Acute Limb Ischemia on Diabetic Patient: A Case Report and Literature Review

Achmad Bima Aryaputra[1], Hendry Purnasidha Bagaswoto[2], Taufiq Nugroho[3], and Ana Fauziyati[4(✉)]

[1] General Practitioner, RSU Islam Klaten, Klaten, Indonesia
[2] Department of Cardiology and Vascular Medicine, Faculty of Medicine, Public Health, and Nursing, Universitas Gadjah Mada – Dr. Sardjito Hospital, Yogyakarta, Indonesia
[3] Department of Surgery, Faculty of Medicine, Universitas Islam Indonesia, Yogyakarta, Indonesia
[4] Department of Internal Medicine, Faculty of Medicine, Universitas Islam Indonesia, Yogyakarta, Indonesia
047110434@uii.ac.id

Abstract. It's estimated that 236.62 million people aged 25 years and older had peripheral artery disease around the world. Diabetes was also highly linked to PAD. Most likely due to neuropathy, patients with both diabetes and PAD have a rapid progression of their PAD. We report the case of a 58 years old woman, presented with acute onset of left foot pain within 1 week of symptom onset. She indicated that her proximal left foot pain felt like "on fire", and she cannot feel the distal part. She had a history of diabetes for three years prior, with routine glimepiride and metformin consumption. On extremity examination, the left foot was cold, partly mottled, with fixed blue staining on the distal part. Patient was unable to move her toes, but she's able to actively move her left foot although limited because of the pain. On vascular examination, there was no evidence on femoral bruits, but pulsation of left popliteal arteries were diminished as confirmed by Doppler Ultrasonography, compared to the right side. On neurological examination, we found complete loss of light touch sensation in the distal part of the left foot. Due to the terminal state of the illness, patients were indicated for surgical above knee amputation. Post-surgical evaluation, patients had neither fever nor other complications. Minimal patient understanding about symptoms of time-critical conditions can lead to treatment delay and worse outcomes..

Keywords: Acute limb ischemia · Diabetes · Peripheral artery disease

1 Introduction

Peripheral Artery Disease (PAD), the term used to describe the arterial occlusive disease of the lower and upper extremities, was determined in 1554 males and 1759 females from 1995 to 1998. It's found that PAD was present in 3.9% of males and 3.3% of females. However, the prevalence of claudication was only 1.9% in males and 0.8% in females, suggesting that only half of men and only a quarter of women had symptoms

© The Author(s) 2023
H. Nurdiyanto et al. (Eds.): ICCvD 2021, AHSR 52, pp. 161–172, 2023.
https://doi.org/10.2991/978-94-6463-048-0_19

or recognized their symptoms [1]. Seven thousand Europeans were evaluated for PAD in the Rotterdam study; One to twenty percent of patients in these studies diagnosed with PAD had self-reported claudication or symptoms; this supports the conclusion that most individuals with PAD remain either asymptomatic or limit their activities due to numerous variables. Nearly 10% of asymptomatic individuals have advanced PAD with severe obstruction to blood flow in their lower extremities [2].

In the 20th century, It's estimated that 236.62 million people aged 25 years and older had peripheral artery disease in 2015, which is 73% were from low-middle income countries (LMICs). Generally, the prevalence of peripheral artery disease increased with increasing age, but the largest share of the case was aged 65–69 years old in high-income countries and 45–49 years old in low-middle income countries. Worldwide, 52% of people with PAD were women. Indonesia with other 14 countries contained more than two-thirds of the global peripheral artery disease in 2015. South-east Asia region was in second place between LMICs region and in third place worldwide for peripheral artery disease cases [3]. According to the Global Burden of Disease of 2017, the worldwide number of prevalent cases of peripheral artery disease in 2017 was 118.1 million and the number of incident cases was 10.8 million, with only one-third of prevalent cases of symptomatic claudication due to peripheral artery disease [4].

