MAEDICA – a Journal of Clinical Medicine
2023; 18(4): 665-671
https://doi.org/10.26574/maedica.2023.18.4.665

MAEDICA - a Journal of Clinical Medicine

REVIEW

Cilostazol Effects after Lower Extremity Revascularization. Historical Background and Review of the Literature

Georgia CHONDROU[a], George PHILIPPIDIS[a], Panagiotis GEORGAKOPOULOS[a], Evaggelos MAVROMMATIS[a]

[a]Medical School, National and Kapodistrian University of Athens, Athens, Greece

ABSTRACT

Introduction: *Cilostazol is a selective cyclic inhibitor of the 3-phosphodiesterase type (PDE3) that is recommended to be administered in cases of symptomatic peripheral vascular disease (YEI). It was discovered as a chemical compound in the 1980s, in Takao Nishi laboratory in Japan.*

Objective: *The purpose of the present review was to evaluate the efficacy of cilostazol administration in a YEI with intermittent claudication or moderate to severe lower extremity ischemia.*

Material and method: *A systematic review of the literature was carried out where articles were searched in the international database PubMed. The year 2005 was set as a time limit for the publication date of the articles. The following keywords were used: cilostazol, peripheral arterial disease, revascularization and lower limb. A total of 95 articles were found, of which only 10 were selected for the present study.*

Results: *According to the results of the current review, the use of cilostazol increases the ability to walk, improves the quality of life, reduces the rates of re-narrowing of vessels and stents, reduces the likelihood of amputation and is co-administered with other antiplatelet and anticoagulant agents.*

Conclusions: *Cilostazol administration should be a possible treatment option for symptomatic YEI. Further research is necessary to determine its safety after three years.*

Keywords: selective cyclic inhibitor of type 3-phosphodiesterase (PDE3), peripheral vascular disease, angioplasty.

INTRODUCTION

Cilostazol (Figure 1) is a selective cyclic inhibitor of the 3-phosphodiesterase type (PDE3). It is an antithrombotic that reverses platelet aggregation, while at the same time causing arterial vasodilation; it is indicated for second-line use in patients in whom lifestyle changes (including smoking cessation and exercise programs) and other appropriate therapeutic interventions have failed to adequately improve the symptoms of their intermittent lameness. It was approved for use in England by the National Institute of Clinical Excellence (NICE) and has been licensed for use in the United States since 1999 after being approved by the Food and Drug Administration (FDA). It is used to treat patients suffering from intermittent claudication without

Address for correspondence:
Evaggelos Mavrommatis
75 Mikras Asias street, 11527 PC, Athens, Greece
Tel.: 00306976778252; email: evagmavrommatis@protonmail.com

Article received on the 11th of September 2023 and accepted for publication on the 28th of November 2023

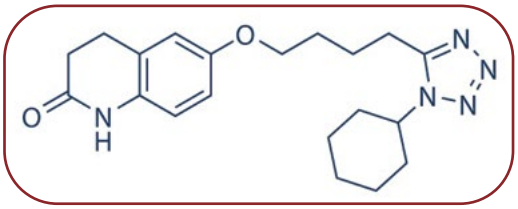

FIGURE 1. The skeletal formula of cilostazol, a potent cyclic nucleotide phosphodiesterase type 3 (PDE3) inhibitor with IC50 of 0.2 μM and inhibitor of adenosine uptake

rest pain and without peripheral tissue necrosis as it improves pain-free walking distance (peripheral arterial artery disease Fontaine stage II, Intermittent claudication) (1-5).

Peripheral vascular disease (PVD) and coronary heart disease (CHD) are responsible for a high mortality and morbidity rate, especially in the Western world, causing a huge financial burden for health service providers. The growing popularity and availability of endovascular treatments for arterial disease is attributed to their obvious high success rate and minimal intrusiveness compared to traditional bypass surgery. However, the long-term results are not so good due to the reunion of the vessel that ultimately causes failure. Conventional medical treatments have not been able to completely eliminate this problem to date (6).

