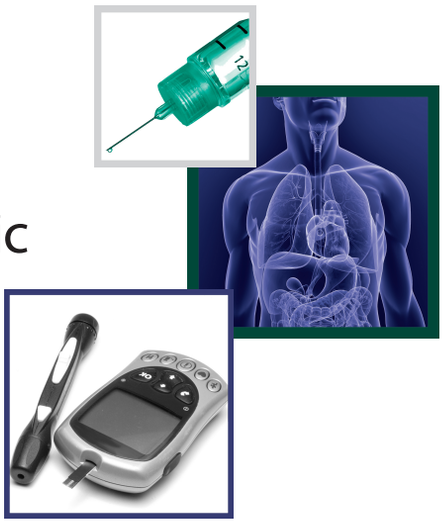

Integrated management of the diabetic ischemic foot

Alberto Piaggesi[†] & Lanfroi Graziani[1]

Practice Points

- One out of five newly diagnosed Type 2 diabetic patients has signs of peripheral macroangiopathy.
- Critical limb ischemia is generally hyposymptomatic and patients should be actively tested for this.
- Endovascular revascularization is the first-line option to treat critical limb ischemia patients with diabetic foot.
- Local conservative surgery and systemic medical management are integral parts of the therapy.
- The management of critical patients should be carried out in highly specialized centers.

SUMMARY Ischemia represents the most important determinant for major amputation in the diabetic foot, and is associated with a higher prevalence of foot infections, systemic comorbidity and mortality. Until recently, prognosis for these patients was very poor; however, despite solid population-based evidence not being presently available, there are still indications that the introduction of both endovascular and surgical revascularization has improved prognosis. Improvements in the materials, technology and procedures in the last 10 years, as well as increasing experience, suggest that revascularization should no longer be considered a limb-saving option, but instead, a first-line intervention with a wide range of indications in the ischemic diabetic foot. This approach, when integrated into a therapeutic strategy that includes both local surgery and systemic medical management and applied in highly specialized centers, allows high healing rates with a significant reduction of major amputations.

The complications of diabetes at the lower limbs, commonly known as diabetic foot (DF), still represents the most prevalent cause of lower extremity amputation (LEA), such that it has been estimated that a limb is lost every 30 s due to diabetes [1]. This figure is bound to increase up to fourfold in the next 20 years because of the sharp increase of the incidence of diabetes and its complications [2].

Although DF has a multifactorial pathogenesis in which both neuropathy, immunopathy and peripheral arterial disease (PAD) play a role, it has been demonstrated that PAD is the major risk factor for LEA in diabetic patients, both alone or in association with neuropathy [3,4].

A recent multicenter study involving more than 1200 patients from ten different European countries demonstrated how the presence of PAD

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significantly increases the risk of LEA in DF, to such an extent that the authors suggested considering DF with PAD as a different and worse pathology compared with DF without PAD [5].

In addition to the risk of LEA, ischemic DF has been associated with a higher cardiovascular morbidity and mortality, such that it has been indicated as a marker of severity in diabetic patients, owing to the high prevalence of comorbidity [6].

Far from being a local problem identifiable with a foot ulceration, the ischemic DF as a complex pathology in which both local and systemic aspects contribute to determine a critical condition in a fragile patient, which deserves an integrated therapeutic strategy to avoid LEAs and increase the life expectancy of patients.

Until recently, the prognosis of ischemic DF patients was very bad, with a relative risk of LEA 20-times higher than in a nondiabetic population; however, the pioneering work that opened the way to distal surgical bypasses, and more recently the introduction of endovascular revascularization and conservative surgical techniques for foot salvaging, dramatically improved the prognosis of patients [7,8].

This article will focus on the management of critical ischemic DF patients with a modern approach, which takes into account the new revascularization options as well as the local surgical management and the systemic aspects of this complex condition.

Peripheral vascular involvement in diabetes

The involvement of the peripheral vascular system in the evolution of diabetes is early and frequent. More than 20% of Type 2 diabetic patients show signs of PAD at diagnosis, while more than half of patients over 60 years of age present PAD among the features of their clinical manifestations [9,10].

In addition, and independent of atherosclerotic changes, the popliteal and below-the-knee arteries of diabetic patients are characterized by increased amount of connective tissue, such as fibronectin, collagen and glycoproteins, as well as increased amount of calcium in the medial layer, termed Monckeberg's sclerosis, a constellation termed diabetic macroangiopathy (DMA). Monckeberg's sclerosis, a condition that is characterized by the absence of macrophages and lipid, is common in diabetics and occurs independent from atherosclerosis, implying different etiological mechanisms [11].

The presence of neuropathy in the lower limb, in the same area where peripheral vascular involvement occurs, seems to play an important role in determining many of the differences observed in diabetic subjects: the denervation of the medium layer of the arterial wall and the consequent muscular hypotrophy drives the diffuse deposition of calcium observed in Monkeberg syndrome, while the reduced neurotrophic activity may explain the reduced capacity to form collaterals vessels [12].

