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DIABETIC ANGIOPATHY-RELATED CHRONIC LIMB-THREATENING ISCHEMIA: REVASCULARIZATION STRATEGIES AND DUAL ANTITHROMBOTIC THERAPY

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დიაბეტური ანგიოპათიით გამოწვეული კიდურის ქრონიკული იშემია: რევასკულარიზაციის სტრატეგიები და ორმაგი ანტითრომბოზული თერაპია

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რეზიუმე

სტატიაში განხილულია დიაბეტური ანგიოპათიით გამოწვეული კიდურის ქრონიკული იშემიის პათოფიზიოლოგიური მექანიზმები, რევასკულარიზაციის თანამედროვე მიდგომები და ორმაგი ანტითრომბოზული თერაპიის როლი პაციენტის პოსტოპერაციულ მართვაში. აღწერილია, რომ დიაბეტურ პაციენტებში არტერიული დაზიანება გამოირჩევა დისტალური, მრავალსეგმენტური და დიფუზური ხასიათით, ენდოთელური დისფუნქციით, მიკროცირკულაციის დარღვევითა და მომატებული თრომბოზული აქტივობით, რაც მნიშვნელოვნად ზრდის რესტენოზისა და რეოკლუზიის რისკს. განხილული თანამედროვე მტკიცებულებები მიუთითებს, რომ რევასკულარიზაციასთან ერთად ანტითრომბოციტული პრეპარატის და დაბალი დოზის ანტიკოაგულანტის კომბინირებული გამოყენება აუმჯობესებს სისხლძარღვოვან გამავლიანობას, ამცირებს მწვავე იშემიური მოვლენებისა და განმეორებითი ჩარევის საჭიროებას. ამასთანავე, ხაზგასმულია სისხლდენის რისკის ინდივიდუალური შეფასების აუცილებლობა და პერსონალიზებული თერაპიული მიდგომის მნიშვნელობა მაღალი რისკის მქონე პაციენტებში.

1. Introduction

Diabetes mellitus has a high prevalence worldwide and remains important challenge for healthcare systems. It is related to many complications that increase cardiovascular morbidity and mortality. Among its most dangerous complications is diabetic angiopathy, a complex vascular disorder that affects both macrovascular and microvascular beds. Diabetic angiopathy significantly accelerates the development of peripheral arterial disease (PAD). In patients with diabetes, PAD often progresses to chronic limb-threatening ischemia (CLTI), the most severe clinical manifestation of lower-extremity ischemia, associated with high risks of limb loss, disability and death [1,2].

There is a big difference between Diabetic angiopathy–related CLTI and PAD in non-diabetic patients (Table #1). Diabetic angiopathy–related CLTI is characterized by diffuse, multilevel, distal arterial involvement. In most cases collateral circulation is not well-developed, there is endothelial dysfunction, and a prothrombotic state. In addition, diabetic neuropathy frequently masks ischemic pain, leading to delay of diagnosis and patients come at the clinic at advanced stages, when non-healing ulcers, infection, or gangrene will be developed. These factors can worse prognosis, cause higher rates of amputation, and generally they can increase healthcare load in diabetic populations [3].

Peripheral arterial revascularization is the most important procedure for prevention of poor outcomes in CLTI and is recommended by new guidelines whenever technically possible. **Both endovascular and open surgical approaches** are beneficial in treatment of complex lesions. However, despite technical success, post-revascularization outcomes in diabetic patients remain suboptimal, because there is described high rates of complications - restenosis, reocclusion, and recurrent ischemic events. This indicates the importance of medical therapy for improving vascular health and preventing thrombotic complications.

Antithrombotic therapy plays a crucial role in the management of patients after peripheral revascularization. Traditionally, antiplatelet therapy with aspirin alone or in combination with a P2Y12 inhibitor has been the standard approach. Diabetes itself is associated with increased platelet activity, hypercoagulation, and endothelial dysfunction. These factors may limit the effectiveness of antiplatelet monotherapy. Recent clinical researches have suggested that a dual-antithrombotic therapy may provide superior protection against thrombotic complications in patients with PAD, including those underwent revascularization.