Peripheral vascular disease, a manifestation of systemic atherosclerosis, is a major health problem, affecting eight million people *per* year in the USA (7). Despite the fact that PVD refers to all peripheral arteries, the present literature review focuses specifically on the arteries of the lower extremities. The disease is characterized by partial or complete failure of the arterial system in terms of oxygenated blood supply to the peripheral tissue. Atherosclerosis is by far the most common etiology of lower extremity PVD. However, many other procedures, including arterial entrapment, clot, spastic cyst, embolism, fibromuscular dysplasia, incision of the vessel. trauma, vasculitis and vasospasm, can lead to the clinical syndrome of pan-angiopathy. The ankle-brachial index (ABI), which is defined as the systolic blood pressure measured in the ankle and divided by the systolic blood pressure measured in the arm during rest in a supine resting position, is the most widely used quantitative measurement to determine the presence and severity of PVD. An abnormal ABI value of 0.90 or less is generally considered to be the best baseline of the PVD determination, while the normal values of the indicator range between 0.9 and 1.3. The prevalence of lower extremity PVD is 16% in the general population over the age of 55. Studies have shown that 20% of males and females aged 55 to 74 years had an ABI value of 0.90 or less and thus, they were diagnosed as pan-angiopathy-angiopathy sufferers. The prevalence of the disease increases with age, while it is higher in males than in females at all ages (8).

The most common symptom of mild to moderate PVD is intermittent claudication, which occurs in about a third of symptomatic patients and affects 2% of people over 65 years of age annually (9-11). Although the risk of a patient with lameness for the development of critical ischemia of the lower extremities and amputation is only about 1% per year, the risk of death, especially from coronary or cerebrovascular episodes, is about 5% to 10%, that is three to four times greater than the risk corresponding to people of the same age who do not show lameness (12-13). Due to the strong association with cardiovascular morbidity and mortality, patients with PVD are less likely to receive appropriate treatment for atherosclerotic risk factors, as opposed to those treated for CHD. Nevertheless, there is no doubt that aggressive treatment of atherosclerosis can slow down or stop the progression of the PVD of the lower extremities and contribute to an increase in life expectancy. The goals of treatment, be it surgical or non-surgical, are to stop the progress of systemic atherosclerosis, to achieve a relative reduction of morbidity and mortality, to prevent limb loss and finally, to improve the functional capacity of symptomatic patients, but also using pharmaceutical preparations such as statins, antiplatelet therapies and antithrombotic strategies. Cilostazol is a relatively new option in the treatment of PVD and its symptoms (14). ❑

MATERIAL AND METHOD

This is a systematic review of the literature where articles were searched for the collection of data in the electronic database PubMed. The following keywords were used: cilostazol, peripheral arterial disease, revascularization and lower limb. First of all, the title and summary of each article were read. All studies that were not relevant to the subject were rejected. The main

characteristics of the identified studies, including the name(s) of author(s), country of origin, year of publication, study population, methodology and main results, were all recorded. The following entry criteria were used for the inclusion of studies: a) English as the language for publication, and b) only articles written between 2008-2019. The exclusion criteria were as follows: a) articles published in a language other than English, b) articles written prior to the year 2005, c) case studies, and d) studies to which there was no access. ❑

RESULTS

A total of 98 studies were found based on the keywords used by us. After evaluation, 87 articles were excluded. The remaining 11 studies, which were conducted in Japan-angiopathy (seven), the USA (three) and Spain (one) were included in the present review. The chart flow is illustrated in Figure 2, and Table 1 summarizes the total number of selected studies.

In 2018, Hiatt *et al* conducted a multicenter, randomized, double-blind placebo-control study that compared the effect of cilostazol against placebo in patients with intermittent claudication due to pan-angiopathy. Patients continued to be monitored for 3.5 years every 26 weeks. Cilostazol demonstrated a mortality rate of at least 95%, which was equal to what was expected. Thus, the research concluded that cilostazol did not improve mortality rates in patients with pan-angiopathy, an answer that concerned the main question of the study. Nevertheless, 60% of all study participants abandoned cilostazol intake by 36 months, so the analysis was eventually limited to this time interval (15).

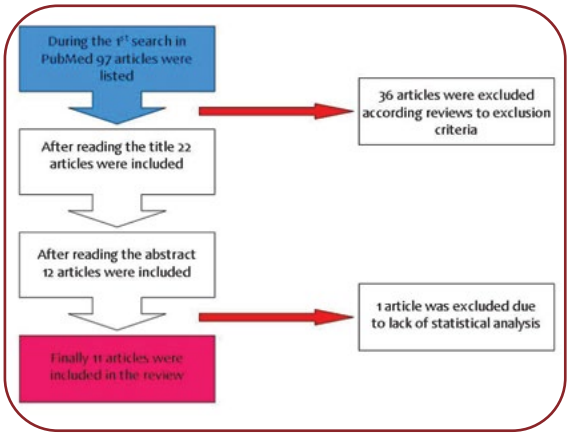

FIGURE 2. Flowchart of the study

In 2009, Soga *et al* conducted a multicenter randomized open trial in which they compared the combined use of cilostazol and aspirin versus aspirin monotherapy in patients with pan-angiopathy who underwent intravascular occlusion and found that the number of those who under-

