



Published in final edited form as:

Adv Surg. 2023 September ; 57(1): 103–113. doi:10.1016/j.yasu.2023.04.009.

Current Management of Intermittent Claudication

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Keywords

Intermittent claudication; Peripheral artery disease; Claudication; Cardiovascular

INTRODUCTION

Peripheral artery disease (PAD) is a common condition that is becoming more prevalent globally and is associated with comorbid cardiovascular conditions and high health-care costs. This is especially true in the United States where the population is aging and nearly 1 in 6 persons aged 70 years or older have PAD. PAD represents a spectrum of clinical disease spanning from asymptomatic disease to severe chronic limb-threatening ischemia. It is defined by narrowing in the arterial system that prevents the cardiovascular system from meeting the metabolic demands of the dependent vascular bed, which is usually the lower extremity involving the calf (in the case of femoropopliteal PAD), and less commonly the buttock or thigh (in the case of aortoiliac PAD). The first symptom is usually reproducible pain with exertion of a downstream muscle group that classically resolves with rest; this is known as intermittent claudication and is the effect of the transiently elevated metabolic requirement that is unmet by the cardiovascular system. Most persons with intermittent claudication (>70%) will have stable disease at least 5 years after diagnosis [1]. However, 20% to 30% of persons with intermittent claudication will experience progressive claudication, and a small subset (1%–3% of all patients with claudication) will progress to chronic limb-threatening ischemia.

Despite the fact that most patients with intermittent claudication remain stable, it is clearly a marker of systemic cardiovascular risk. The 5-year mortality in all-comers with intermittent claudication is as high as 15%, and another 20% of patients will experience a stroke or myocardial infarction in as many years. Modifiable risk factors for PAD include hypertension, diabetes, hyperlipemia, and smoking. Management of intermittent

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DISCLOSURE

D.P. Stonko reports no relevant conflicts of interest. C.W. Hicks is a consultant for W.L. Gore, Cook Medical LLC, and Silk Road Medical.

claudication includes modifying these risk factors with lifestyle changes or pharmacologic interventions, exercise therapy, and, in selected patients, revascularization [1–3].

CLINICAL PRESENTATION AND PHYSIOLOGY

The difference between asymptomatic PAD and intermittent claudication largely revolves around a patient's activity level, the extent of their atherosclerotic disease, and their collateral networks. Physiologically, intermittent claudication only happens when the balance between oxygen delivery and metabolic demand scale tips toward cardiovascular insufficiency. This is, as named, intermittent and only occurs when the demand transiently increases, and resolves with rest. The term claudication is from Latin, *claudicare* meaning “to limp.” Patients affected with intermittent claudication find exercise challenging because of lower extremity pain. Exertion is necessary, however, to modify disease progression.

The progression of PAD relates to the evolution of atherosclerosis in the arterial system, although stable PAD may be unmasked (ie, worsening of symptoms) by worsening cardiac function or other changes in comorbidities. Chronic PAD is associated also with decreased muscle mass, increased lactic acid accumulation during exertion, endothelial dysfunction in the involved muscle groups, and systemic inflammatory and coagulation markers. This compensation follows teleologically as downstream tissue attempts to reduce oxygen demand to meet the waning supply.

INITIAL EVALUATION AND SURVEILLANCE

A history and physical is the cornerstone of the initial evaluation of a patient complaining of lower extremity pain. Patients with claudication typically have reproducible symptoms, with muscle cramping occurring around the same distance or degree of exertion that resolves at rest. Symptoms typically involve the same muscle groups each time and are not usually associated with tenderness to palpation. Joint pain or tenderness to palpation requires investigation of musculoskeletal or alternative causes of leg pain. Confounding causes of lower extremity pain include nerve pain, arthritis, venous disease, or bony or ligamentous trauma. None of these, however, tends to have both the typical history and chronicity associated with PAD.