Diabetes mellitus is a group of metabolic diseases characterized by hyperglycemia resulting from defects in insulin secretion, insulin action, or both. The chronic hyperglycemia of diabetes is associated with long-term damage, dysfunction, and failure of various organs, especially nerves, heart, and blood vessels [5]. Based on the National Report of Basic Health Research (RISKESDAS) in 2018, diabetes mellitus prevalence in Indonesia was 2.0%, increasing 0.5% since the past 5 years, women had a higher prevalence than men [6]. Peripheral artery disease was presented in 10.9% of diabetic patients who were admitted to RSUP Dr Cipto Mangunkusumo in 2011 [7].

2 Method

2.1 Patient History

A 58 years old woman, presented to ER with acute onset of left foot pain within 1 week of symptom onset. She indicated that her proximal left foot pain, described as "on fire" worsened, and she could not feel the distal part. She denied any trauma or fever. All other reviews of systems were unremarkable, including no history of chest pain or palpitation. She had a history of diabetes mellitus for three years prior, with routine medication of Glibenclamide and Metformin. She had no other cardiovascular risk factors.

2.2 Physical Examination

The patient seemed uncomfortable as evidenced by her groaning in pain from her left foot. The initial vital sign included a blood pressure of 138/88 mmHg, heart rate of 90 beats/min, respiratory rate of 20 breaths/min, SpO2 98% on room air, and casual plasma glucose of 213 mg/dL. On extremity examination, the left foot was cold, partly mottled, with fixed blue staining on the distal part (Fig. 1) (Fig. 2). On vascular examination, she

Fig. 1. Clinical presentation of the disease

Fig. 2. Partly mottled, with fixed blue staining on the distal part of the feet

had palpable femoral artery on both legs and no evidence of femoral bruits, but there was diminished pulsation of popliteal artery and not palpable left posterior tibial artery, compared to the right side. On neurological examination, we found complete loss of light touch sensation in the distal part of the left foot, an inability to move toes, but she's able to actively move her left foot although limited because of the pain. There were no varicosities in the left lower extremity. Cardiopulmonary and abdominal examination was unremarkable.

2.3 Emergency Department Course

This patient's conditions lead to be at high risk for Acute Limb Ischemia (ALI) due to the constellation of signs, symptoms, and risk factors, which included an acute onset of extremely leg pain, asymmetrical diminished pulses, discoloration of left foot, local neurologic disorder, and history of diabetes mellitus. Several tests were carried out to ensure the diagnosis. The blood test revealed the following results: total leucocyte count, 12.100/uL; haemoglobin, 9.4 g/dL; platelets, 188,000/ul; D-dimer, 2000 ng/mL; aPTT, 37.9 s; and PT, 14.1 s. Chest X-ray result was suggestive for pneumonia due to inhomogeneous opacity in both lungs, but antigen test for Covid 19 was negative. On ECG, we found normal sinus rhythm and no axis deviation.

Because the patient presented with no significant risk factors for arterial occlusions, such as atrial fibrillation, we maintained a broad differential diagnosis, including venous thrombosis and vasculitis. To confirm the diagnosis, the duplex echocardiography was performed. The Doppler ultrasound showed an echogenic material obstructing the popliteal artery, anterior tibial artery, and posterior tibial artery, with no flow, undetectable Peak Systolic Velocity (PSV), whereas the presence of an aneurysm was excluded. In femoral artery, thrombus was not found with PSV was 41.8 cm/sec. The patient had no thigh and leg varicose veins; no thrombophlebitis. (Fig. 3).