In diabetic subjects with critical limb ischemia (CLI), collaterals contribution is typically poor due to the depression of the arteriogenic and collateral growth process in response to ischemia, particularly in below-the-knee arteries [13]. In particular, chronic hyperglycemia negatively affects the different phases of arteriogenesis: impaired shear-induced vasodilatation, impaired outward collateral growth, which is reflected in the number of collaterals and blood volume index, and inhibition of monocyte chemotaxis [12]. Moreover, early and generalized hemodynamic modifications due to fixed neuropathic vasodilation could justify the multiple involvement of the infrapopliteal arteries in DM **(Figure 1)** [14].

In a recent study, out of 2893 arterial lesions in 417 ulcerated DM patients with CLI, only 1% were in the iliac arteries, while 74% were in the infrapopliteal arteries. Among these, 66% were occlusions and 50% were occlusions longer than 10 cm [15]. Multilevel involvement was the most common condition, whereas an exclusive infrapopliteal involvement was found in only 25% of all cases.

Based on these findings a new classification of DMA into seven different classes has been proposed, which is closer to the real pattern of the pathology and which has been demonstrated to inversely correlate with local transcutaneous oxygen tension ($TcPO_2$) as an index of local perfusion **(Figure 2)**

The result of this complex and multifactorial extensive vasculopathy is a diffuse disease that affects patients 10 years earlier, without sex differences, and with a higher tendency to develop into severe forms, compared with the PAD that occurs in nondiabetic patients **(Table 1)** [8].

Other characteristics of DMA are the reduced symptoms secondary to peripheral neuropathy, which delay clinical manifestation and contribute to the underestimation of the severity of the pathology, and trophic lesions and necrosis are common onset

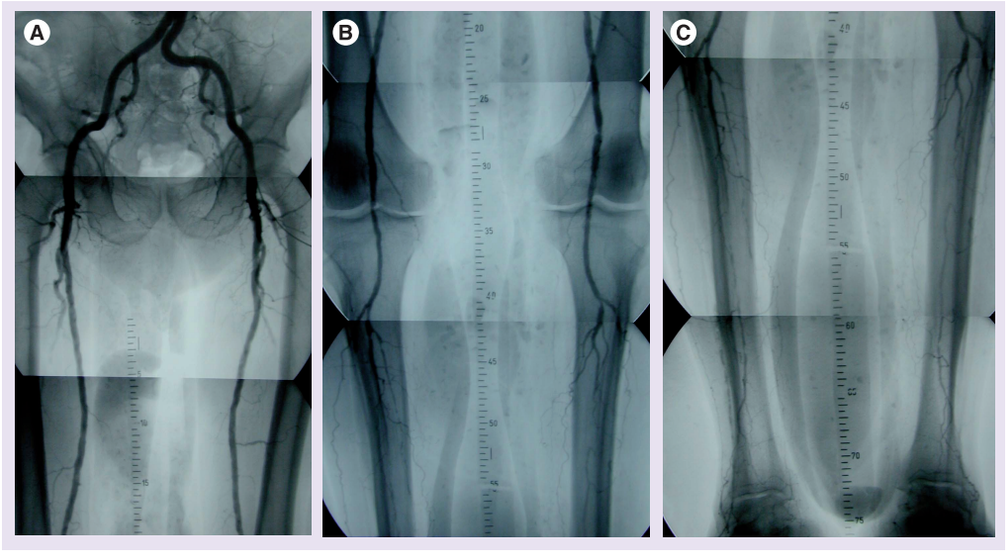

Figure 1. The characteristic angiographic presentation of peripheral diabetic macroangiopathy. Compared with a substantially preserved circulation both in the **(A)** femoral and **(B)** popliteal districts, there is a bilateral involvement of all the three vessels in the infrapopliteal district **(C)**.

features of DMA [5]. Intermittent claudication, the pathognomonic feature of PAD, is infrequent in DMA, and when present, indicates a clinical situation far worse than what could be expected; the same can be said about rest pain, which is uncommon but, when present, should be considered as a indicator of extreme severity [16].

Ischemic lesions and necrosis are common features of DMA: they predominantly localize in the margins of the foot, distally to the dorsal pedis and plantar arches, where even in the presence of a large natural anastomosis such as the plantar arch, occlusion of distal arteries cannot rely on the possibility of collateral compensation. Pale skin, cyanosis, skin edema and nail hypotrophy, associated with a reduction in skin temperature, are frequent signs of DMA and should be tested for whenever the condition is suspected, as well as the absence of peripheral arterial pulses at the ankle [10].

When skin lesions or necrosis are present together despite the absence of rest pain, with a significant reduction of blood pressure at the ankle (<50 mmHg) or in the first toe (<30 mmHg), CLI should be suspected in diabetic patients [17].

In **Figure 3**, three cases of initial clinical presentation of CLI in diabetic patients are shown; in all three patients pain was absent and no symptoms were described by the patients, which were referred by their GPs because of clinical examination of the feet. In all the three cases ankle blood pressure was lower than 50 mmHg and $TcPO_2$ was lower than 30 mmHg.

Indications for revascularization

The possibility of restoring the peripheral direct blood supply to the foot with surgical and endovascular techniques changed the prognosis of DMA and contributed to significantly reduced rates of lower limb amputations in patients [18,19].

What was considered an unavoidably deteriorating condition has gradually became a treatable disease, at least in the majority of cases, thanks to a process similar to that which, 30 years ago, changed the clinical course of myocardial ischemia.