Physical examination findings associated with intermittent claudication include dry skin secondary to apocrine dysfunction, muscle wasting, weakened or absent pulses, and reduced hair growth over the involved muscle group. A pulse examination is the most critical aspect of evaluating a patient with suspected intermittent claudication [1–3]. Patients with nonpalpable femoral pulses are more likely to have inflow (aortoiliac) disease, whereas patients with palpable femoral pulses but nonpalpable popliteal and pedal pulses are more likely to have outflow (femoropopliteal and/or tibial) disease. An examination or history significant for nonhealing wounds or skin breakdown, tissue loss, or rest pain suggests more advanced disease. Fontaine's stages and Rutherford's grades of PAD (Table 1) are useful for classifying the stage of PAD, with Fontaine stage II and Rutherford grade I or categories 1 to 3 representing claudication. Understanding these classification systems can help clarify patient symptoms, facilitate treatment decision-making, and educate patients.

An important component of the history and physical of a patient with suspect intermittent claudication is a vascular laboratory evaluation with the Ankle-Brachial Index (ABI). The ABI is computed for each leg by dividing the higher systolic pressure of either the posterior tibial or dorsalis pedis artery of that leg by the higher of the systolic pressures from either the right brachial or left brachial artery. This provides a single number for each leg where, in the absence of trauma or acute change, an ABI less than 0.9 has a high sensitivity and specificity for PAD. A resting ABI of 0.5 to 0.7 is consistent with claudication, although these values are not exact, and it is important to recognize that a diagnosis of claudication depends largely on patient symptoms. In patients with significant calcific disease and noncompliant ankle vessels, the ABI may be falsely elevated, and thus noninformative. This is important because elevated ABIs occur particularly in patients with diabetes and those on dialysis. In patients with elevated ABIs (>1.4), toe pressure measurements and volume plethysmography are informative. In patients with inflow disease, ABIs can occasionally be normal despite severe symptoms. In the scenario where patient symptoms are highly suspicious for claudication but resting ABIs are normal, an exercise ABI can be used to assess for PAD. This is performed by performing ABIs at rest, and then having the patient walk until he or she can no longer tolerate, or for a maximum of 5 minutes. A repeat ABI is performed immediately following cessation of walking. In patients without PAD, the ABI should increase with exercise, representing increased perfusion in response to metabolic demand. In patients with PAD, the ABI obtained immediately following exercise will paradoxically decrease compared with baseline in the affected limb, representing inadequate compensation of perfusion with stress.

Additional vascular laboratory investigation can also be informative in the initial evaluation and surveillance of PAD. These investigations include duplex ultrasound, volume plethysmography, and segmental limb pressures. These tests can provide additional information regarding level of disease, and can be helpful for understanding the character and quality of perfusion to different muscle groups.

Fig. 1 is a lower extremity noninvasive arterial Doppler evaluation demonstrating normal perfusion to the right lower extremity and mild arterial insufficiency to the left lower extremity in a patient with left lower extremity claudication.

In general, CT angiography or conventional angiography is not necessary as part of the initial workup for a patient with intermittent claudication except in the rare patient where revascularization is being considered for surgical planning.

TREATMENT

The initial treatment of intermittent claudication focuses on medical optimization of comorbid conditions, aspirin, and statin therapy, smoking cessation, and supervised exercise therapy (SET) for all patients able to participate. Second-line therapy involves the initiation of cilostazol in eligible patients which, when combined SET, can help augment peripheral collateral networks to reduce symptom burden. Once medically optimized, the third-line treatment of those patients who fail to improve after SET may include revascularization in select patients (Fig. 2).

Management of comorbid diseases, risk factors, and smoking

Hypertension increases arterial wall shear forces and turbulent flow, which can lead to the progression of atherosclerosis and arterial remodeling. It is therefore important to control hypertension in patients with PAD to avoid progression, which may also help reduce their associated cardiovascular (nonlimb) related outcomes [1–3]. Current guidelines recommend treatment of hypertension to maintain systolic blood pressure less than 140/90 mm Hg for patients aged 65 years or older, or less than 130/80 mm Hg for patients aged less than 65 years, with preferential treatment using angiotensin-converting enzyme inhibitors or angiotensin-receptor blockers. Although beta blockade was once thought to be associated with increased claudication symptoms, this has never been demonstrated in randomized control trials.