TABLE 1. The studies selected for the current review (15-24)

N	Researchers, year, country or region of conduct	Type of study	Population	Results
1	Hiatt *et al*, 2008, USA	Randomized	n=1435, cilostazol=717, placebo=718	Cilostazol did not improve mortality rates in patients with PAN-ANGIOPATHY
2	Soga *et al*, 2009, Japan	Randomized	n=78, cilostazol+aspirin=39, aspirin=39	Cilostazol reduced rates of restenosis and re-clogging in patients with femoral-popliteal disease and intermittent claudication
3	Soga *et al*, 2011, Japan	Retrospective	n=615, cilostazol=356, non-cilostazol=259	Cilostazol improves free amputation time after intravascular reperfusion
4	Soga *et al*, 2012, Japan	Retrospective	n=63, cilostazol=32, other intervention=31	Cilostazol was associated with decreased rates of restenosis and re-clogging
5	Goldenberg *et al*, 2014, Colorado, USA	Randomized	n=163, cilostazol+carnitine=80, cilostazol+placebo =13	Cilostazol in coadministration with l-carnitine improved walking performance and quality of life
6	Nell *et al*, 2015, USA	Retrospective	n=22954, cilostazol=1999, non-cilostazol=20995	Cilostazol improved the free amputation period even in patients with chronic renal failure and diabetes mellitus
7	Zen *et al*, 2016, Japan	Randomized	n=475, cilostazol=93, non-cilostazol=382	Cilostazol improved the rate of reunification after one year of drug-eluting stent implantation
8	Soga *et al*, 2017, Japan	Randomized	n=51, cilostazol+aspirin=38, aspirin=13	Cilostazol did not improve the success rates of balloon boreal boreal of the vessel in areas below the gonny joint
9	Soga *et al*, 2018, Japan	Randomized	n=191, cilostazol=93, non-cilostazol=98	Cilostazol reduced the rate of clinical revascularization over the three-year period
10	Miura et al, 2018, Japan	Randomized	n=255, cilostazol=85, non-cilostazol=170	Cilostazol reduced the rate of reunification within the stent after one year in bare-metal nitinol stents, but not in drug eluted stents
11	Chisari *et al*, 2019, Spain	Randomized	n=80, cilostazol=40, non-cilostazol=40	Cilostazol improved asymptomatic walking distance

went stent placement was statistically clearly larger in the group that received cilostazol. It is worth noting that one patient of the control group showed worsening of lameness postoperatively and was given cilostazol to improve it (16). In 2011, Soga *et al* conducted a multicenter retrospective study on a database in which they showed that cilostazol improved free amputation time after intravascular reperfusion with stent placement, but survival and the need for new surgery did not differ statistically significantly (43.9% *vs* 46.0%, p=0.24) (17). In 2012, Soga *et al* conducted another retrospective multicenter non-randomized clinical recording study, in which cilostazol was statistically significantly associated with decreased rates of re-narrowing (56.8% *vs* 86.0%, p=0.015), p=0.015) and re-clogging (20.5% *vs* 43.6%, p=0.015) after angioplasty (18). In 2012, Goldenberg *et al* published a study where they combined the administration of cilostazol with l-carnitine with very well-tolerated results (19).

In 2015, Nell *et al* conducted a retrospective clinical study analyzing electronic recording data in a patient with a PVD in the tibial arteries. The study included patients who underwent open reperfusion surgery or endovascular intervention and showed that cilostazol was also beneficial for those with chronic renal failure and diabetes mellitus even one year after medication start (14.8% *vs* 24.0%, p< 0.0001) (20). In 2016, Zen *et al* published a randomized multicenter study in which they investigated the administration of cilostazol after the use of ZilvEr PTX stents. The study population had comorbidities including diabetes mellitus (71% of subjects), hemodialysis due to renal failure (31%) and severe lower extremity ischemia (29%). After one year, cilostazol statistically significantly reduced the rate of re-narrowing by 33% in the group receiving cilostazol and 51% in the control group (21).