The progress in the operative techniques, as well as impressive technological developments, has rapidly extended the indications for revascularization for DMA, from a limb-salvage procedure, strictly reserved for extremely severe cases, to a more suitable option that addresses a wider range of patients, depending on the degree of severity of local and systemic conditions, as part of an integrated therapeutic strategy [20].

Critical limb ischemia still remains the clinical indication for revascularization, as indicated by all clinical guidelines, but its definition has been specifically adapted, in many experienced centers of excellence, to the features of DMA [21–24]. In particular, the systemic clinical evaluation of cases has more relevance compared with

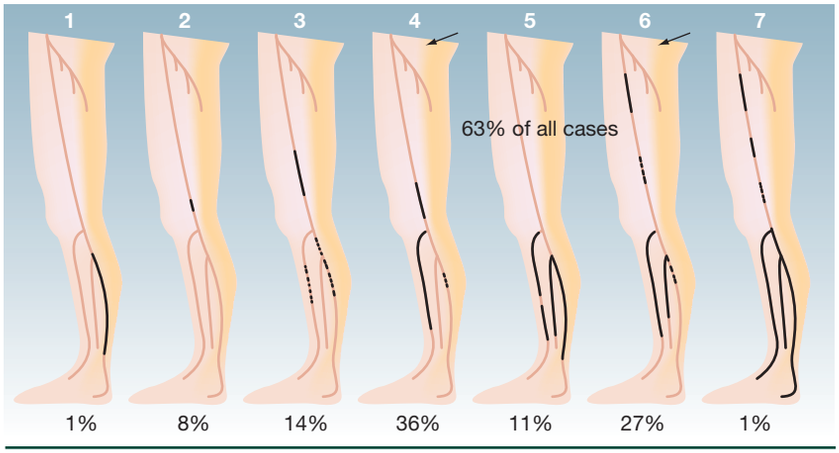

Figure 2. A classification and scoring system based on the severity and sites of involvement of lower limb vessels in diabetic macroangiopathy. The progressive severity of the disease is paralleled by an increasing score. Patterns in 4 and 6 (arrows) represent the most frequent presentations (63% of all cases). Modified with permission from [15].

a rigid interpretation of the signs and symptoms, owing to the frequent comorbidity of these patients, which influences the decision-making process regarding the therapeutic strategy. Thus, the same local condition may lead to different therapeutic options depending on the general conditions of the patient, especially when renal and cardiac insufficiency complicate, which frequently occurs [25].

The wider use of contrast medium, both for coronary and peripheral revascularization increased the number of cases of contrast medium-induced nephropathy, which has been estimated to be among the most frequent causes of acute renal failure in admitted patients [26,27].

Strategies that have been demonstrated to be effective in preventing and treating contrast medium-induced nephropathy include the hydration of patients with saline, the use of bicarbonate and acetyl-cisteine as a detoxificant, and hemofiltration [28,29]. Thanks to these preventive measures and the adoption of advanced technical solutions, such as low-osmolarity contrast media, the dilution of contrast media with saline and the limitation of the number of diagnostic procedures in favor of the 'one-step approach', allowed the extension of revascularization procedures to patients with an impaired renal function [25,30,31].

Another important aspect is related to the risk–benefit ratio of revascularization procedures and to the quality of life of patients. Though the risks related to the interventions have been significantly reduced in the last few years, both surgical and endovascular procedures still have a risk profile, which should be considered in relation to each patient: a bedridden patient with lower limb anchilosis and CLI is not a candidate for a potentially risky revascularizing procedure, but would eventually benefit from a major amputation; the same consideration could be applied to patients with a short life expectancy [32].

On the otherhand, the psychological refusal of amputation may constitute, in some patients, an additional indication for revascularization. In any case, a major amputation should never be performed without an in-depth accurate evaluation of lower limb circulation to explore the possibility of revascularization, performed by a multidisciplinary team involving a diabetologist, a vascular surgeon and a endovascular specialist [33,34].

Endovascular, surgical & combined approaches

The first reports of peripheral revascularization in diabetic patients date back to the early 1980s and are the results of the work carried out at the Vascular Surgery Department of the Deaconess Hospital in Boston (MA, USA). The work demonstrated for the first time that giving direct flow to a foot artery with a pedal surgical bypass was

Table 1. Differences in presentation and clinical manifestation between diabetic macroangiopathy and peripheral arterial disease.

Feature	Diabetic macroangiopathy	Peripheral arterial disease
Age at presentation (years)	40–50	50–60
Sex	No sex prevalence	Male prevalence
Localization	Infrapopliteal	Femoropopliteal
Involvement	Multivessel/bilateral	Single-vessel/monolateral
Collateral circulation	Rare	Frequent
Evolution	Critical limb ischemia	Chronic ischemia
Clinical symptoms	Reduced/absent	Claudication/rest pain
Trophic lesions/necosis	Frequent	Exceptional

Figure 3. Initial presentations of critical limb ischemia in the foot. (A) The skin is pale, there is acrocyanosis but no evident lesion is present. **(B)** An initial necrosis at the margin of the nails of the first, fourth and fifth toes is associated with skin hypotrophy and absence of hair. **(C)** An evident necrosis of the tip of the first and second toe is associated with cyanosis and edema of the whole foot, with dystrophic skin changes.

not only feasible in diabetic patients, but that it was also able to stop the progression of CLI and to produce durable results, changing the fate of a large number of patients who would otherwise be subject to amputation [35,36].

