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CICLO XX

Clinical and technical aspects in the multidisciplinary management of peripheral arterial disease: limb salvage by means of integrated care strategy with percutaneous angioplasty in the treatment of critical limb ischemia

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SUMMARY

INTRODUCTION AND AIM OF THE STUDY: Percutaneous transluminal angioplasty (PTA) has revolutionized the management of peripheral arterial disease. Even in the setting of critical limb ischemia (CLI), similar outcomes have been obtained when PTA and bypass surgery are compared. With PTA, local anesthesia can be used, hospital stay is shorter, and morbidity and mortality rates may be lower. The best results may be achieved when the revascularization with PTA is a part of a strategy of integrated care. Aim of this study was to assess the feasibility of this strategy and to evaluate the mid-term results, mainly in terms of mortality, limb salvage (LS), progression of disease (DP), and need of further revascularizations. **METHODS**: Between January 2007 and June 2008, 105 patients with 137 critical arterial lesions (137 limbs) underwent elective PTA for CLI in one single centre (Clinique Pasteur – Toulouse – France). The decision to perform PTA was jointly considered by vascular specialist, interventional cardiologist and vascular surgeon. Arterial lesions were codified according to TASC classification, and the arterial tree was categorized into three groups: the aorta and iliac arteries (A-I), the common, superficial and profunda femoral arteries (Fem), and the popliteal and tibial arteries (Pop-Tib). Clinical follow-up was obtained for all patients by office visit or direct telephone call. Periodical non-invasive assessment with duplex ultrasound was systematically performed at 1, 3 and 6 months. All angiographic controls were ischemia-driven. **RESULTS**: The mean age was 77±10 years, 59 patients (56.2%) were males and 58 (55.2%) were diabetic. Eighty-nine patients (84.8%) were hypertensive, 57 (54.3%) had dyslipidemia, and 71 (67.6%) had significant renal disease. Ten patients (9.5%) had a previous peripheral graft. History of coronary artery disease (CAD) was present in 35 (33.3%) patients and history of cardiac heart failure in 28 (26.7%). Mean left ventricular ejection fraction (LVEF) was 56±10%. Indication to PTA was rest pain with non-healing ulcer in 96 patients (91.4%) and with gangrene in 9 (8.6%). Mean Hct value was 36±5%, mean C reactive protein (CRP) 41±59 mg/l, mean

fibrinogen 4.4±1.2 g/l and mean pro-BNP 2343±4278 pg/ml. Five lesions (3.6%) were included in A-I group, 60 (43.8%) in Fem group, and 68 (49.6%) in Pop-Tib group. In four cases (2.9%) PTA concerned lesions in previous grafts. Concerning TASC classification, lesions were mostly type B3 (71.5%) and type C1 (13.9%). Mean lesion diameter was 5.3±1.7 mm and mean lesion length was 55±32 mm. Balloon angioplasty was performed in 127 (92.7%) lesions and stent implantation was required in 81 (59.1%). Mean stent diameter was 6±1.4 mm and mean stent length was 69±44 mm. Subintimal angioplasty was performed to treat occlusions in 46/77 cases (59.7%). Procedural success was achieved in 125 lesions (91.2%). There were 3 (2.2%) procedural complications and 2 in-hospital death (1.9%). The mean hospital stay was 5.3±4.7 days. Clinical follow-up was available for 100% of patients over a mean of 304±161 days. At follow-up, 26 patients (24.8%) had died, 20 (19%) of them for cardiovascular causes. Twelve patients (11.4%) were amputated, and 7 of them (58.3%) were still alive. LS was achieved in 124 (90.5%) limbs. Target lesion revascularization (TLR) was performed in 12 lesions (8.8%) and DP was found in 19 (13.9%). Continuing CLI was found in 15 patients (14.3%). Independent predictors of mortality were LVEF<60% and a level of plasma fibrinogen≥4.3 g/l. TLR was associated with smoking habit, dyslipidemia, a previous peripheral graft, and higher plasmatic levels of pro-BNP. DP was associated with a higher prevalence of CAD, the presence of a significant renal disease and placement of shorter stents. LS was associated with lower plasmatic levels of CRP. **CONCLUSIONS**: PTA in the treatment of CLI is safe, with favourable in-hospital and mid-term outcomes, especially when considered as a part of a strategy of integrated care. Despite its high mortality rate, partly due to the mean age of the population and the presence of significant comorbidities, the high rate of LS and the low TLR rate underline the role of this reperfusion strategy even in a subset of fragile patients with severe and diffused PAD. Moreover, this data confirms that patients with severe arterial disease are prone to die mostly due to cardiac causes and that inflammatory and infection markers may be useful in the pre-procedural risk stratification.