Despite increasing interest in dual antithrombotic therapy, its role in diabetic angiopathy–related CLTI is not well understood. Key questions exist about patient selection, comparative effectiveness versus standard antiplatelet regimens, safety and bleeding risk, also potential difference between type 1 and type 2 diabetic patients. Answers on these questions are very important for maintanence balance between thrombosis and bleeding in this high-risk population.

Therefore, our study goal is evaluation of revascularization strategies in patients with diabetic angiopathy–related CLTI and assessment of the clinical impact of dual antithrombotic therapy compared with traditional single antiplatelet treatment. By focusing on thrombotic outcomes, limb salvage, and safety, this work seeks to contribute to evidence-based optimization of post-revascularization strategies and to support a personalized therapeutic management for patients with diabetic CLTI [4].

Table #1 - Key Differences Between Diabetic and Non-Diabetic CLTI

Feature	Diabetic CLTI	Non-Diabetic CLTI
Arterial involvement	Diffuse, multilevel, predominantly distal (infrapopliteal, pedal)	More proximal, mainly segmental
Medial arterial calcification	Common (Monckeberg's sclerosis)	Rare
Collateral formation	Impaired	Mainly preserved
Microvascular dysfunction	Prominent	Limited
Neuropathy	Frequent (masks ischemic pain)	Rare
Wound healing	Delayed	Relatively preserved
Thrombotic risk	High	Moderate
Restenosis after revascularization	High	Lower
Amputation risk	Significantly increased	Lower

2. Pathophysiology of Diabetic Angiopathy

Diabetic angiopathy is a complex and multifactorial vascular disorder that develops as a result of chronic hyperglycemia and metabolic dysregulation in diabetes mellitus. It affects both macrovascular and microvascular circulation and plays a central role in the development of peripheral arterial disease (PAD) and chronic limb-threatening ischemia (CLTI). The pathophysiology of diabetic angiopathy involves a dynamic interaction between endothelial dysfunction, inflammation, oxidative stress, coagulation abnormalities, and structural remodeling of the vascular wall (Figure #1).