For a long period the surgical approach, consisting of pedal bypass, was considered the standard for treatment of DMA, mainly because of the multidistrictual infrapopliteal localization of the lesions, while the endovascular approach was limited to the femoropopliteal disease, which characterizes PAD. This philosophy was captured in the guidelines produced by both the Intersociety Consensus for the Management of Peripheral Arterial Disease (TASC II), and by the American Heart Association and American College of Cardiology Association Guidelines, which *de facto* contraindicated the endovascular approach for long, multiple and infrapopliteal lesions, the typical pattern of DMA [17,37].

In the late 1990s, thanks to the pioneering results gained from a collaboration between diabetologists and endovascular interventionists in Italy, the endovascular approach was proposed as a valid alternative to traditional surgical techniques. In a seminal multicenter prospective trial, Faglia *et al.* demonstrated that endovascular procedures dramatically reduced the rate of amputations in a large cohort of patients followed for up to 5 years after the procedure [18].

The study had wide resonance – although it elicited some criticism for its design – and more recently other authors have reported similar results, such as DeRubertis *et al.*, who, in a cohort of 1000 patients undergoing percutaneous endovascular revascularization of the lower limb, reported a 2-year success of 80%, concluding that percutaneous transluminal angioplasty (PTA) 'should be considered first-line therapy in patients with chronic lower extremity ischemia' [38].

The application of endovascular techniques extended the possibilities of intervention both transversally owing to its lower risk profile, more patients with more severe systemic conditions were eligible for revascularization, and longitudinally (because of its reproducibility, the procedure could be repeated in a single patient in case of recurrences).

New indications for PTA were set, such as dialysed and geriatric patients, who could benefit from an effective intervention, without running the risks of a major surgical procedure [32,33].

A multicenter prospective trial comparing surgical and endovascular strategies in patients who were suitable for both indications demonstrated a better safety profile for endovascular disease compared with surgery, and furthermore, a reduction in cost [39].

An intention-to-treat analysis of the results of the trial after a 5-year follow-up confirmed the previous results for the whole cohort of

patients, both for amputation-free survival and overall survival, but showed a significant improvement in overall survival in the cohort of patients who survived more than 2 years from revascularization, when treated with bypass compared with those treated with angioplasty [40].

Another aspect of the dissemination of endovascular procedures is related to the development of the techniques and materials, which in produced a significant increase the technical possibilities for many different options in a complex field such as DMA: from subintimal revascularization to the angioplasty of collaterals and the application of drug-eluting stents to cryoplasty, while clinical experience with these techniques has increased, most still lack robust evidence of efficacy [41,42].

In **Figure 4** a typical distal PTA in DMA is shown, while in **Figure 5**, an endovascular solution to restore anastomotic circulation of the forefoot is shown.

Vascular surgery has also changed in recent years, increasing the indications and therapeutic options for patients with DMA. Vascular surgeons are becoming more and more convinced by the usefulness of the endovascular approach [43,44]. A promising option is to treat complex cases, integrating endovascular and traditional surgical techniques. A femoropopliteal by-pass may be integrated with angioplasty of the tibial and peroneal arteries to ensure direct blood flow to the foot and increase the durability of the bypass [45]. Another aspect that has emerged during the last few years is the possibility of repeating a revascularizing procedure in a patient in which a previous one has failed or, as very frequently happens in DMA, following restenosis, which can occur after a period of patency, re-establishing CLI [46].

In many specialized centers there are diabetic patients who have undergone more than one endovascular procedure with different technical solutions, each time with the indication of limb salvage.

The role of medical therapy

Despite the improvement in techniques and the extention of the indications for revascularization, there are still a number of DMA patients for whom revascularization, endovascular or surgical, is not indicated or not feasible, although this is now to a lesser extent than in the past. Contraindications arise from the general condition of the patients, who may be simply too ill to sustain any invasive procedure, or who have