RIASSUNTO

INTRODUZIONE E SCOPO DELLO STUDIO: l'angioplastica transluminale percutanea (PTA) ha rivoluzionato il trattamento dell'arteriopatia periferica. Persino nei casi d'ischemia critica dell'arto (CLI), sono stati ottenuti risultati paragonabili a quelli della chirurgia. La PTA consente l'uso dell'anestesia locale, il periodo di ricovero è più breve, morbilità e mortalità si riducono. I risultati migliori vengono raggiunti quando la rivascolarizzazione con PTA è inserita in una strategia di assistenza globale. Lo scopo di questa tesi era accertare la fattibilità di tale strategia e valutarne i risultati a medio termine, in particolare concernenti la mortalità, il salvataggio dell'arto (LS), la progressione della malattia (DP) e la necessità di nuove rivascolarizzazioni. **METODI**: Nel periodo tra gennaio 2007 e giugno 2008, 105 pazienti con 137 lesioni arteriose critiche (137 gambe) sono stati sottoposti a PTA elettiva per CLI in uno stesso centro (Clinique Pasteur – Toulouse – France). La decisione di eseguire la PTA era presa congiuntamente dall'angiologo, dal cardiologo interventista e dal chirurgo vascolare. Le lesioni arteriose erano codificate secondo la classificazione della TASC, e l'albero arterioso era stato inoltre suddiviso in tre parti: l'aorta e le arterie iliache (A-I), l'arteria femorale comune, superficiale e profonda (Fem), e le arterie poplitee e tibiali (Pop-Tib). Il follow-up clinico è stato ottenuto tramite visite ambulatoriali o conversazione telefonica. Una valutazione periodica non-invasiva mediante eco-doppler veniva eseguita al primo, terzo e sesto mese dalla procedura. I controlli angiografici venivano eseguiti in caso di persistenza dell'ischemia critica. **RISULTATI**: L'età media della popolazione studiata era 77±10 anni, 59 pazienti (56.2%) erano maschi e 58 (55.2%) diabetici. Ottantanove pazienti (84.8%) erano ipertesi, 57 (54.3%) affetti da dislipidemia, e 71 (67.6%) avevano una rilevante alterazione della funzione renale. Dieci pazienti (9.5%) erano già stati sottoposti a un precedente intervento chirurgico di bypass. Una storia di malattia coronarica (CAD) riguardava 35 (33.3%) pazienti e 28 (26.7%) avevano un'anamnesi positiva per scompenso cardiaco. La frazione di