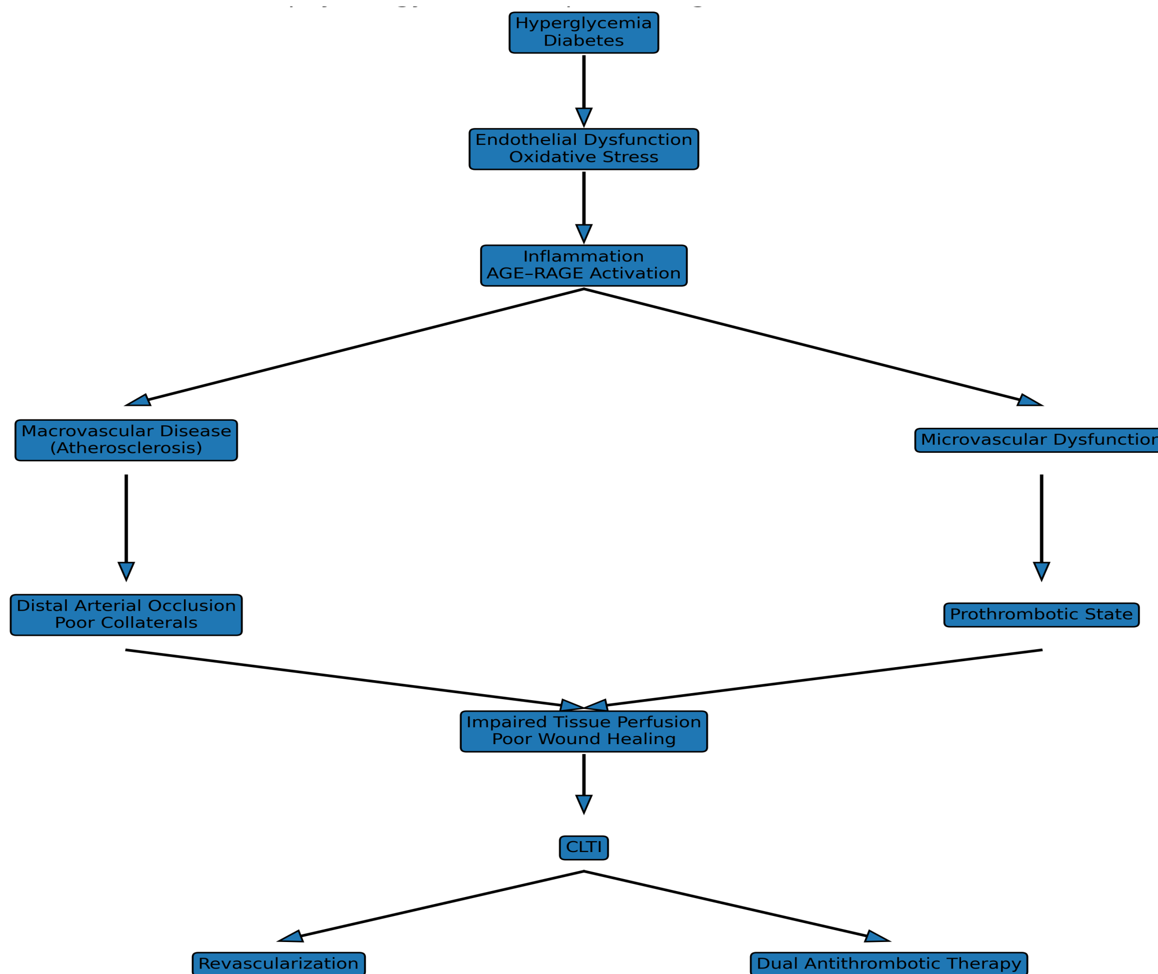
Hyperglycemia-Induced Endothelial Dysfunction. Endothelial dysfunction is one of the earliest events in diabetic angiopathy. Chronic hyperglycemia causes excessive glucose uptake by endothelial cells, activates several biochemical pathways, including the polyol pathway, protein kinase C (PKC) pathway, and the hexosamine pathway. These processes can lead to dysregulation of endothelial homeostasis and impairment of vasodilatory capacity [5].

A key factor of endothelial dysfunction is decreased bioavailability of nitric oxide (NO), a critical regulator of vascular tone, platelet inhibition, and anti-inflammatory signaling. Hyperglycemia increases oxidative stress through the overproduction of reactive oxygen species (ROS). ROS can inactivate NO and

cause vasoconstriction [6,7]. Simultaneously, overexpression of vasoconstrictive mediators such as endothelin-1 aggravates microvascular and macrovascular perfusion problems.

Endothelial dysfunction also increases vascular permeability and leukocyte adhesion through upregulation of adhesion molecules, including VCAM-1, ICAM-1, and selectins. This maintains chronic vascular inflammation, a hallmark of diabetic angiopathy.

Figure #1 - Pathophysiology and Therapeutic Targets in Diabetic CLTI



Advanced Glycation and Vascular Injury. Advanced glycation end products (AGEs) play an important role in the development and progression of diabetic angiopathy. AGEs are formed through non-enzymatic glycation of proteins, lipids, and nucleic acids during long-term hyperglycemia. Storage of AGEs within the blood vessel's wall impairs the structural integrity of extracellular matrix proteins like collagen and elastin, as a result arterial compliance will be decreased due to wall stiffness [8].

Interaction of AGEs with their cellular receptor (RAGE) activates multiple intracellular signaling cascades, including nuclear factor kappa B (NF-κB), which activates inflammatory gene expression. This is the key factor in endothelial activation, smooth muscle cell proliferation, and oxidative stress formation. In diabetic patients, AGE–RAGE signaling leads to development and progression of atherosclerosis [6,7,8].

