canine coronary arteries. *Am J Cardiol* 1980; 45(3): 591–598.
30. Steele PM, Chesebro JH, Stanson AW, et al. Balloon angioplasty. Natural history of the pathophysiological response to injury in a pig model. *Circ Res* 1985; 57(1): 105–112.
31. Wilentz JR, Sanborn TA, Haudenschild CC, et al. Platelet accumulation in experimental angioplasty: time course and relation to vascular injury. *Circulation* 1987; 75(3): 636–642.
32. Okura H, Shimodozono S, Hayase M, et al. Impact of deep vessel wall injury and vessel stretching on subsequent arterial remodeling after balloon angioplasty: a serial intravascular ultrasound study. *Am Heart J* 2002; 144(2): 323–328.
33. Andersen HR, Maeng M, Thorwest M, et al. Remodeling rather than neointimal formation explains luminal narrowing after deep vessel wall injury: insights from a porcine coronary (re)stenosis model. *Circulation* 1996; 93(9): 1716–1724.
34. Sarembock IJ, LaVeau PJ, Sigal SL, et al. Influence of inflation pressure and balloon size on the development of intimal hyperplasia after balloon angioplasty. A study in the atherosclerotic rabbit. *Circulation* 1989; 80(4): 1029–1040.
35. Guzman LA, Mick MJ, Arnold AM, et al. Role of intimal hyperplasia and arterial remodeling after balloon angioplasty: an experimental study in the atherosclerotic rabbit model. *Arterioscler Thromb Vasc Biol* 1996; 16(3): 479–487.
36. Roubin GS, Douglas JS Jr, King SB 3rd, et al. Influence of balloon size on initial success, acute complications, and restenosis after percutaneous transluminal coronary angioplasty. A prospective randomized study. *Circulation* 1988; 78(3): 557–565.
37. Bauters C, Meurice T, Hamon M, et al. Mechanisms and prevention of restenosis: from experimental models to clinical practice. *Cardiovasc Res* 1996; 31(6): 835–846.
38. Chandrasekar B and Tanguay JF. Platelets and restenosis. *J Am Coll Cardiol* 2000; 35(3): 555–562.
39. Ward MR, Kanellakis P, Ramsey D, et al. Response to balloon injury is vascular bed specific: a consequence of de novo vessel structure? *Atherosclerosis* 2000; 151(2): 407–414.
40. Baumann F, Fust J, Engelberger RP, et al. Early recoil after balloon angioplasty of tibial artery obstructions in patients with critical limb ischemia. *J Endovasc Ther* 2014; 21(1): 44–51.
41. Block PC, Myler RK, Stertzer S, et al. Morphology after transluminal angioplasty in human beings. *N Engl J Med* 1981; 305(7): 382–385.
42. Essed CE, Van den Brand M and Becker AE. Transluminal coronary angioplasty and early restenosis. Fibrocellular occlusion after wall laceration. *Br Heart J* 1983; 49(4): 393–396.
43. Faxon DP, Sanborn TA, Haudenschild CC, et al. Effect of antiplatelet therapy on restenosis after experimental angioplasty. *Am J Cardiol* 1984; 53(12): 72C–76C.
44. Hess H, Mietaschk A and Deichsel G. Drug-induced inhibition of platelet function delays progression of peripheral occlusive arterial disease. A prospective double-blind arteriographically controlled trial. *Lancet* 1985; 1(8426): 415–419.
45. Heiss HW, Just H, Middleton D, et al. Reocclusion prophylaxis with dipyridamole combined with acetylsalicylic acid following PTA. *Angiology* 1990; 41(4): 263–269.
46. Platelet inhibition with ASA/dipyridamole after percutaneous balloon angioplasty in patients with symptomatic lower limb arterial disease. A prospective double-blind trial. Study group on pharmacological treatment after PTA. *Eur J Vasc Surg* 1994; 8(1): 83–88.
47. Ranke C, Creutzig A, Luska G, et al. Controlled trial of high- versus low-dose aspirin treatment after percutaneous transluminal angioplasty in patients with peripheral vascular disease. *Clin Investig* 1994; 72(9): 673–680.
48. Weichert W, Meents H, Abt K, et al. Acetylsalicylic acid – reocclusion – prophylaxis after angioplasty (ARPA-study). A randomized double-blind trial of two different dosages of ASA in patients with peripheral occlusive arterial disease. *Vasa* 1994; 23(1): 57–65.