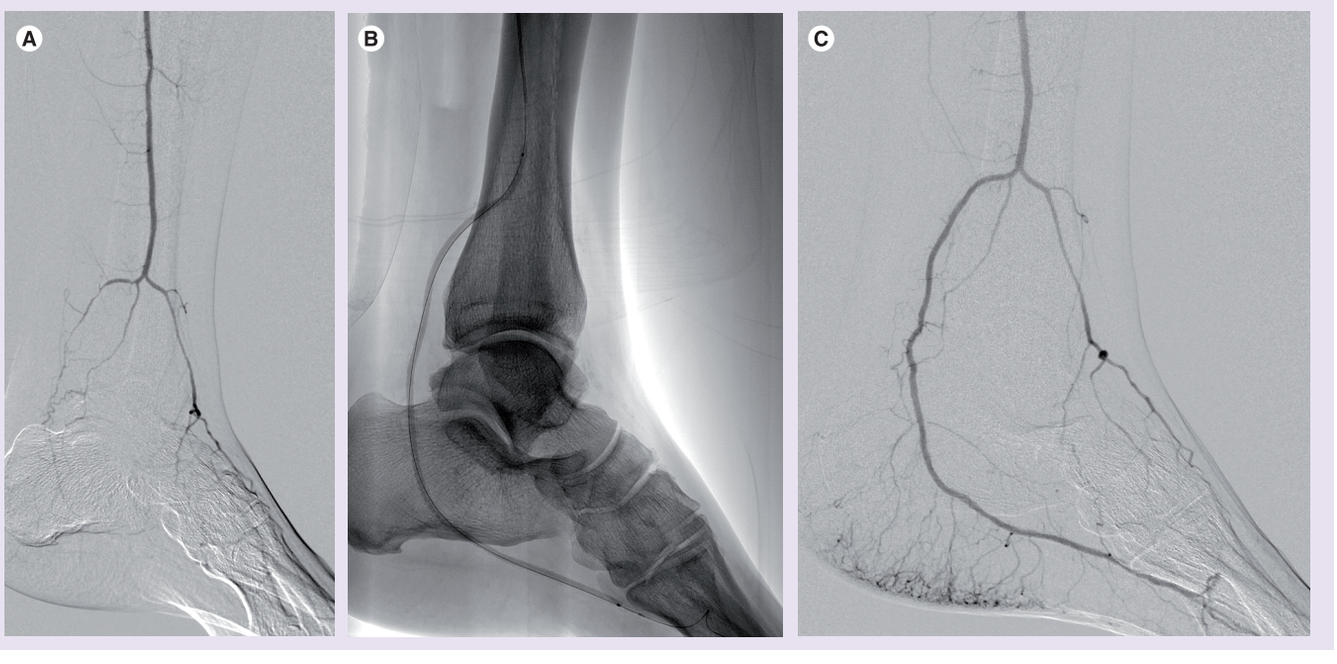

Figure 4. Occlusion of both anterior and posterior tibial artery with typical poor development of collaterals from the patent peroneal artery. (A) The initial attempt of complete tibial arteries recanalization failed. It was then decided to perform balloon angioplasty recanalization of the pedal and plantar arch through a collateral branch with a good result **(B & C)**.