Diabetes is associated with increased vascular inflammation and endothelial cell dysfunction, alterations in blood cell and platelet function, and vascular smooth muscle changes. This milieu is thought to contribute to the progression of atherosclerosis and can be, at least in part, slowed with optimal glucose and dyslipidemia management. Diabetes is also associated with peripheral neuropathy and poor wound healing, increasing the risk of limb loss in patients with PAD. Indeed, trials have shown that patients with diabetes and PAD have more than 10 times the risk of major amputation compared with patients with no diabetes and the same degree of PAD. Furthermore, patients with long-term uncontrolled diabetes also tend to have poor renal function, and end-stage renal disease is known to further compound the risks associated with PAD. Diabetes management is therefore paramount to the management of patients with claudication [1–3].

Dyslipidemia is associated with inflammation, plaque formation, and overall cardiovascular risk. The management of dyslipidemia with statin therapy is critical to the management of intermittent claudication. Standard treatment of dyslipidemia generally targets a low-density lipoprotein of less than 100 mg/dL. Patients with concomitant coronary artery disease or those who are high risk for stroke should target an LDL of less than 70 mg/dL. However, there are increasing data to suggest that high-dose (≥ 40 mg daily of atorvastatin or equivalent) statin therapy provides additional anti-inflammatory and plaque stabilization benefits beyond simply lowering cholesterol levels [1–3]. As a result, all patients with intermittent claudication should be initiated on statin therapy regardless of their cholesterol levels.

Obesity management is another important tenet to risk factor mitigation in PAD. Although there are limited data to recommend specific novel weight loss medications such as Tirzepatide at this time, they are acceptable components of a patient-centered approach to the global management of metabolic syndrome and obesity. One in 3 patients with PAD also has hyperhomocysteinemia but reducing these levels with folate or B12 has not been shown to improve outcomes and may actually worsen outcomes.

Smoking is an important and modifiable risk factor for atherosclerotic cardiovascular disease. More than 80% of patients with PAD are current or past smokers. Smoking cessation alone has been shown to reduce claudication symptoms, and also helps reduce limb and other cardiovascular risks. Patients with PAD who smoke and undergo

revascularization are also 3 times more likely to experience revascularization failure than nonsmokers; as a result, revascularization is contraindicated in patients with intermittent claudication and active smoking. Patients may be specifically motivated to stop smoking if they are told that tobacco cessation may reduce their symptoms and decrease the likelihood and number of future vascular interventions. There are a number of published strategies to help encourage smoking cessation. The American College of Cardiology has the “5 A’s” framework (Ask, Assess, Advise, Assist, Arrange), which has been shown to be associated with increased service use by patients but ultimately each physician should develop a dedicated, patient focused strategy for education and smoking cessation [3]. Medical therapy is more effective than simply informing patients about smoking risks and suggesting that they stop, and should be in the standard armamentarium of any physician treating patients with intermittent claudication. Bupropion and varenicline both have data suggesting that they increase the rates of long-term smoking cessation compared with placebo. Varenicline is a highly selective partial agonist and, over longer time frames, also antagonist of the nicotine acetylcholine receptor. It has a greater reduction of cravings compared with bupropion and has the greatest efficacy with respect to sustained smoking abstinence. Bupropion is an atypical antidepressant that is thought to not only inhibit norepinephrine and dopamine uptake but also antagonize the nicotine acetylcholine receptor. Although bupropion is useful for its primary indications in mental health, it has the side effect of also helping with smoking cessation and can be a useful adjunct with a well-understood safety profile. Nicotine replacement therapy may also be used as an adjunct to address nicotine cravings, although there are no good data to suggest that electronic cigarettes or similar technologies improve outcomes in PAD.

Pharmacologic management of peripheral artery disease

Antiplatelet therapy with daily aspirin in the range of 81 to 325 mg is recommended for all patients with a diagnosis of PAD. Because PAD is a marker of systemic cardiovascular event risk (eg, myocardial infarction, stroke), daily aspirin has the purpose of both reducing limb-related events and these other cardiovascular events. There are no high-quality data to suggest a particular dose of aspirin for PAD but 81 mg daily seems to be sufficient without significantly increasing the risk of side effects. For those patients with aspirin sensitivity, clopidogrel can be used as an alternative. Dual antiplatelet therapy (DAPT), however, is not indicated if it is only being considered for first-line management of PAD without some concomitant application (eg, prior coronary stent, recent lower extremity revascularization). Specifically, DAPT has not demonstrated better limb-related outcomes in PAD compared with aspirin monotherapy but has been associated with an increased risk of major and lifethreatening bleeding.