In 2017, Soga *et al* published a multicenter randomized clinical open study blind to the final record. The authors investigated the administration of cilostazol to patients who underwent balloon angioplasty for a period of three months from the operation in the area below the knee joint. The three-month rate of resuscitation was 82% in the group receiving cilostazol in addition to aspirin and 81% in the group not receiving cilostazol, without showing a statistically significant difference (p=0.914). Therefore, cilostazol did not improve the success rates of balloon boreal boreal boreula in areas below the gonny joint (22). In 2018, Soga *et al* published a multicenter randomized study that aimed to compare the rates of restenosis after angioplasty in patients treated with cilostazol in combination with aspirin and in those with aspirin monotherapy. Patients' follow-up after surgery was 38.1 months. The patency of the vessels was statistically significantly greater in the cilostazol group, 69% *vs* 54% (p=0.026). The time period free from new endovascular surgery also 78% *vs* 63% (p=0.014). However, there was no statistically significant difference in overall survival between the two groups (p=0.95) (23).

In 2018, Miura *et al* published a randomized clinical open multicenter study involving patients with de novo PVD of the femoral-popliteal region. Three groups were studied. First-generation Baremetal Nitinol Stents (BNS) were placed in two groups, with cilostazol being administered in combination with aspirin in the first group, and not in the second one. In the third group, Drug-Eluting Stents (DES) were placed, with an average length of 10 mm being defined as the area of damage. One year as a control interval after surgery did not show a statistically significant difference in intra-stent re-narrowing between the three groups (28.4% *vs* 12.2% *vs* 21.0%, p=0,052). Although at one year there was no statistically significant difference between the BNS group with cilostazol and the DES group (p=0.16), there was nevertheless a statistically significant difference between the BNS groups with and without cilostazol (24). In 2019, Megaly *et al* saw an increase in the walking distance in patients with symptomatic PVD (25). ❑

DISCUSSION

During the 1980s in the laboratory of Takao Nishi of the Japanese pharmaceutical company Otsuka, the quinolone derivative cilostamide was firstly synthesized to inhibit platelet aggregation, and it was also shown that the drug had vasodilating properties (26). However, it was a chemical compound incriminated to cause persistent tachycardias. Research had soon revealed that, with a simple modification of an amide side chain, the new chemical compound had the same effect but with a reduced risk for tachycardia. This was cilostazol (27). Due to the

properties of cilostazol, its impact was so considerable that it was included among the most desired best seller drugs worldwide (28).

Cilostazol is a medication that appears to improve the rates for vascular re-narrowing due to pan-angiopathy. However, the safety of the drug for long-term administration has not been established despite its approval by the FDA. Investigations show that there is no change in mortality among groups of patients who receive cilostazol and those from control or placebo groups. It has not been established that the administration of cilostazol was altering the cause of death regarding cardiovascular diseases. In a review conducted by Hiatt *et al*, the authors did not rule out the possibility of reduced safety during treatment with cilostazol and reported that they did not notice a statistically significant change in the risk of bleeding. However, some side effects of the drug such as headache and diarrhea were recorded. They also pointed out that the PROMISE study showed increased levels of mortality in people with type III or I V heart failure who were taking milrinone, a phosphodiesterase inhibitor, which has been also raising questions about the administration of cilostazol (15, 23).

Thus, the effectiveness of cilostazol in reducing the rates of re-narrowing or re-clogging was reported by several studies (17, 19, 23). It seems that regarding the separation in the upper and lower knee areas, this does not play a role in the effectiveness of cilostazol (16, 21). The use of cilostazol also helped patients with severe lower extremity ischemia, even in cases of comorbidity (eg, diabetes mellitus) (17). Other studies noted an increase in the free time interval from amputation (18, 20) or an improvement in the stenosis of the stent, especially in the case of BNS rather than DES (21, 24). In 2009, Soga *et al* found that cilostazol administration statistically significantly has reduced restenosis of the vessels after angioplasty even when the length of the lesion was greater than in the control group. They also observed that the use of cilostazol improved the walking distance and reduced symptoms of patients with pan-angiopathy (16). However, their research had only a small number of participants, precisely 36 patients, of which only 16 received cilostazol. The above-cited authors observed that cilostazol also improved microcirculation, thus helping save the pathological lower extremity (17). Soga *et al* have also noted that the use of cilostazol statistically significantly reduced the rate of re-stenosis due to the hyperplasia of the new inner layer (neointima) within the stent and suppressed the migration and proliferation of vascular smooth muscle cells caused by platelet-derived growth factor (PDGF) (18). The same was argued by Zen *et al*, who also noted that cilostazol reduced the rate of re-stenosis due to its vasodilating activity (21). Nell *et al* reported that cilostazol reduced platelet reactivity, especially in people with diabetes mellitus (20). In addition, even the triple antiplatelet drug administration of aspirin, clopidogrel and cilostazol were not involved in the occurrence of a serious bleeding event (21).