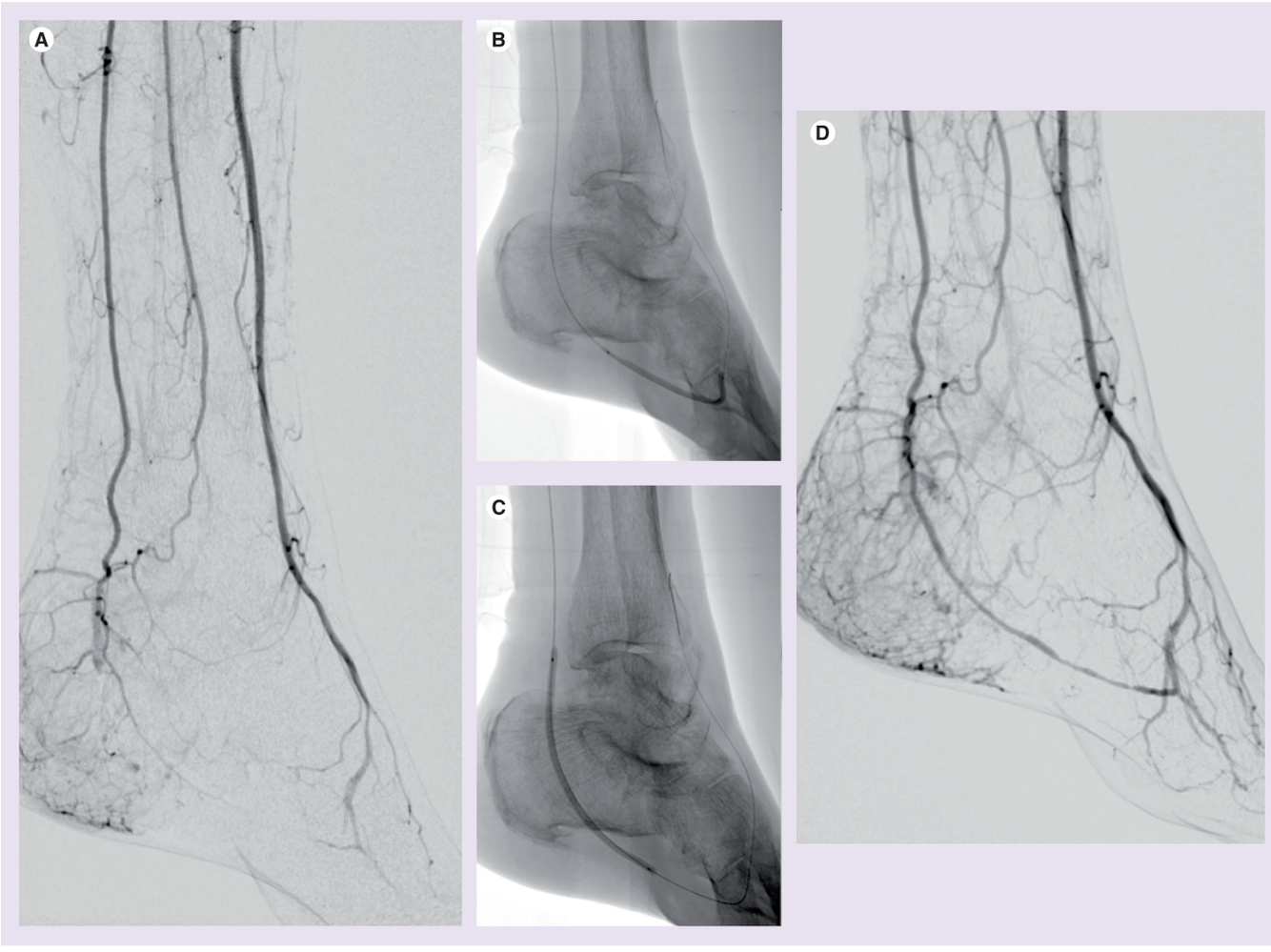

Figure 5. Endovascular reconstruction of the atherosclerotic circulation in the foot. (A) Isolate occlusion of the lateral plantar artery in a diabetic with ischemic heel ulceration. **(B & C)** Angioplasty balloon dilatation, **(D)** with complete recanalization of the plantar arch.

a short life expectancy, or from local vascular conditions, which may be too compromised to allow an intervention.

While in the first case the evaluation is only related to the actual condition of the patient, in the second case it is also related to the expertise of the center that manages the case: depending on their expertise, different specialists would make a different decision in the same situation.

Since experience plays a crucial role from this point of view, it would be advisable that any case in which revascularization has been judged unfeasible would be submitted to a second opinion in a center with documented activity in the field of lower limb revascularization in DMA [34].

In the cases where it is impossible to perform revascularization, there are options that can be evaluated as alternatives to a major amputation.

Iloprost has been proven to reduce the rate of amputation and to extend the survival of limbs in DMA patients with CLI, both as an alternative to revascularzation and as an adjunct [47,48]. In a cohort of patients with DMA not suitable for vascular reconstruction, Melillo *et al.* demonstrated how repeated cycles of iloprost infusion were able to improve $TcPO_2$ and save the limb of a significant number of patients, also reducing rest pain [49]. Iloprost infusion has been confirmed as a suitable option in cases of impossible revascularization in the TASC II guidelines [17].

A very important issue is represented by the antithrombotic therapy in patients with DMA, both as an adjuvant to revascularizations and as a medical chronic therapy *per se*. Despite its relevance, no definitive evidence is available in

diabetic patients with peripheral arterial disease, although a variety of therapeutic regimens have been proposed [50–52].

Antiplatelet therapy has been proven to be effective in reducing acute cardiovascular events in diabetic patients with multidistrict macroangiopathy, and to extend the duration of revascularizations in a significant number of trials, long-term administration in these patients is recommended by the Diabetologic Societies' guidelines [17,37,53].

Nevertheless, there is not yet a definitive agreement as far as agents, doses or associations of drugs are concerned, although the majority of authors favor the use of more than one agent in diabetic patients with DMA [54–56].

Anticoagulants have a limited role in patients with multiple involvement of both the peripheral and carotid region, to prevent stroke, especially when chronic myocardial ischemia is present [57,58].

Low molecular weight heparins have been proposed as a possible alternative to revascularization when ischemic pain is present and the quality of patients is impaired [58], and a multicenter prospective trial is ongoing to challenge this hypothesis.

Hyperbaric oxygen therapy was proposed as etiologic treatment for CLI before endovascular revascularization became available for the majority of cases; despite its frequent use, evidence to support use of hyperbaric oxygen therapy as a first-line treatment in CLI is scarce. Instead, a complementary application, to maximize the effect of revascularization, has been proposed in DMA patients with CLI [59–61].

Local & systemic management of the ischemic diabetic foot patient

As the EURODIALE study recently confirmed, peripheral ischemia is frequently associated with infection in diabetic patients and the consequences of this association will most probably result in a major amputation, while the frequent association of systemic comorbidities exposes patients to a higher risk of mortality [5,6]. Thus, any realistic treatment strategy for these patients has to encompass both the management of the local aspects of the pathology at the level of the foot and the systemic aspects of the disease.

At the level of the foot ischemia not only causes a higher prevalence of infections, which range from superficial soft tissue to deep facial infection (from abscesses to osteomyelitis), but also ischemic necrosis of segments of the foot.

All of these conditions require a surgical approach, aimed at draining and debriding in the case of infection, and in eliminating the necrosis in the case of necrosis or gangrene [62]. Thus, surgery plays a crucial role in the treatment of the ischemic diabetic foot, alongside, and in conjunction with, revascularization: its application should be aimed at restoring the function of the revascularized foot, eliminating the parts of it that are no longer viable, and reconstructing an organ that is biomechanically effective [63]. In **Figure 6** a clinical case is reported as an example.

The coordination of the surgical management of the foot with revascularization procedures is also important. While in the case of necrosis the surgical intervention is usually performed after the revascularization, to benefit from restored vascular conditions, in the case of acute infection or gangrene, surgery should be performed as soon as possible to avoid the local spread of pathology and systemic consequences. In a cohort of patients with infection or gangrene, Faglia *et al.* demonstrated that those who received surgical intervention within 24 h of diagnosis had a more favorable outcome than those in which the intervention was delayed [64].