Oxidative Stress and Chronic Inflammation. Oxidative stress is tightly linked to hyperglycemia and has a crucial role in vascular pathology. Excess ROS production in diabetes is a result of mitochondrial dysfunction, NADPH oxidase activation, and insufficient antioxidant pathways. Oxidative stress damages vascular endothelial cells, changes intracellular signaling, and alleviates lipid oxidation, finally it accelerates atherogenesis [9].

Oxidative stress is always accompanied by chronic low-grade inflammation in diabetic angiopathy. Elevated levels of inflammatory cytokines in the bloodstream- tumor necrosis factor-α (TNF-α), interleukin-6 (IL-6), and C-reactive protein- lead to endothelial dysfunction and atherosclerotic plaque instability. Macrophage infiltration of the vascular wall accentuates inflammation and enhances formation of unstable atherosclerotic plaques, particularly in lower-extremity arteries, distal to the popliteal [8,9].

Smooth Myocytes Dysfunction and Vascular Remodeling. Diabetes mellitus affects vascular smooth muscle cell (VSMC) physiology. Hyperglycemia and inflammatory cytokines stimulate VSMC migration and proliferation from the media into the intima, causing intimal hyperplasia and progressive vasoconstriction. This process is especially sped up after vascular bed injury or revascularization procedures, leads to restenosis and reocclusion [10].

Structural remodeling in diabetic angiopathy includes medial calcification (Monckeberg sclerosis), which is highly prevalent in diabetic patients. Medial arterial calcification increases arterial wall stiffness, reduces arterial compliance, and impairs normal hemodynamic regulation. Calcification makes it more difficult to diagnose angiopathy by using of classic methods, including pressure-based ankle–brachial index.

Prothrombotic State and Coagulation Abnormalities. A classic feature of diabetic angiopathy is a persistent hypercoagulation state. Diabetes is associated with increased platelet aggregation, and unresponsiveness to endogenous antithrombotic mechanisms. Platelets in diabetic patients characterized by overexpression of surface adhesion molecules and increased sensitivity to agonists, lead to thrombus formation [10,11].

In diabetic angiopathy coagulation cascade is dysregulated, because levels of fibrinogen, factor VII, and plasminogen activator inhibitor-1 (PAI-1) are increased. Additionally leading fibrinolysis process is impaired. After endothelial injury subendothelial procoagulant surface exposure promotes thrombin overproduction. These significantly increase the risk of acute thrombosis, graft failure, and reocclusion after peripheral revascularization [12].

Microvascular Dysfunction and Impaired Tissue Perfusion. Diabetic angiopathy is associated with not only macrovascular disorder, but also microvascular bed dysfunction. Capillary basement membrane will become thicker, pericytes will be lost, and autoregulation processes won't be sufficient – these reduce tissue perfusion even in the presence of intact large arteries [13]. This phenomenon is effective answer why some diabetic patients suffer from ischemic ulcers despite adequate macrovascular flow.

Microvascular impairment also impairs oxygen diffusion and nutrient delivery, results in wound healing and increased vulnerability to infection. In the context of CLTI, combined macrovascular obstruction and microcirculatory failure create a big imbalance between tissue metabolic demand and blood supply, contribute to development of necrosis and limb loss.

Integration into CLTI Pathogenesis. The processes of endothelial dysfunction, atherosclerosis, vascular calcification, inflammation, thrombosis, and microvascular failure result in the development of diabetic angiopathy–related CLTI. Compared with non-diabetic patients, individuals with diabetes are under the higher risk of earlier onset, more diffuse arterial disease, poorer collateralization, and reocclusion after intervention. These pathophysiological features explain the poorer outcomes observed in diabetic CLTI and underline the need for complex treatment strategies after mechanical revascularization.

Understanding the complex pathophysiology of diabetic angiopathy gives us a biological logic explanation for combined therapeutic management, including aggressive risk-factor modification,

revascularization, and optimized antithrombotic therapy. Such an integrated strategy is crucial to improve limb saving and life survival percentage in this population [14].