Statin therapy is the other cornerstone of PAD treatment. As mentioned above, treatment with a high-dose statin should be initiated in all patients with PAD who can tolerate it, regardless of their cholesterol levels.

The other PAD-specific pharmacologic intervention to consider as a second-line treatment of intermittent claudication is *cilostazol*, which is a phosphodiesterase III inhibitor. Several randomized control trials have shown that cilostazol improves initial and absolute walking

distances and improved quality of life in patients with intermittent claudication. Cilostazol works in PAD through several mechanisms including its supplemental antiplatelet inhibition, by acting as a vasodilator on vascular smooth muscle, and via its metabolic effect on high-density lipoprotein and cholesterol. It is important to note that cilostazol is more effective when used in combination with SET. However, it is associated with gastrointestinal side effects and is strictly contraindicated in patients with heart failure. As a result, a transthoracic echocardiogram should be obtained in all patients before initiation of this therapy.

Supervised exercise therapy

SET therapy has been established in multiple societal guidelines as the first-line therapy for intermittent claudication [4]. The physiologic changes associated with SET are incompletely understood but are thought to be related to repetitive ischemia-inducing oxidative stress and inflammation in affected muscle beds, resulting in changes to endothelial function, angiogenesis, and muscle composition. Exercise should therefore be of sufficient intensity to induce claudication, followed by a brief period of rest, followed by continued walking for at least 30 to 60 minutes. Over time, SET should increase the total distance walked and total distance before symptom onset. Interestingly, this effect has been associated with symptom improvement but not significant improvements in ABI.

The SET strategy for treating intermittent claudication was studied in The Claudication: Exercise Versus Endoluminal Revascularization (CLEVER) Study, which compared optimal medical therapy (antiplatelet and cilostazol) versus optimal medical therapy plus SET versus optimal medical therapy plus revascularization by stenting in patients with aortoiliac disease and claudication. After 6 months, the SET plus optimal medical therapy group had the greatest improvement in treadmill walking distance. Patients receiving stenting also had an improvement from baseline but had additional costs of up to US\$5000 per patient. Because of this and multiple other high-quality studies showing improved patient outcomes, SET is now considered standard of care for first-line therapy of intermittent claudication.

With increasing data to support its use, the Center of Medicare and Medicaid Services (CMS) now reimburses up to 36 SET sessions (30–60 minutes in length) during a 12-week period for symptomatic patients when conducted in either a hospital outpatient or physician's office by qualified providers under the supervision of a physician. When SET therapy is unavailable, alternative unsupervised exercise therapy may be considered. Patients may be prescribed clear walking programs that can be followed easily at home and are designed to accomplish the same functional outcomes as formal SET. Although there is moderate-quality and high-quality evidence that SET has a greater benefit in treadmill walking distance compared with home-based exercise therapy and walking advice, respectively, any exercise program that induces repetitive stress and recovery to affected muscle groups is preferable to no walking program.

Despite the high-level evidence, broad guideline support, and CMS reimbursement, SET continues to have variable consistency and application. To improve SET usage, the Society of Vascular Surgery has created a smartphone application (app) to facilitate broader application. This app allows patients to work alongside their physician counterparts,

coaches, and multidisciplinary clinic team members in a collaborative way (Fig. 3) and aims to improve outcomes in home-based walking therapy. The efficacy and long-term outcomes of this initiative are pending.

As SET therapy continues to evolve, patient reported outcome measures and quality of life measures have also been increasingly integrated into defining what high-quality care means in PAD. This has been not only partially spurred by CMS and their requirements for reimbursement but also endorsed by societies including the American Heart Association and the Society for Vascular Surgery. Understanding patient perspectives may prove useful for the longitudinal management of those with PAD, including capturing and augmenting patient expectations regarding surgery, explaining why walking despite leg pain may be beneficial in SET, and increasing patient understanding around how the modification of risk factors may improve disease trajectory.

Surveillance

Current professional guidelines suggest that patients be treated for intermittent claudication using a conservative approach (meaning first-line and second-line therapies as described above) for a minimum of 3 to 6 months before consideration of revascularization.