The management of the systemic aspects of the pathology plays a crucial role not only in ensuring the success of the actual condition of the patients, but also in improving their prognosis, since it has been noted that the mortality rate of these patients is higher than that of many forms of cancer [65].

Evaluating cardiovascular, renal and general metabolic condition of patients at admission, stabilizing and monitoring them throughout the clinical management is essential, especially when renal or left ventricular insufficiency is present. This, in view not only of the high mortality rate, but also of the low prevalence of symptoms due to the presence of peripheral neuropathy, is a warranty for the patient [66,67].

Evaluation of outcomes

From a patient's perspective, amputation-free survival, healing of ulceration, relief of pain and prevention of recurrences have to be considered the most important markers of success of revascularization of lower limbs, although they are poorly quantifiable and need to be integrated by qualitative measures.

Until recently, as is still reflected in the actual guidelines, the success of revascularizing interventions was measured by the patency of the vessels treated, irrespectively of the actual clinical

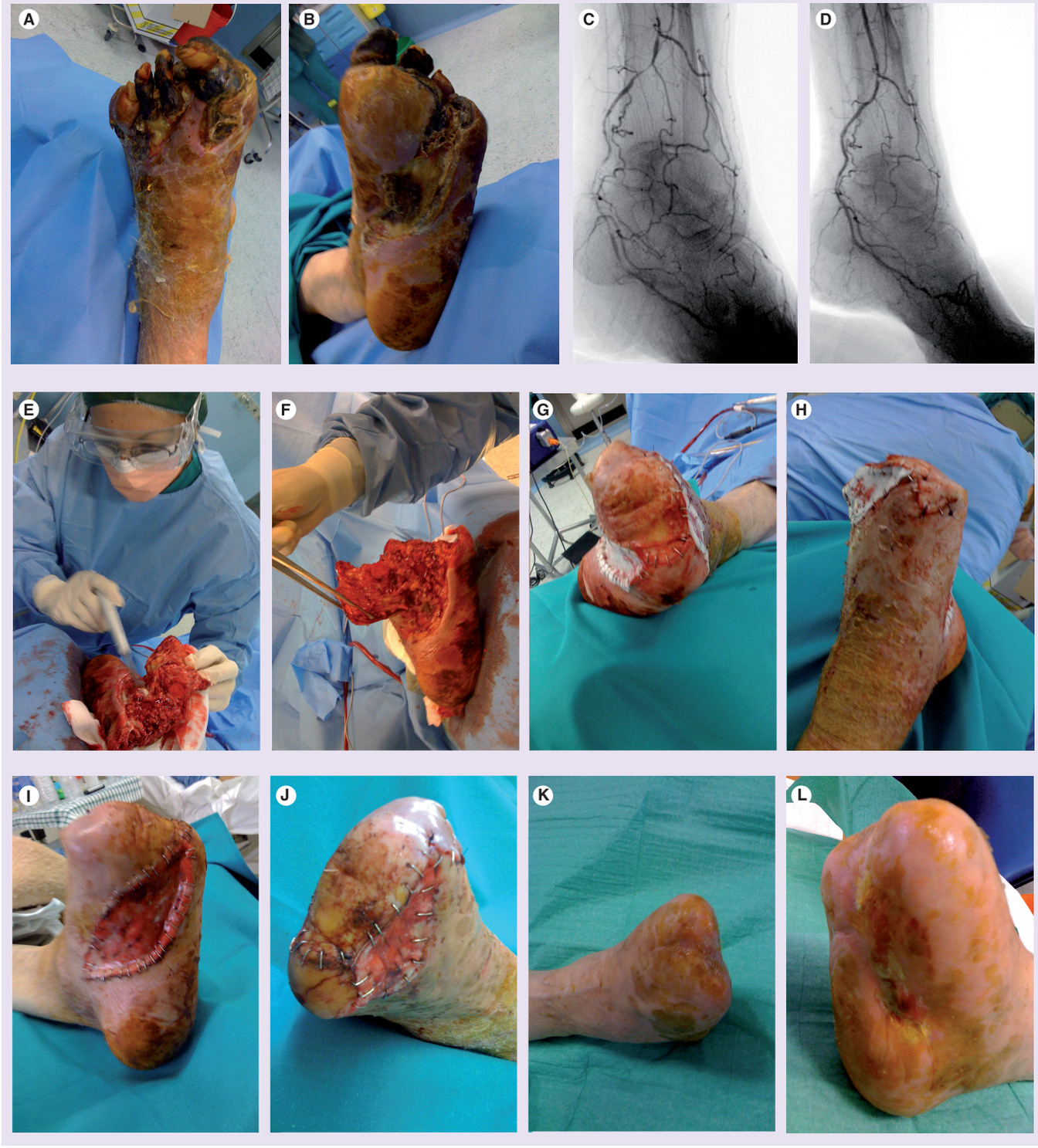

Figure 6. A case describing the integrated approach to complex ischemic foot. The foot presents with forefoot gangrene **(A)** associated with plantar fascitis and necrosis **(B)**. The angiography shows severely compromised circulation in the foot **(C)**, which can be restored with distal percutaneous transluminal angioplasty **(D)**. The day after the endovascular revascularization the patient undergoes an extensive demolitive debridement **(E & F)**, along with reconstruction in the same surgical step, with rotational flaps and dermal substitutes **(G & H)**. After 15 days the foot shows good signs of recovery **(I & J)**, and after 2 months is completely healed **(K & L)**.

outcomes [68]. This way of looking at things, beyond being reductive as it does not take into account the reason the procedure has been performed, is particularly difficult to apply to DMA, a multilevel vascular condition in which the choice of treating one vessel instead of another one depends on the local conditions, the expertise of the surgeon and by the vascular anatomy, where the artery feeding the lesion is to be preferred [46].