3. Revascularization in Diabetic CLTI

Revascularization stays as the central procedure for limb salvage in patients with chronic limb-threatening ischemia (CLTI). It is particularly essential in the setting of diabetic angiopathy. The primary goal of the revascularization procedure is to restore blood flow to ischemic tissues, accelerate wound healing, alleviate ischemic pain, and prevent major complications, including amputation. However, revascularization in diabetic CLTI is widely challenging due to diffuse arterial disease, distal vessel involvement, impaired collateral circulation, and a high thrombotic and inflammatory activity (Table #2).

Table #2 - Revascularization Approaches in Diabetic CLTI

Strategy	Advantages	Limitations
Endovascular (PTA, DCB, stents)	Minimally invasive, repeatable, lower perioperative risk	High restenosis, limited duration in long calcified lesions
Surgical bypass	Durable patency with good conduit	Higher perioperative risk, wound complications
Infrapopliteal intervention	Targets distal disease	Technical complexity
Angiosome-guided revascularization	Improved wound healing	Not always anatomically feasible
Hybrid procedures	Anatomical flexibility	Requires expertise

Reasons and Objectives of Revascularisation. CLTI is associated with higher likelihood of amputation and death in diabetic patients if it is left untreated. Modern guidelines suggest revascularization as long as it is anatomically possible and clinically indicated. Revascularization does not focus only on angiographic success, but also includes restoration of tissue perfusion, saving of the limb, and functional recovery. Whereas intermittent claudication seeks to relieve symptoms initially (if there is relief from pain), revascularization in CLTI is motivated by limb-threatening pathology including rest pain, non-healing ulcers, and gangrene. In diabetic patients, slight improvements in perfusion may still be enough to help in wound healing. This suggests that personalized treatment approach is necessary for all individuals and it’s a part of patient-centered understanding of the disease [15].

The anatomical and pathophysiological challenges in diabetes. Diabetic CLTI is well-recognized, multilevel atherosclerotic disease with high rate of toward infrapopliteal and pedal arteries involvement. Lesions are typically long, calcified and occlusive, it compresses multiple segments at the same time. Medial arterial calcification, common in diabetes, aggravates arterial stiffness and complicates diagnostic examination and interventional assessment. Indeed, diabetic patients often have poor collateral circulation and concurrent microvascular dysfunction. Therefore, good proximal revascularization not always is successful in restoration of appropriate tissue-level perfusion. Therefore, distal and focused revascularization techniques are more relevant. These anatomical and physiologic factors predispose to higher technical complexity, restenosis and reocclusion rates when compared to non-diabetic patients.

Top-line and endovascular revascularization strategies. Due to its minimally invasive nature and a lower perioperative risk profile of endovascular therapy in patients with CLTI (clinical and non-clinical), it is the predominant first-line revascularization type in many patients with diabetes. Most techniques include percutaneous transluminal angioplasty, drug-coated balloons, stent implantation, and atherectomy, typically used in conjunction with these method for management of complex lesions. For diabetic CLTI, the primary distal disease makes infrapopliteal endovascular interventions highly relevant.

Due to new developments in device technology and imaging treatment od long and calcified lesions is easier than before. Restenosis, however, still represents a key complication, related to intimal hyperplasia and persistent inflammatory and thrombotic activity. However, endovascular revascularization has advantages in the diabetic patient in terms of less surgical trauma, less general anesthesia, and the prospect of subsequent procedures. These considerations are especially helpful in patients with multiple comorbid conditions and low physiologic reserve [16].

Surgical Revascularization. Open surgical revascularization (often via bypass graft) still is an important therapy in certain cases of diabetic CLTI, especially where endovascular therapy is not possible to do or has become ineffective. Although surgical revascularization in diabetic patients translates to a higher perioperative risk, such as wound complications, infection and cardiovascular events. Finally, combination of careful patient selection and multidisciplinary decisions should be taken for an open surgery.

Angiosome-Mediated and Targeted Refocusing.