Soga *et al* in one of their many studies found that cilostazol did not statistically significantly improve the rates of re-narrowing of the vessel after balloon surgery in areas below the knee joint (22). In patients with damage to the femur-popliteal region involving the small vessels, endovascular intervention is more difficult. In short-range vessels (<4.0 mm), balloon angioplasty is superior to BNS stenting over a period of three years after the intervention. In addition, the endovascular use of a drug-coated balloon was more effective than balloon angioplasty to reduce restenosis, especially in patients with diabetes or women. Flow cross-section after the balloon has been dilated; BNS stents with cilostazol are relatively superior to DES stents in reducing re-narrowing in small vessels; BNS with cilostazol co-administration are therefore recommended when metal stents should be used (24). Moreover, it inhibits vascular smooth muscle cell proliferation *via* phosphodiesterase III inhibition, thus mitigating further restenosis (25).

Patients with multivascular disease, such as a combination of ischemic stroke and pan-angiopathy, have a higher incidence of recurrent vascular events and mortality than those with monovascular disease – re-narrowing relative to monovascular sufferers was 40.5% *vs* 25.5% after three years of follow-up. In addition, patients with pan-angiopathy have the highest mortality rates from cardiovascular disease or hospitalization for atherothrombotic events from other cardiovascular diseases. However, cilostazol should be administered with the installation of intermittent claudication. The drug may be beneficial for patients with ischemic stroke who have pan-angiopathy as it reduces the risk of stroke. Con-

comitant administration of cilostazol and clopidogrel shows no effect on platelet counts, prothrombin time (PT) or activated partial thromboplastin time (aPTT). Prolongation of bleeding time during the administration of clopidogrel on its own and simultaneous administration with cilostazol does not lead to a statistically significant additional effect on bleeding time. Caution is advised when co-administering cilostazol with any drug that inhibits platelet aggregation. Intermittent monitoring of bleeding time is necessary (5). While triple administration of aspirin, clopidogrel and cilostazol has also been deemed beneficial without the occurrence of severe bleeding episodes, studies are usually limited to the dual therapeutic approach (22).

Patients with a PVD show a reduced response to oxygen uptake at the start of exercise despite the unchanged blood flow at this early point of muscle function. Acetyl carnitine accumulates in plasma and skeletal muscles in cases of secondary carnitine deficiency, which is associated with reduced exercise performance in those who suffer from pan-angiopathy. Decreased activity of the basic enzymes of mitochondria in the electron transport chain may also contribute to the reduced ability to produce ATP (adenosino-triphosphate-acid) and may be responsible for reduced exercise performance. Based on these data, the addition of l-carnitine as basic therapeutic approach in combination with cilostazol is promising for the improvement of intermittent claudication due to pan-angiopathy. Oral administration of l-carnitine 1 g twice daily in combination with cilostazol is adviced (19). Strangely, exercise may be the key factor for initially PVD diagnosis; on the other hand, exercise therapy is a crucial and essential treatment for PVD added to a cilostazol administration program, with the exception of critical limb ischemia cases (29).

Cilostazol has a number of side effects such as rash, hives, itching, difficulty breathing, swelling of the face or lips or tongue, pain in the chest, lower jaw, fainting tendency, cardiac arrhythmias, feeling of weakness, swelling of the upper and lower extremities, bleeding, infections, headache that may lead to drug discontinuation. Cilostazol is taken two times daily orally with a recommended dose of 100 mg (50 mg two times a day). Cilostazol should be taken 30 minutes before breakfast and dinner. Taking cilostazol with food has been shown to increase the maximum plasma concentrations (Cmax) of cilostazol, which can be associated with an increased frequency of adverse reactions. As in most studies compliance with the reception is recorded and reported only by research participants, it is a fact that in many cases it could lead to controversial results in terms of effectiveness. For this reason, it is suggested that individual patient tolerability to treatment with cilostazol should be checked (24).