eiezione ventricolare sinistra (LVEF) media era 56±10%. L'indicazione a eseguire la PTA era la presenza di dolori a riposo associata a ulcere persistenti in 96 pazienti (91.4%) e a gangrena in 9 (8.6%). Il valore medio di Hct era 36±5%, il valore medio di proteina C reattiva (CRP) era 41±59 mg/l, quello di fibrinogeno plasmatico 4.4±1.2 g/l e quello di pro-BNP 2343±4278 pg/ml. Cinque lesioni (3.6%) facevano parte del gruppo A-I, 60 (43.8%) del gruppo Fem, e 68 (49.6%) del gruppo Pop-Tib. In 4 casi (2.9%) la PTA riguardava lesioni in precedenti bypass. Riguardo alla classificazione della TASC, le lesioni erano perlopiù di tipo B3 (71.5%) e di tipo C1 (13.9%). Il diametro medio delle lesioni era 5.3±1.7 mm e la lunghezza media 55±32 mm. La PTA col pallone è stata eseguita in 127 (92.7%) lesioni e il posizionamento di uno stent è stato necessario in 81 (59.1%). Il diametro medio dello stent era 6±1.4 mm e la lunghezza media 69±44 mm. L'angioplastica con tecnica subintimale per il trattamento delle occlusioni è stata utilizzata in 46/77 casi (59.7%). Il successo immediato al termine della procedura è stato ottenuto in 125 lesioni (91.2%). Si sono verificati 2 (1.9%) decessi intra-ospedalieri e 3 (2.2%) complicazioni procedurali. Il tempo medio di ricovero è stato di 5.3±4.7 giorni. Il follow-up clinico è stato possibile nel 100% dei pazienti a una media di 304±161 giorni dalla procedura. Al follow-up, 26 pazienti (24.8%) erano morti, 20 (19%) di essi per cause cardiovascolari. Dodici pazienti (11.4%) erano stati amputati, e 7 di essi (58.3%) erano ancora vivi. Il LS è stato ottenuto per 124 gambe (90.5%). La rivascolarizzazione nel precedente sito della PTA (TLR) è stata eseguita in 12 lesioni (8.8%), e una progressione di malattia è stata riscontrata in 19 (13.9%). La persistenza di CLI è stata rilevata in 15 pazienti (14.3%). Una LVEF<60% e un valore plasmatico di fibrinogeno≥4.3 g/l erano predittori indipendenti di mortalità. La TLR era associata con il fumo, la dislipidemia, un precedente bypass ed elevati valori di pro-BNP. La progressione di malattia era associata con una più alta prevalenza di CAD, la presenza di una rilevante alterazione della funzione renale e il posizionamento di stents più corti. Il salvataggio dell'arto era associato a bassi livelli plasmatici di CRP. **CONCLUSIONI**: L'uso della PTA nel trattamento della CLI è sicuro, con risultati favorevoli

sia durante il ricovero che nel breve termine, specialmente quando inserita in una strategia di assistenza globale al paziente. Nonostante l'elevato tasso di mortalità, in parte dovuto all'età media della popolazione e alla presenza di rilevanti co-morbidità, l'alto tasso di LS e il basso tasso di TLR sottolineano il ruolo di tale strategia di riperfusione, persino nei pazienti fragili, con arteriopatia severa e diffusa. Inoltre, questi dati confermano che nei pazienti con arteriopatia grave, la principale causa di morte è costituita dagli eventi cardiovascolari, e che i markers infiammatori e infettivi possono essere utili nella stratificazione del rischio pre-procedurale.

ANATOMY OF PERIPHERAL ARTERIES[1]

Bifurcation of abdominal aorta and common iliac arteries

The abdominal aorta divides, on the left side of the body of the fourth lumbar vertebra, into the two common iliac arteries (Fig.1). Each is about 5 cm in length. They diverge from the termination of the aorta, pass downward and lateralward, and divide, opposite the intervertebral fibrocartilage between the last lumbar vertebra and the sacrum, into two branches, the external iliac and hypogastric arteries; the former supplies the lower extremity; the latter, the viscera and parietes of the pelvis. The right common iliac artery is somewhat longer than the left, and passes more obliquely across the body of the last lumbar vertebra. In front of it are the peritoneum, the small intestines, branches of the sympathetic nerves, and, at its point of division, the ureter. Behind, it is separated from the bodies of the fourth and fifth lumbar vertebræ, and the intervening fibrocartilage, by the terminations of the two common iliac veins and the commencement of the inferior vena cava. Laterally, it is in relation, above, with the inferior vena cava and the right common iliac vein; and, below, with the Psoas major. Medial to it, above, is the left common iliac vein.

The left common iliac artery is in relation, in front, with the peritoneum, the small intestines, branches of the sympathetic nerves, and the superior hemorrhoidal artery; and is crossed at its point of bifurcation by the ureter. It rests on the bodies of the fourth and fifth lumbar vertebræ, and the intervening fibrocartilage. The left common iliac vein lies partly medial to, and partly behind the artery; laterally, the artery is in relation with the Psoas major.