Since the duplex scan ensured the presence of thrombotic material in the popliteal artery and tibial arteries, the patient was diagnosed with Peripheral artery disease-Acute

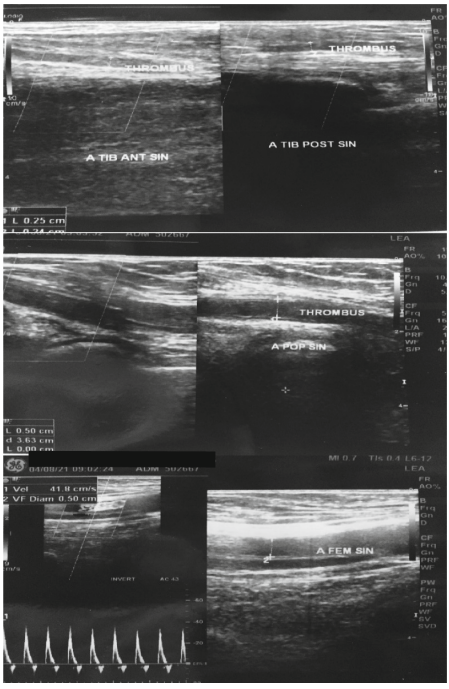

Fig. 3. On the Doppler ultrasound, we found echogenic material obstructing the popliteal artery, anterior tibial artery, and posterior tibial artery, with no flow.

limb ischemia Rutherford III and Diabetes. Because there was evidence of thrombus and no evidence of active bleeding, intravenous once daily 25 mg Fondaparinux was initiated. For mitigation of any cardiovascular event, 75 mg Clopidogrel and 40 mg Atorvastatin once daily were given. As casual plasma glucose was still uncontrollable, Oral antidiabetic drugs were switched to an adjusted dose of subcutaneous insulin injection. Patients were also medicated for the pain.

2.4 Surgical Care

Taking into consideration the fact that the terminal state of the illness, the patient was indicated for surgical above-knee amputation. On regional spinal anesthesia, left leg connective tissues were incised sequentially from blood vessels, nerves, muscles, then femoral bone. The post-surgery period was uneventful, with complete remission of symptoms. A day later, the patient was discharged without any complaint post-surgery. One week later, on post-surgical evaluation, he had neither fever nor other complications.

3 Result and Discussion

3.1 Peripheral Artery Disease

Peripheral vascular disease, peripheral arterial disease (PAD), peripheral arterial occlusive disease, and arteriosclerosis obliterans are some of the terms used to describe arterial occlusive disease of the lower and upper extremities. The spectrum itself ranges from asymptomatic to limb loss. Acute limb ischemia is sudden, acute (<14 days) severe, hypoperfusion of limb that is characterized by the "6 P's": Pain, Pallor, Pulselessness, Poikilothermia, Paraesthesia, and Paralysis. In comparison to chronic limb-threatening ischemia (CLTI), also called critical limb ischemia (CLI), distinguished from ALI by chronicity (>14 days) and symptoms like ischemic rest pain, non-healing wounds, or gangrene [8].

3.1.1 Pathophysiology of PAD

The basic pathophysiology of PAD is blood flow limitation during exercise and progressive myocyte damage with muscle remodeling. At rest, in the presence of significant vascular stenosis, vascular resistance decreases to maintain calf muscle perfusion despite a decrease in systolic pressure. However, in the exercising muscle, this compensation mechanism fails to sufficiently increase blood flow to match metabolic demands, with ensuing muscle ischemia. The occurrence of repetitive cycles of exercise-induced ischemia followed by reperfusion, triggers the formation of reactive oxygen species, leading to abnormal myocyte metabolism and impaired contractility [9]. Some risk factors have been proposed to induce ALI or worsening the condition. The one who has classic risk factors of cardiovascular disease such as smoking, hypertension, dyslipidemia, and diabetes, have a higher risk for PAD [10].

3.1.2 Diabetes as Risk Factor and Comorbid

Our patient had a history of diabetes mellitus with routine daily medication, still she had the disease. Diabetes, as previously indicated, was highly linked to PAD, with ORs ranging from 1.9 to 4 in population studies. The risk of PAD rises as the duration of diabetes rises [10]. Most likely due to neuropathy, patients with both diabetes and PAD have worse lower extremity function and rapid progression of their PAD and for developing Coronary Artery Disease (CAD) than individuals with PAD without diabetes [11]. Diabetes, when combined with cardiovascular risk factors, confers a three-fold higher risk of PAD, even in the absence of CAD. The largest risk of PAD was found to be among current smokers [12]. In consequence, diabetes management in patients with PAD should be coordinated among members of the healthcare team [8].