Many scholars believe that the use of cilostazol is a therapeutic addition that could possibly mitigate symptoms of PVD such as pain or intermittent claudication (30-31), while others note a statistically significant improvement (30). Indeed, a recent meta-analysis carried out by Megaly *et al* in 2019 reported a positive effect of cilostazol, which produced a statistically significant reduction in symptoms of pan-angiopathy and the period of time of free amputation in cases of severe ischemia (32). Balinski and Preuss' review regarding the benefits of cilostazol reached the same conclusion (33). ❑

CONCLUSIONS

Cilostazol is indicated for the improvement of maximum and pain-free walking distances in patients with intermittent pan-angiopathy due to PVD. Despite the reported side effects of cilostazol, the drug appears to be well tolerated without a statistically significant increase in bleeding or mortality episodes. Its long-term use is recommended in cases of symptomatic PVD even though its safety has not been established, since the duration of most studies varied between a few months and three years maximum. Co-administration with other antiplatelet or anticoagulant agents as well as with other substances such as l-carnitine is suggested. It has been shown that cilostazol produced a statistically significant reduction in reunification after angioplasty of the vessel, or intravascular stent. It was shown not only to reduce the rate of re-clogging of the vessel and odds of amputation but also to improve patients' quality of life. In cases of severe ischemia of the lower extremity, cilostazol prolongs the period of amputation. Cilostazol is contraindicated in patients with heart failure, bleeding, or cardiac arrhythmias. Some studies have a small number of participants or controversial results and it is usually recommended to

further study cilostazol regarding its administration in cases of symptomatic PVD. ❑

Conflicts of interest: none declared.
Financial support: none declared.