Angiosome-guided revascularization is becoming a leader strategy in diabetic CLTI. This approach is to get direct arterial inflow back to the particular blood region which is delivering the wound or ischemic site. A number of articles have noted better wound healing and increased limb saving rates with direct revascularization as opposed to indirect collateral-based perfusion, especially in diabetic individuals when microvascular reserves are limited. However, angiosome-assisted revascularization is not always beneficial and technically possible procedure based on anatomical limitations. In these exact cases, if it can deliver any inline flow to the foot, it could still be used in treatment. Therefore, strategies of revascularization should consider anatomical variability and physiological reserves [17].

Results and Constraints of Revascularization in Diabetic CLTI. While revascularization provides benefits in limb-saving process relative to conservative management, end results in diabetic CLTI still remain unclear compared to non-diabetic patients. The rates of restenosis, reocclusion and repeat intervention are higher which suggests that diabetic vascular disease has a complex pathophysiology. Furthermore, revascularization alone is not enough to reduse hypercoagulation or inflammation. Nowadays multimodal management of post-revascularization condition, including strict glycemic control, aggressive cardiovascular modulations, wound care optimization, and appropriate antithrombotic therapy. The benefits of revascularization without such a broad approach may not be clinically enough.

Integration of Revascularization into Multimodal Care. Revascularization must be considered one aspect of a larger, multidisciplinary approach to diabetic CLTI therapy. Main goal by revascularization will be best achieved when revascularization used in conjunction with medical therapy, infection control and close follow-up. Collaboration between vascular specialists, endocrinologists, foot care specialists, and wound care teams is required to help improvement condition of this population.

4. Dual Antithrombotic Therapy

Diabetic chronic limb-threatening ischemia (CLTI) patients are a disproportionately high-risk cohort for thrombotic complications. These patients have predisposition to acute thrombosis, restenosis, and reocclusion after peripheral revascularization. As a result, antithrombotic therapy optimization is an essential consideration for post-revascularization diabetic CLTI. Because of its complex pathophysiological natureof thrombotic events in diabetic patients treatment with antiplatelet alone is not enough in most cases. Conceptually, combined antiplatelet treatment with a low-dose anticoagulant (dual antithrombotic therapy) is therefore attractive, as it attacks the complementary aspects of thrombus occurrence.

Clinical Evidence Supporting Dual Antithrombotic Therapy. Recent studies demonstrate that dual antithrombotic therapy in patients with peripheral arterial disease has the potential to prevent major

undesirable limb events, such as acute limb ischemia and recurrent revascularization. In all subgroup analyses, patients with diabetes benefit greatly from this treatment strategy because of their increased thrombotic risk. Within the post-revascularization environment, dual antithrombotic therapy also responsible for better vessel patency and decreased complication rates compared to antiplatelet monotherapy. Among patients, modest, acceptable increase in major bleeding risk is noted when low-dose anticoagulation is used.

Table #3- Antithrombotic Strategies After Peripheral Revascularization

Regimen	Mechanism	Benefits	Limitations
Aspirin monotherapy	Platelet inhibition	Simple, low bleeding risk	Insufficient in high-risk diabetics
Dual antiplatelet therapy (DAPT)	Enhanced platelet inhibition	Reduced platelet-mediated thrombosis	Limited effect on thrombin pathway
Dual antithrombotic therapy (Aspirin + low-dose anticoagulant)	Platelet + thrombin inhibition	↓ acute limb ischemia, ↓ reocclusion, ↓ MACE/MALE	Increased bleeding risk (patient selection critical)
Full-dose anticoagulation	Strong thrombin suppression	Effective thrombosis prevention	High bleeding risk

Safety Matters and Bleeding Risk. Bleeding risk continues to be a major problem with the introduction of further antithrombotic therapy. Patients with diabetic CLTI usually present with advanced age, kidney disease, anemia, and several agents present together which, together, may increase predisposition to bleeding. Hence, personalized risk assessment is necessary. Recent data show that low-dose anticoagulant therapy in combination with antiplatelet therapy offer an optimal ratio of effectiveness to safety compared to a monotherapy. Continuous monitoring and dose reduction in renal failure and prevention of polypharmacy are essential to prevent bleeding complications. In practice, a decision to start dual antithrombotic therapy must consider risks and benefits.