3.1.3 Diagnosis PAD

Patients with PAD may experience a symptom of claudication, as a matter of fact the majority of patients had asymptomatic or atypical leg symptoms [2]. The vascular examination for PAD includes pulse palpation, auscultation for femoral bruits, and inspection of the legs and feet. Lower extremity pulses are assessed and rated as follows: 0, absent; 1, diminished; 2, normal; or 3, bounding [8]. PAD has several presentations and degrees of severity, classified as stated by Fontaine and Rutherford Classification. The resting ankle-brachial index (ABI) is the first-line study for the diagnosis of PAD, according to US and European standards. Both organizations advised against using computed tomography angiography, magnetic resonance angiography, or catheter-based angiography as a screening tool in the first diagnosis. [8, 10]. However, duplex ultrasonography should be performed as a first-line imaging tool to confirm Lower Extremity Artery Disease (LEAD) lesions, according to the ESC Guideline [10]. Due to the presence of typical clinical signs and symptoms of peripheral artery disease in our patient, we bypassed the guideline advice and went straight to imaging to confirm the lesion's location.

3.1.4 Management of PAD

Pharmacotherapy for the patient with PAD includes antiplatelet and statin agents and is customized to additional risk factors, such as whether the patient also has diabetes mellitus or hypertension. Several medications were endorsed to halt the progression of peripheral artery disease. The U.S. and European guidelines both recommend antiplatelet monotherapy, either aspirin (75–325 mg per day) or clopidogrel (75 mg per day), in symptomatic PAD patients. In both guidelines, aspirin receives a Class I indication for symptomatic PAD and is placed at a similar level to clopidogrel. However, The European guidelines suggest clopidogrel may be superior to aspirin, largely based on the results of the CAPRIE (Clopidogrel Versus Aspirin in Patients at Risk of Ischemic Events) trial [8, 10]. We use daily 75mg Clopidogrel as recommended on our patient to prevent any potential atherosclerotic risk.

Other than Clopidogrel, we also use 40 mg of Atorvastatin, a high-intensity statin therapy. In both guidelines, the recommendations for statins derive from a single randomized clinical trial: the HPS (Heart Protection Study). In HPS, MI, stroke, or revascularization was significantly reduced over 5 years of follow-up in patients who use

daily 40 mg simvastatin [8, 10]. Statins work by decreasing circulating LDL-C levels. Plaques may become less occlusive and less likely to rupture and induce thrombosis with decreased plasma LDL-C values (i.e., plaque stabilization) [13]. Even if a plaque ruptures, patients receiving statins may be at a lower risk of thrombosis as a result of the inhibition of platelet activity and reduced plasma levels of procoagulants [14].

In contrast to the recommendations for atherosclerotic risk reduction, medications recommended for symptomatic improvement vary significantly. The U.S. guidelines recommend the use of cilostazol based on a Cochrane review supporting its efficacy (Class I). In contrast, the ESC/ESVS writing group reports that objective documentation of beneficial effects on, if any, are generally mild to moderate, with large variability and so does not recommend the therapy [15]. Headaches, flushing sensations, and diarrhea are all common side effects, and it's also increasing the risk of bleeding [16]. Considering these results, cilostazol was not used in our patient. Instead, we are focusing on atherosclerotic and Major Adverse Cardiovascular Event (MACE) risk reduction.

3.2 Acute Limb Ischemia (ALI)

ALI is a medical emergency that requires immediate attention. The time limit is imposed because the skeletal muscle can only sustain ischemia for 4 to 6 h. ALI can cause both discomfort and loss of function in the lower extremities. The longer these symptoms are present, the less likely the possibility of limb salvage. Clinical assessment must include symptom duration, pain intensity, motor and sensory deficit severity to distinguish a threatened from a nonviable extremity [8].