References

1. Cardiovascular system-Peripheral vasodilators and related drugs-Cilostazol. British National Formulary 2008; 56: http://www.bnf.org/bnf/bnf/current/119724.htm?q=%22cilostazol%22#_hit. Accessed November 10th 2019.
2. Center for Drug Evaluation and Research. Approval of Cilostazol. US Food and Drug Administration 1999. http://www.fda.gov/cder/news/cilostazol/approval.htm. Accessed November 10th 2019.
3. **Kumar M, Bhattacharya V.** Cilostazol: A new drug in the treatment intermittent claudication. *Recent Patents Cardiovasc Drug Discov* 2007;2:181-185.
4. **Grouse JR, MB.** Clinical manifestation of atherosclerotic peripheral arterial disease and the role of cilostazol in treatment of intermittent claudication. *J Clin Pharmacol* 2002;42:1291-1298.
5. **Jeng JS, Sun Y, Lee JT, et al.** The efficacy and safety of cilostazol in ischemic stroke patients with peripheral arterial disease (SPAD): protocol of a randomized, double-blind, placebo-controlled multicenter trial. *Protocols World Stroke Organization* 2015;10:123-127.
6. **Dindyal S, Kyriakides C.** A Review of Cilostazol, a Phosphodiesterase Inhibitor, and its Role in Preventing Both Coronary and Peripheral Arterial Restenosis Following Endovascular Therapy. *Recent Patents on Cardiovascular Drug Discovery* 2009;4:6-14.
7. **Hirsch AT, Criqui MH, Treat-Jacobson D, et al.** Peripheral arterial disease detection, awareness, and treatment in primary care. *JAMA* 2001;286:1317-1324.
8. **AW, Afaq A.** Management of Lower Extremity Peripheral Arterial Disease. *J Cardiopul Rehabil Prev* 2008;28:349-357.
9. **Criqui MH, Fronek A, Klauber MR, et al.** The sensitivity, specificity, and predictive value of traditional clinical evaluation of peripheral arterial disease: results from noninvasive testing in a defined population. *Circulation* 1985;71:516-522.
10. **Kannel WB, McGee DL.** Update on some epidemiologic features of intermittent claudication: the Framingham Study. *J Am Geriatr Soc* 1985;33:13-18.
11. **Fowkes FG, Housley E, Cawood EH, et al.** Edinburgh Artery Study: prevalence of asymptomatic and symptomatic peripheral arterial disease in the general population. *Int J Epidemiol* 1991;20:384-392.
12. **Hiatt WR, Regensteiner JG, Hargarten ME, et al.** Benefit of exercise conditioning for patients with peripheral arterial disease. *Circulation* 1990;81:602-609.
13. **Hiatt WR, Wolfel EE, Meier RH, et al.** Superiority of treadmill walking exercise versus strength training for patients with peripheral arterial disease. Implications for the mechanism of the training response. *Circulation* 1994;90:1866-1874.
14. **Lumsden AB, Rice TW.** Medical Management of Peripheral Arterial Disease: A Therapeutic Algorithm. *J Endovasc Ther* 2006;13(Suppl II):II-19-II-29.
15. **Hiatt WR, Money SR, Brass EP.** 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;47:330-336.
16. **Soga Y, Yokoi H, Kawasaki, et al.** Efficacy of Cilostazol After Endovascular Therapy for Femoropopliteal Artery Disease in Patients With Intermittent Claudication. *J Am Coll Cardiol* 2009;53:48-53.
17. **Soga Y, Iida O, Hirano K, et al.** Impact of cilostazol after endovascular treatment for infrainguinal disease in patients with critical limb ischemia. *J Vasc Surg* 2011;54:1659-1667.
18. **Soga Y, Iida O, Kawasaki D, et al.** Impact of Cilostazol on Angiographic Restenosis after Balloon Angioplasty for Infrapopliteal Artery Disease in Patients with Critical Limb Ischemia. *Eur J Vasc Endovasc Surg* 2012;44:577-581.
19. **Goldenberg N, Krantz MJ, Hiatt WR.** Carnitine plus cilostazol versus cilostazol alone for the treatment of claudication in patients with peripheral artery disease: A multicenter, randomized, double-blind, placebo-controlled trial. *Vasc Med* 2012;17:145-154.
20. **Neel D, Kruse RL, Dombrovskiy V, et al.** Cilostazol and freedom from amputation after lower extremity revascularization. *J Vasc Surg* 2015;61:960-964.
21. **Zen K, Takahara M, Iida O, et al.** Drug-eluting stenting for femoropopliteal lesions, followed by cilostazol treatment, reduces stent restenosis in patients with symptomatic peripheral artery disease. *J Vasc Surg* 2017;65:720-725.
22. **Soga Y, Takahara M, Iida O, et al.** Efficacy of CilostAzol for Below-the-knee artery disease after Balloon AnGioplasty in patiEnts with severe limb ischemia (CABBAGE trial). *Annals Vasc Surg* 2017;45:22-28.
23. **Soga Y, Hamasaki T, Edahiro R, et al.** Sustained Effectiveness of Cilostazol After Endovascular Treatment of Femoropopliteal Lesions: Midterm Follow-up From the Sufficient Treatment of Peripheral Intervention by Cilostazol (STOP-IC) Study. *J Endovasc Ther* 2018;25:306-312.
24. **Miura T, Miyashita Y, Soga Y, et al.** Drug-Eluting Versus Bare-Metal Stent Implantation With or Without Cilostazol in the Treatment of the Superficial Femoral Artery. The DEBATE in SFA Study. *Circ Cardiovasc Interv* 2018;11:e006564.
25. **Manolis AA, Manolis TA, Melita H, et al.** Update on Cilostazol: A Critical Review of Its Antithrombotic and Cardiovascular Actions and Its Clinical Applications. *J Clin Pharmacol* 2022;62:320-358.
26. **Nishi T, Kimura Y, Nakagawa K.** Research and development of cilostazol: an antiplatelet agent. *Yakugaku Zasshi* 2000;120:1247-1260.
27. **Kambayashi J, Liu Y, Sun B, et al.** Cilostazol as a unique antithrombotic agent. *Curr Pharm Des* 2003;9:2289-2302.
28. **Vardanyan R, Hruby V.** Synthesis of Best-Seller Drugs. London, Elsevier, 2016.
29. **Yasu T.** Comprehensive cardiac rehabilitation program for peripheral arterial diseases. *J Cardiol* 2022;80:303-305.
30. **Chisari LM, Malaguarnera S, Grasso A, et al.** Cilostazol reduces dry eye symptoms and improve walking distance in patients with peripheral artery disease. *Clin Ter* 2019;170:e357-e363.
31. **Ratchford EV.** Medical management of claudication. *J Vasc Surg* 2017;66:275-280.
32. **Megaly M, Abraham B, Saad M, et al.** Outcomes with cilostazol after endovascular therapy of peripheral artery disease. *Vasc Med* 2019;24:313-323.
33. **Balinski AM, Preuss CV.** Cilostazol. StatPearls Publishing, Treasure Island, 2019.