The function of dual antithrombotic therapy in insulin-dependent diabetes. Insulin-dependent diabetic patients are a subpopulation of particularly vulnerable individuals with high vascular disease at risk of thrombotic bleeding. Increased platelet activation, greater inflammation, and diffuse arterial involvement make to worse outcomes after revascularization. There is emerging evidence that dual antithrombotic therapy has benefits in this population by improving of prothrombotic condition. Nevertheless, insulin-dependent patients often have comorbidities that also increase bleeding risk. It highlights that personalized treatment approaches are crucial. Clinical features, procedural characteristics, and bleeding risk score stratification will also helpful during identification of dual therapy advantages.

Further studies and clinical ramifications. However, despite good results, numerous problems of dual antithrombotic therapy in patients with diabetic CLTI remain active. It is necessary for improved length of administration, choice of antithrombotic agents and the individual characteristics of those patients who might receive benefit most, to be further explored. Future studies specific to diabetic CLTI groups are warranted to make treatment algorithms and develop evidence-based guidelines. This is why dual antithrombotic therapy is still a valid option to optimise the outcome after revascularization in treatment of patients with diabetic CLTI. By treating platelet and coagulation-mediated mechanisms in thrombosis, this method aims to overcome important pathophysiological events of restenosis and reocclusion.

Conclusions. Diabetic angiopathy related chronic limb-threatening ischemia is among the most severe manifestations of peripheral arterial disease. It has diffuse vascular involvement, reduced tissue

perfusion, and a markedly elevated risk of limb loss and general mortality. Although revascularization approaches have been improved and postoperative outcomes are acceptable, clinical aspects in diabetic CLTI are still under the high thrombotic risk, restenosis and reocclusion. Revascularization is still the mainstay of limb salvage intervention in diabetic CLTI and should be undertaken when anatomically feasible and clinically appropriate. As a result, mechanical restoration of blood flow is generally not enough to manage the complex pathophysiological problems of the diabetic vascular disease, which include endothelial dysfunction, inflammation, microvascular impairment and a prolonged hypergoagulability. Dual antithrombotic therapy including combined antiplatelet and low-dose anticoagulant agents represents a pathophysiologically better and clinically suitable strategy to prevent post-revascularization adverse events in diabetic CLTI. This approach protects vascular bed more than antiplatelet monotherapy. Recent studies demonstrate that dual antithrombotic therapy is especially useful for high-risk patients with more aggressive vascular disease such as insulin-dependent diabetic patients with an acute increase in thrombotic risk. However, bleeding risk must be an important factor in patient management, which should be the focus of personalized treatment options, based on a full evaluation of thrombotic and hemorrhagic risk. Finally, proper management of diabetic CLTI needs an individualized strategy involving revascularization, selective antithrombotics, and comprehensive care together with patient and clinician. Prospective studies focusing exclusively on diabetic CLTI populations suggest to optimize patient selection, establish optimal duration of treatment, and devise antithrombotic algorithms based on best evidence. Such efforts are essential to achieving limb salvage, functional outcomes, and long-term survival in this extremely high-risk population.

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SUMMARY

Diabetic angiopathy is a main complication of diabetes mellitus and a leading cause of chronic limb-threatening ischemia (CLTI). Patients with diabetes have higher risk for aggressive peripheral arterial disease, which is characterized by distal, multilevel arterial involvement, impaired wound healing, high risk of thrombosis and limb loss. Despite importance of peripheral revascularization in limb saving process, optimal post-revascularization antithrombotic therapy has a big role for prevention of complications, particularly in diabetic populations.

Keywords: Diabetic, angiopathy, limb ischemia, revascularization, dual antithrombotic Therapy