49. Minar E, Ahmadi A, Koppensteiner R, et al. Comparison of effects of high-dose and low-dose aspirin on restenosis after femoropopliteal percutaneous transluminal angioplasty. *Circulation* 1995; 91(8): 2167–2173.
50. Girolami B, Bernardi E, Prins MH, et al. Antiplatelet therapy and other interventions after revascularisation procedures in patients with peripheral arterial disease: a meta-analysis. *Eur J Vasc Endovasc Surg* 2000; 19(4): 370–380.
51. Watson HR and Bergqvist D. Antithrombotic agents after peripheral transluminal angioplasty: a review of the studies, methods and evidence for their use. *Eur J Vasc Endovasc Surg* 2000; 19(5): 445–450.
52. Robertson L, Ghouri MA and Kovacs F. Antiplatelet and anticoagulant drugs for prevention of restenosis/reocclusion following peripheral endovascular treatment. *Cochrane Database Syst Rev* 2012; 8: CD002071.
53. Serruys PW, de Jaegere P, Kiemeneij F, et al. A comparison of balloon-expandable-stent implantation with balloon angioplasty in patients with coronary artery disease. *N Engl J Med* 1994; 331(8): 489–495.
54. Fischman DL, Leon MB, Baim DS, et al. A randomized comparison of coronary-stent placement and balloon angioplasty in the treatment of coronary artery disease. Stent Restenosis Study Investigators. *N Engl J Med* 1994; 331(8): 496–501.
55. Topol EJ. Caveats about elective coronary stenting. *N Engl J Med* 1994; 331(8): 539–541.
56. Neumann FJ, Gawaz M, Ott I, et al. Prospective evaluation of hemostatic predictors of subacute stent thrombosis after coronary Palmaz-Schatz stenting. *J Am Coll Cardiol* 1996; 27(1): 15–21.
57. Schomig A, Neumann FJ, Kastrati A, et al. A randomized comparison of antiplatelet and anticoagulant therapy after the placement of coronary-artery stents. *N Engl J Med* 1996; 334(17): 1084–1089.
58. Leon MB, Baim DS, Popma JJ, et al. A clinical trial comparing three antithrombotic-drug regimens after coronary-artery stenting. Stent Anticoagulation Restenosis Study Investigators. *N Engl J Med* 1998; 339(23): 1665–1671.
59. Antithrombotic Trialists' Collaboration. Collaborative meta-analysis of randomised trials of antiplatelet therapy for prevention of death, myocardial infarction, and stroke in high risk patients. *BMJ* 2002; 324(7329): 71–86.
60. Catalano M, Born G and Peto R. Prevention of serious vascular events by aspirin amongst patients with peripheral arterial disease: randomized, double-blind trial. *J Intern Med* 2007; 261(3): 276–284.
61. Belch J, MacCuish A, Campbell I, et al. Prevention of Progression of Arterial Disease and Diabetes Study Group; Diabetes Registry Group; Royal College of Physicians Edinburgh. The prevention

of progression of arterial disease and diabetes (POPADAD) trial: factorial randomised placebo controlled trial of aspirin and antioxidants in patients with diabetes and asymptomatic peripheral arterial disease. *BMJ* 2008; 337: a1840.
62. CAPRIE Steering Committee. A randomised, blinded, trial of clopidogrel versus aspirin in patients at risk of ischaemic events (CAPRIE). *Lancet* 1996; 348(9038): 1329–1339.
63. Cacoub PP, Bhatt DL, Steg PG, et al. Patients with peripheral arterial disease in the CHARISMA trial. *Eur Heart J* 2009; 30: 192–201.
64. Hiatt WR, Fowkes FG, Heizer G, et al. Ticagrelor versus clopidogrel in symptomatic peripheral artery disease. *N Engl J Med* 2017; 376: 32–40.
65. Bonaca MP, Bhatt DL, Storey RF, et al. Ticagrelor for prevention of ischemic events after myocardial infarction in patients with peripheral artery disease. *J Am Coll Cardiol* 2016; 67(23): 2719–2728.
66. Wisman PP, Teraa M, de Borst GJ, et al. Baseline platelet activation and reactivity in patients with critical limb ischemia. *PLoS One* 2015; 10(7): e0131356.
67. Clavijo LC, Al-Asady N, Dhillon A, et al. Prevalence of high on-treatment (aspirin and clopidogrel) platelet reactivity in patients with critical limb ischemia. *Cardiovasc Revasc Med* 2018; 19(5 pt A): 516–520.