Acute Limb Ischemia, in particular, can be caused by variety of conditions, such as arterial thrombosis owing to plaque progression and complication (40%), arterial embolism (30%), graft thrombosis (20%) thrombosis of a popliteal aneurysm (5%), or trauma (5%) [17]. Native artery occlusions are most common in severe and complex atherosclerotic plaques. In people with hypercoagulable disorders, in situ thrombosis can occur in a previously normal artery [18]. Some other conditions that also contribute to the development of ALI is embolism from intracardiac mass, atheroembolism, and calcified debris after transcatheter aortic valve implantation (TAVI).

3.2.1 ALI Classification

ESC and AHA use the ALI classification proposed by Rutherford as the basis to measure the severity of the disease, based on sensory loss, motor deficit, and Doppler examination result. They favour clinical presentation and salvageability to decide the best management strategy [8, 10] (Table 1).

3.2.2 Prognosis of ALI

Even in the setting of rapid and effective revascularization, the 1-year morbidity and mortality rates of ALI are high [8]. Reflecting from the COMPASS trial, who study Major Adverse Limb Event (MALE) in PAD, enrolled 7470 patients with PAD (ABI $<$ 0.90). A total of 128 (2.0%) participants experienced MALE (ALI or CLI). In 1 year after the Major Adverse Limb Event, 61.5% of patients were readmitted to the hospital,

Table 1. Acute limb ischemia classification by Rutherford

Category	Description/prognosis	Findings		Dopler	
		Sensor loss	Muscle waekness	Aretrial	Venous
I.Viable	Not immediately threatened	None	None	Audible	Audible
IIa.Threatened marginally	Salvageable if promptly treated	Minimal (toes) or none	None	Inaudible	Audible
IIb. Threatened immediately	Salvageable with immediate revascularization	More than toes, associated with rest pain	None	Inaudible	Audible
III.Reversible	Major tissue loss or permanent nerve damage inventables	Profound, aesthetic	Profound, paralysis (rigor)	Inaudible	Inaudible

20.5% had entire vascular amputations, 8.3% died, and 3.7% had MACE. In terms of risk assessment, MALE raises the risk of re-hospitalization, total vascular amputations, death, and the composite of MACE [19]. Other study suggest that patients with PAD and diabetes had a significantly higher risk to have CV death, myocardial infarction (MI), major amputation, and all-cause mortality than those without diabetes (5.68 vs. 3.65 per 100 patient-years), The HR was 1.43 (95% CI: 1.28 to 1.61; $p < 0.0001$). Patients with diabetes also had a 86% increased risk for major amputation ($p < 0.0001$), as compared with those without diabetes [20].

3.2.3 Treatment Strategy of ALI

Patients with suspected ALI should be evaluated by clinicians with sufficient experience to assess limb viability. Considering the limb viability, the clinician can decide which is the best strategy for the patient. In terms of anticoagulants, ESC and AHA both agree that heparin should be given to patients with ALI, unless contraindicated (Class I) [8, 10], along with analgesia [10]. But anticoagulation is not recommended to be used to reduce the risk of cardiovascular ischemic events in patients with PAD (Class III Harm) [8]. In our condition, fondaparinux was given with close observation of any sign of bleeding.

Both guidelines noted that the level of emergency and the therapeutic method to be used are determined by the clinical presentation, particularly the existence of neurological impairments [8, 10]. Local resources and patient characteristics (e.g., cause and degree of ischemia) should dictate the revascularization technique in patients with ALI (Class I) [8].