As a result, patients should undergo PAD surveillance following a new diagnosis of intermittent claudication. We typically see a patient back at 3 months following their initial diagnosis of claudication with repeat exercise ABIs, after which a q6 month follow-up is appropriate. The initial close follow-up allows for a check-in regarding any comorbid or risk modification interventions (eg, antihypertensive treatment, antiplatelet and statin therapy), and reinforcement about the importance of smoking cessation and SET. As noted above, ABIs should not be expected to improve with conservative PAD management; rather, physicians should pay mind to notable decreases in ABI or worsening symptomatology, which suggests the progression of PAD. Patients with intermittent claudication typically have stable disease for many years if their risks factors are controlled and smoking cessation can be achieved. However, regular follow-up with a physician trained in the management of intermittent claudication is helpful for continued medical optimization, imaging surveillance, and early detection of disease progression.

Revascularization

Revascularization in patients with intermittent claudication should be reserved for patients with lifestyle-limiting symptoms who are fully optimized on medical therapy and have had comprehensive risk factor mitigation, including completion of SET or a home walking program for a minimum of 3 to 6 months. Active smoking is a contraindication to revascularization because outcomes are significantly worse among patients with active smoking compared with those with former or never smoking. The main goal of revascularization is to improve functional status and facilitate participation in exercise therapy and life-style improvements. Revascularization techniques and surgical approaches are not a focus of this article but are discussed in the text elsewhere in dedicated sections.

SUMMARY

Claudication is associated with significant cardiovascular risk but low risk of limb loss and is best initially managed by medical optimization, smoking cessation, daily aspirin, statin therapy, and SET. Additional interventions may be considered in those who complete first-line therapy and remain symptomatic, including consideration of cilostazol (second-line therapy) and revascularization (third-line therapy). The surgical management of intermittent claudication should be considered in only selected patients after optimal medical therapy is achieved.

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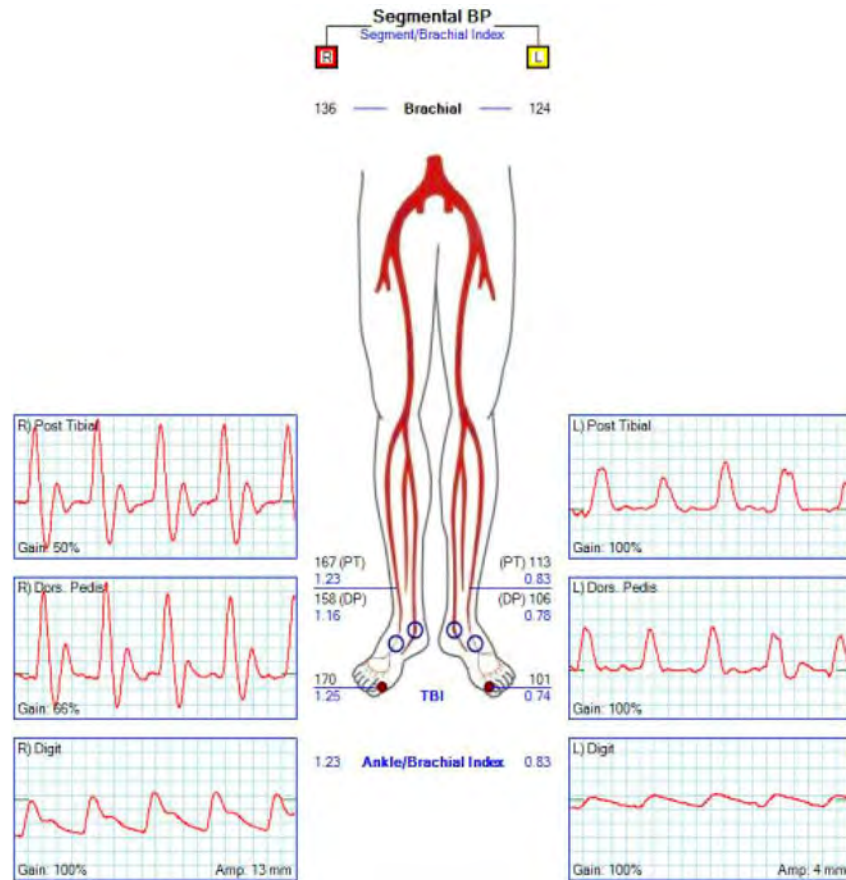
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Key points