68. Clavijo LC, Dhillon A, Al-Asady N, et al. Switch to Ticagrelor in critical limb ischemia antiplatelet study (STT-CLIPS). *Cardiovasc Revasc Med* 2018; 19(3 pt B): 319–323.
69. Peeters Weem SMO, Leunissen TC, Teraa TCM, et al. Personalized antiplatelet therapy following endovascular revascularization in peripheral artery occlusive disease: a novel concept. *EJVES Short Rep* 2015; 29: 11–17.
70. Price MJ, Berger PB, Teirstein PS, et al. Standard- vs high-dose clopidogrel based on platelet function testing after percutaneous coronary intervention: the GRAVITAS randomized trial. *JAMA* 2011; 305: 1097–1105.
71. Montalescot G, Range G, Silvain J, et al. High on-treatment platelet reactivity as a risk factor for secondary prevention after coronary stent revascularization: a landmark analysis of the ARCTIC study. *Circulation* 2014; 129: 2136–2143.
72. Sørensen R, Hansen ML, Abildstrom SZ, et al. Risk of bleeding in patients with acute myocardial infarction treated with different combinations of aspirin, clopidogrel, and vitamin K antagonists in Denmark: a retrospective analysis of nationwide registry data. *Lancet* 2009; 374(9706): 1967–1974.
73. Varenne O, Cook S, Sideris G, et al. Drug-eluting stents in elderly patients with coronary artery disease (SENIOR): a randomised single-blind trial. *Lancet* 2018; 391(10115): 41–50.
74. Subherwal S, Bach RG, Chen AY, et al. Baseline risk of major bleeding in non-ST-segment-elevation myocardial infarction: the CRUSADE (Can Rapid risk stratification of Unstable angina patients Suppress ADverse outcomes with Early implementation of the ACC/AHA Guidelines) bleeding score. *Circulation* 2009; 119(14): 1873–1882.
75. Mehran R, Pocock SJ, Nikolsky E, et al. A risk score to predict bleeding in patients with acute coronary syndromes. *J Am Coll Cardiol* 2010; 55(23): 2556–2566.
76. Costa F, van Klaveren D, James S, et al. Derivation and validation of the predicting bleeding complications in patients undergoing stent implantation and subsequent dual antiplatelet therapy (PRECISE-DAPT) score: a pooled analysis of individual-patient datasets from clinical trials. *Lancet* 2017; 389(10073): 1025–1034.
77. Hur DJ, Kizilgul M, Aung WW, et al. Frequency of coronary artery disease in patients undergoing peripheral artery disease surgery. *Am J Cardiol* 2012; 110(5): 736–740.
78. Nishijima A, Yamamoto N, Yoshida R, et al. Coronary artery disease in patients with critical limb ischemia undergoing major amputation or not. *Plast Reconstr Surg Glob Open* 2017; 5(6): e1377.
79. Lee MS, Rha SW, Han SK, et al. Clinical outcomes of patients with critical limb ischemia who undergo routine coronary angiography and subsequent percutaneous coronary intervention. *J Invasive Cardiol* 2015; 27(4): 213–217.
80. McFalls EO, Ward HB, Moritz TE, et al. Coronary-artery revascularization before elective major vascular surgery. *N Engl J Med* 2004; 351: 2795–2804.
81. Gerhard-Herman MD, Gornik HL, Barrett C, et al. 2016 AHA/ACC guideline on the management of patients with lower extremity peripheral artery disease. *J Am Coll Cardiol* 2017; 69(11): e71–e126.
82. Narula N, Dannenberg AJ, Olin JW, et al. Pathology of peripheral artery disease in patients with critical limb ischemia. *J Am Coll Cardiol* 2018; 72: 2152–2163.
83. Bonaca MP, Gutierrez JA, Creager MA, et al. Acute limb ischemia and outcomes with vorapaxar in patients with peripheral artery disease: results from the trial to assess the effects of vorapaxar in preventing heart attack and stroke in patients with atherosclerosis-thrombolysis in myocardial infarction 50 (TRA2°P-TIMI 50). *Circulation* 2016; 133(10): 997–1005.
84. Anand SS, Caron F, Eikelboom JW, et al. Major adverse limb events and mortality in patients with peripheral artery disease: the COMPASS trial. *J Am Coll Cardiol* 2018; 71(20): 2306–2315.