3.2.4 Revascularization

If a patient has a neurological deficit, immediate revascularization is necessary, and imaging should not delay the therapy. Percutaneous catheter-directed thrombolytic therapy, percutaneous mechanical thrombus extraction or thrombo-aspiration (with or without thrombolytic therapy), and surgical thrombectomy, bypass, and/or arterial repair are some of the revascularization options [10]. Catheter-based thrombolysis was recommended by the US Guideline for patients with ALI who had a salvageable limb (Class I) [8]. However, in patients with a non-salvageable limb, amputation should be performed first (Class I) [8, 10].

The authorities in the field, our cardiologist and surgeon, determined that our patient's limb was non-salvageable (Rutherford III), and so we decided to amputate the leg, as endorsed in the therapy strategy algorithm of the United States and Europe Guideline. Thus the patient was not referred to an angiography center due to treatment options.

If the situation were different, revascularization for marginally or immediately endangered limbs (Category IIa and IIb ALI) should be done right away (within 6 h). Revascularization should be done as soon as possible (between 6–24 h) for viable limbs (Category I ALI). Catheter-directed thrombolysis to surgical thromboembolectomy are all options for revascularization [8].

3.3 Amputations

Taking into consideration the fact that the limb was unsalvageable, diminished pulsation popliteal artery, poikilothermia has reached the knee, and identified thrombus on the popliteal artery, Above-the-knee amputation (AKA) must be done. Also considering up to one-third of below-knee amputations may require further surgery or an above-knee amputation due to poor healing [21]. However, we are conscious that this technique is not without risk. From 2000 to 2008, a research including 3 million PAD patients, 186,338 patients (or 6.8% of the PAD group) had significant lower extremity (LE) amputations. Patients with major LE amputation had significantly higher rates of all-cause mortality than patients with PAD who did not have major LE amputation. Nevertheless, patients with PAD who had a large LE amputation had a reduced incidence of MI and stroke than those who did not have a major LE amputation. Other causes are independently associated with death after amputation, like the aging process, history of heart failure, renal disease, cancer, and chronic obstructive pulmonary disease [22].

The performance of AKA was associated with a statistically significant higher hazard of death when compared with more distal LE amputation locations (HR 1.30). Three-year mortality rates were 76.6% in patients undergoing AKA, whereas 3-year mortality rates were 63.1% in patients undergoing Below-the-Knee Amputation (BKA) [22]. Another study also presents similar findings; patients had a greater 30-day mortality rate (7% vs. 3%) following AKA than after BKA, but had fewer postoperative complications (12 percent vs. 18 percent) ($P < 0.001$). A total of 1% of AKAs and 2% of BKAs followed by myocardial infarction ($P = 0.034$). Infection rates and respiratory problems did not differ statistically [23].

3.4 Delayed of Treatment

Our patient just started to seek medical care after suffering 1 week of symptoms. Prolonged duration of ischemia is the most common factor in patients requiring amputation for treatment of ALI. Patients who have an insensate and immobile limb in the setting of prolonged ischemia (>6 to 8 h) are unlikely to have potential for limb salvage with revascularization [8].

In a study conducted in Denmark, Londero et al. found that the average period between the onset of symptoms and the first contact with a doctor was 27.25 h. That period is determined to be the most important factor in treatment delay. Despite the fact that the patients were not directly asked about the causes for the delay, it appears safe to assume that greater public knowledge is required to promote immediate revascularization and improve results. Public campaigns emphasizing the importance of ALI therapy as soon as possible could help to improve outcomes [24]. According to a study conducted in the United Kingdom by Normahani et al., the median duration from the onset of symptoms to arriving at the medical institution was 11.35 h. Time to patient presentation, imaging time, wrong diagnosis, and delays in prompt transfer to an appropriate facility are all variables that contribute to this [25]. Reflecting from another case of cardiovascular disease, public awareness campaigns have been shown to reduce pre-hospital delay in patients with chest discomfort [26]. Although pricey, this technique may be justified because the burdens of ALI and STEMI on the population are equivalent.