In more recent times, owing to clinical trials performed in large cohorts of patients, a new and more rational approach to the evaluation of revascularization has been developed, which takes into account the clinical conditions and the functional parameters in addition to the technical outcomes [69].

The Ankle-Brachial Pressure Index (ABPI) has long been the parameter of reference when assessing the vascular conditions of the limb; unfortunately, 20–25% of DMA patients have vascular calcifications that interfere with pressure determination at the ankle, making ABPI inadequate [70].

Transcutaneous oxygen tension measured at the dorsum of the foot has replaced ABPI in diabetic patients as a trustworthy indicator of local vascular conditions: it is a noninvasive measurement that measures the O_2 concentration in tissues, as a variable dependent on local vascular supply. When accurately performed it has been demonstrated to correlate with clinical outcomes and limb salvage [71].

Skin temperature, monitored with an infrared thermometer, is also a reliable indicator of blood supply, although less precise than $TcPO_2$, and can be considered as an integrated measure for evaluating the results of revascularization [72].

The local condition of the lesions are important to evaluate the success of a revascularizion procedure. Sheehan *et al.* demonstrated that the reduction of the ulcer's area in the first weeks after intervention can be a reliable predictor of outcome in diabetic patients [73]. Area, depth and local conditions of the lesions, as well as the persistence of pain, are part of the clinical evaluation of the procedures and can all be integrated in a decisional grid, which may help in the strict follow-up that such patients require **(Table 2)** [74].

The longitudinal observation of the features of the lesions, and their stratification according to the Texas University Score System (TUSS) is another important point to take into account, since a change in the TUSS can be considered an indication of improvement or deterioration of local perfusion [75].

The Texas University Score System identifies four worsening types of lesions, from 0 (no open lesion) to 3 (lesion penetrating to the joint or bone), further characterized by a letter: A (no ischemia, no infection), B (infection), C (ischemia) and D (ischemia and infection), which takes into account the presence of these conditions that may complicate healing of the ulceation at any level of tissue involvement. The TUSS has been validated in a large DF population and it has been shown to reliably identify and stratify DF patients according to their amputative risk [75].

Recently, data from many countries demonstrated a consistent reduction of major amputation in DF patients; although it would be difficult to evaluate all the possible contributors to this important result, at least in one case the parallel increase of revascularization procedures at lower limbs has been correlated with the significant reduction of lower extremity amputation over a 5-year follow-up [7,76].

Conclusion

Revascularization represents the first-line therapy for the critically ischemic DF, and its implementation in the integrated management of this pathology favorably changed the prognosis of patients.

Table 2. Decision grid for the clinical evaluation of a revascularization procedure.

Feature	Successful	Consider a re-PTA	Consider amputation
$\Delta TcPO_2$	>30 mmHg	30–10 mmHg	<10 mmHg
Wound area	Reduced	Unchanged	Increased
Δ skin temperature	>3°C	3–1°C	<1°C
Cyanosis†	Absent	Present	Increased
Necrosis†	Absent	Present	Increased
Pain†	Absent	Present	Increased

†If present at baseline.
PTA: Percutaneous transluminal angioplasty; $TcPO_2$: Transcutaneous oxygen tension.
Modified with permission from [74].

Endovascular procedures, in our opinion, should be considered as a first choice in DMA patients because of their wider indication profile, repeatability and safety, however, surgical and combined approaches should be evaluated by a multidisciplinary team when CLI is present.

The indications for the revascularization and the evaluation of results should take the clinical condition of the patients into account and not rely only on the vascular pattern as described by angiography.

Due to the coexisting comorbidities, revascularization, local surgery and systemic management of the patients should be considered as in integral part of the therapeutic approach and critical patients should preferably be referred to specialized centers with a documented expertise in the field in order to be managed according to the best clinical practice guidelines before considering a major amputation.

Future perspective

The increasing incidence of Type 2 DM and of its chronic complications, as well as the longer life expectancy of DM patients, will lead to a fourfold increase in the number of lower limb complications. Half of these patients will suffer ischemic problems, which frequently affect both peripheral, cardiac and carotid vessels, and which should be considered as a emergency, at least from a caregiver point of view, because of the expected increase in major amputations and deaths.

Limb-salvaging and life-saving treatment of this disease will not only change the prospects of a large number of patients, but will also contribute to saving money and resources that would otherwise be used to manage amputees.

Endovascular techniques and local conservative surgery used in the management of the severely ill diabetic patient may become the standard of care in the next 10 years for ischemic DF patients in highly specialized centers, which will be committed to DF.

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▪▪ **Demonstrates that together infection and ischemia are responsible for the poor prognosis of diabetic foot (DF) patients.**

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