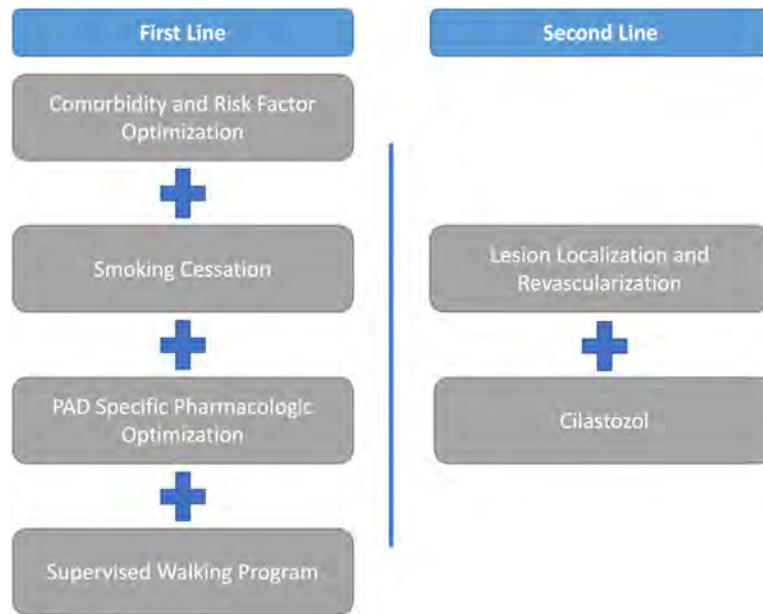
- Claudication is associated with high medical cardiovascular risk but low risk of limb loss.
- First-line therapy is medical optimization including an aspirin and statin, risk factor mitigation including smoking cessation, and completion of a supervised exercise program.
- Further intervention may be considered in those who complete first-line therapy and remain symptomatic, including consideration of cilostazol and then revascularization.
- Surgery should be considered in only selected patients after medical optimization.

CLINICS CARE POINTS

- Patients with peripheral arterial disease require multidisciplinary care to reduce global cardiovascular risk and buy-in from the patient and the entire care team is paramount.
- Many patients desire an upfront surgical solution but this is unlikely to provide durable results. Upfront medical optimization works in most patients, is associated with better outcomes, and is more cost-effective.
- Surveillance is important for monitoring progression, generally with arterial duplex ultrasounds, and can be intertwined with ongoing counseling and education.

**Fig. 1.**

Example of a lower extremity noninvasive arterial Doppler evaluation demonstrating normal perfusion to the right lower extremity and mild arterial insufficiency to the left lower extremity in a patient with left lower extremity claudication.

**Fig. 2.**

Summary overview of treatment paradigm of patients with diagnosis of PAD and intermittent claudication. First-line management of intermittent claudication includes medical optimization of comorbid conditions and risk factors including hypertension, diabetes and dyslipidemia, as well as smoking cessation; and PAD-specific optimization including daily aspirin, statin, and initiation of SET. Second-line therapy involves the initiation of cilostazol in eligible patients. Third-line therapy for patients who are medically optimized and completed SET without benefit can be considered for potential revascularization.



Fig. 3.

The Society for Vascular Surgery SET App features is a physician-prescribed, 12-week home-based program. It also includes educational content, exercise scheduling and recording, a patient reported outcomes reporting system and coaching. It also includes a physician portal for them to follow their patient's progress.

Table 1

Fontaine stage and Rutherford grade of peripheral artery disease

Fontaine’s staging of PAD		Rutherford’s grading of PAD		
Stage	Clinical finding	Grade	Category	Clinical finding
I	Asymptomatic	0	0	Asymptomatic
IIa	Mild claudication, symptoms at distances >200 m of walking	I	1	Mild claudication
IIb	Moderate-to-severe claudication, symptoms at <200 m	I	2	Moderate claudication
		I	3	Severe claudication
III	Ischemic rest pain	II	4	Ischemic rest pain
IV	Ulceration and/or gangrene	III	5	Minor tissue loss
		III	6	Major tissue loss

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