4 Conclusion

The signs and symptoms of ALI necessitate prompt diagnosis and treatment. Emergency doctors should be aware of the disease's early signs and symptoms, as well as the approved treatment options for ALI. Minimal understanding about symptoms of time-critical conditions in patients with risk factors can lead to treatment delay and worse outcomes. Patient education about acute limb ischemia should be given to patients with risk factors to prevent any delay of treatment.

References

1. J.M. Murabito, J.C. Evans, K. Nieto, M.G. Larson , D. Levy , P.W.Wilson, "Prevalence and clinical correlates of peripheral arterial disease in the Framingham Offspring Study," Am Heart J. 2002;143(6):961-965.
2. B.W.T Meijer, A.W Hoes,D. Rutgers, M.L. Bots, A. Hofman, D.E Grobbee, "Peripheral arterial disease in the elderly: The Rotterdam Study," Arterioscler Thromb Vasc Biol. 1998;18(2):185-192.
3. P. Song, D. Rudan, Y. Zhu , F.I Fowkes, K. Rahimi , F.G.R Fowkes, I. Rudan, "Global, regional, and national prevalence and risk factors for peripheral artery disease in 2015: an updated systematic," Lancet. 2019; 7: e1020-e1030
4. S.L James, D. Abate, K.H Abate, S.M Abay, C. Abbafati, N. Abbasi, H. Abbastabar, F. Abd-Allah , et al, "Global, regional, and national incidence, prevalence, and years lived with disability for 354 diseases and injuries for 195 countries and territories, 1990–2017: a systematic analysis for the Global Burden of Disease Study 2017," The Lancet, 2018; 392(10159): 1789-1858, DOI : https://doi.org/10.1016/S0140-6736(18)32279-7

5. American Diabetes Association, "Diagnosis and Classification of Diabetes Mellitus," Diabetes Care Jan 2004, 27 (suppl 1) s5-s10;
6. Badan Penelitian dan Pengembangan Kesehatan Kementerian Kesehatan RI, "Laporan Nasional RISKESDAS 2018", Jakarta : Kementerian Kesehatan, 2018, pp.129–131
7. Pusat Data dan Informasi Kementerian Kesehatan RI. "Situasi dan analisis diabetes". Jakarta: Kementerian Kesehatan RI; 2014, pp.2–8.
8. M.D Gerhard-Herman, H.L Gornik, C. Barret, N.R. Barshes, M.A, Corriere, D.E. Drachman, et al, "2016 AHA/ACC guideline on the management of patients with lower extremity peripheral artery disease: executive summary: a report of the american college of cardiology/american heart association task force on clinical practice guidelines", Circulation, 2017; 135(12), pp. e686-e725 doi: https://doi.org/10.1161/CIR.0000000000000470.
9. U. Campia, M.Gerhard-Herman, G. Piazza, S.Z. Goldhaber, "Peripheral Artery Disease: Past, Present, and Future," The American Journal of Medicine, 2019; 132(10): 1133-1141.
10. V. Aboyans, J.B. Ricco, M.E.L Bartelink, M. Björck, M. Brodmann, T. Cohnert, J.P. Collet, et al., "ESC Scientific Document Group, 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," European Heart Journal,2018; 39(9): 763–816, https://doi.org/10.1093/eurheartj/ehx095
11. T. Wilcox , J. Newman , T. Maldonado , "Peripheral vascular disease risk in diabetic individuals without coronary heart disease". Atherosclerosis. 2018 in press.
12. J.D Newman, C.B Rockman, M. Kosiborod, "Diabetes mellitus is a coronary heart disease risk equivalent for peripheral vascular disease," Am Heart J. 2017; 184:114–120.
13. M. Davis, "The effect of short-term lipid lowering with atorvastatin on carotid artery intima media thickness in patients with peripheral vascular disease: a pilot study", Curr Med Res Opin 2000;16:198-204.
14. H.J Milionis, M.S Elisaf, D.P Mikhailidis, "The effects of lipid- regulating therapy on haemostatic parameter", Curr Pharm Des 2003;9, pp. 2425-2443
15. European Medicines Agency. European Medicines Agency recommends restricting use of cilostazol-containing medicines. Available at: http://www.ema.europa.eu/ema/index.jsp?curl¼pages/news_and_events/news/2013/03/news_detail_001746.jsp&mid¼WC0b01ac058004d5c1. Accessed September 24, 2021.
16. W.R.M.S Hiatt, E.P. Brass, "Long-term safety of cilostazol in patients with peripheral artery disease: the CASTLE study (Cilostazol: A Study in Long-term Effects)," J Vasc Surg 2008;47, pp. 330–336
17. H. Lawall, P.Huppert , G. Rümenapf, "S3-Leitlinien zur Diagnostik, Therapie und Nachsorge der peripheren arteriellen Verschlusskrankheit," Vasa, 2016;45, pp. 11–82
18. R.D. Acar, M. Sahin, C. Kirma. "One of the most urgent vascular circumstances: Acute limb ischemia," Sage Open Med. 2013;1, pp. 1–11. doi: https://doi.org/10.1177/2050312113516110
19. S.S Anand, F. Caron, J.W. Eikelboom, J. Bosch, L. Dyal, V. Aboyans, M.T. Abola, et al., "Major adverse limb events and mortality in patients with peripheral artery disease : The COMPASS Trial", Journal of American College of Cardiology, 2018; 71(20), pp. 2306-2315
20. C.C Low Wang, J.I. Blomster, G. Heizer, J.S. Berger, I. Baumgartner, F.G.R Fowkes, et al, "Cardiovascular and limb outcomes in patients with diabetes and peripheral artery disease: The EUCLID Trial", Journal of American College of Cardiology, 2018; 72(25): 3274–3284
21. J. Dormandy , L. Heeck , S. Vig, "Major amputations: clinical patterns and predictors", Semin Vasc Surg. 1999 Jun;12(2), pp. 154-61. PMID: 10777243

22. W.S. Jones, M.R Patel, D. Dai, S. Vamulapalli, S. Subherwal, J. Stafford, E.D. Peterson., "High mortality risk after major lower extremity amputation in medicare patients with peripheral artery disease", American Heart Journal, 2013; 165(5), pp. 809–815. DOI: https://doi.org/10.1016/j.ahj.2012.12.002
23. J. Gabel, B. Jabo, S. Patel, S. Kiang, C. Bianchi, J Chiriano, et al, "Analysis of patients undergoing major lower extremity amputation in the vascular quality initiative", Annals of Vascular Surgery,2017 ., in press , https://doi.org/10.1016/j.avsg.2017.07.034.
24. L.S. Londero, B. Norgaard, K. Houlind, "Patients delay is the main cause of treatment delay in acute limb ischemia: an investigation of pre- and in-hospital time delay," World Journal of Emergency Surgery, 2014;9(56), pp. 1-7
25. P. Normahani, N.J Standfield, U. Jaffer, "Sources of delay in the acute limb ischemia patient pathway",Annals of Vascular Surgery, 2016; 1 :17, pp. 279-285, https://doi.org/10.1016/j.avsg.2016.05.118
26. J.M. Gaspoz, P.F Unger, P. Urban , J.C Chevrolet, W. Rutishauser , C. Lovis et al, "Impact of a public campaign on pre-hospital delay in patients reporting chest pain" Heart 1996;76, pp. 150-1555

Open Access This chapter is licensed under the terms of the Creative Commons Attribution-NonCommercial 4.0 International License (http://creativecommons.org/licenses/by-nc/4.0/), which permits any noncommercial use, sharing, adaptation, distribution and reproduction in any medium or format, as long as you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons license and indicate if changes were made.

The images or other third party material in this chapter are included in the chapter's Creative Commons license, unless indicated otherwise in a credit line to the material. If material is not included in the chapter's Creative Commons license and your intended use is not permitted by statutory regulation or exceeds the permitted use, you will need to obtain permission directly from the copyright holder.