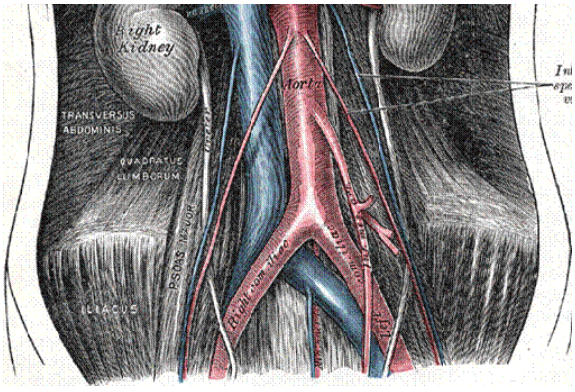


Fig. 1
Bifurcation of abdominal aorta and common iliac arteries

Hypogastric artery

The hypogastric artery (Fig. 2) supplies the walls and viscera of the pelvis, the buttock, the generative organs, and the medial side of the thigh. It is a short, thick vessel, smaller than the external iliac, and about 4 cm in length. It arises at the bifurcation of the common iliac, opposite the lumbosacral articulation, and, passing downward to the upper margin of the greater sciatic foramen, divides into two large trunks, an anterior and a posterior.

External iliac artery

The external iliac artery (Fig. 2) is larger than the hypogastric, and passes obliquely downward and lateralward along the medial border of the Psoas major, from the bifurcation of the common iliac to a point beneath the inguinal ligament, midway between the anterior superior spine of the ilium and the symphysis pubis, where it enters the thigh and becomes the femoral artery.

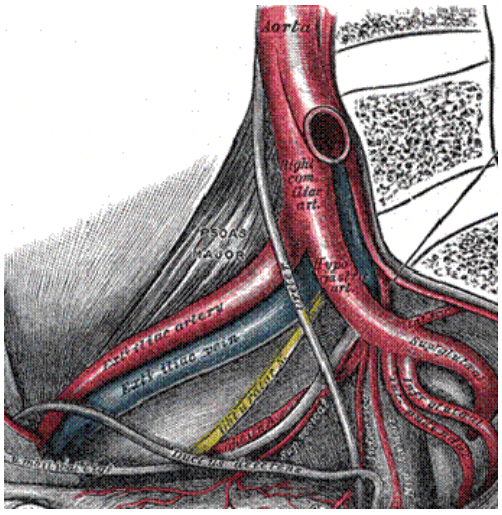


Fig. 2
External iliac and hypogastric arteries

Arteries of the lower extremity

The artery which supplies the greater part of the lower extremity is the direct continuation of the external iliac. It runs as a single trunk from the inguinal ligament to the lower border of the Popliteus, where it divides into

two branches, the anterior and posterior tibial. The upper part of the main trunk is named the femoral, the lower part the popliteal.

Femoral artery (superficial and profunda)

The femoral artery (Fig. 3) begins immediately behind the inguinal ligament, midway between the anterior superior spine of the ilium and the symphysis pubis, and passes down the front and medial side of the thigh. It ends at the junction of the middle with the lower third of the thigh, where it passes through an opening in the Adductor magnus to become the popliteal artery. The vessel, at the upper part of the thigh, lies in front of the hip-joint; in the lower part of its course it lies to the medial side of the body of the femur, and between these two parts, where it crosses the angle between the head and body, the vessel is some distance from the bone. The first 4 cm of the vessel is enclosed, together with the femoral vein, in a fibrous sheath—the femoral sheath. In the upper third of the thigh the femoral artery is contained in the femoral triangle (*Scarpa's triangle*), and in the middle third of the thigh, in the adductor canal (*Hunter's canal*).

The profunda femoris artery (a. profunda femoris; deep femoral artery) (Fig. 3) is a large vessel arising from the lateral and back part of the femoral artery, from 2 to 5 cm below the inguinal ligament. At first it lies lateral to the femoral artery; it then runs behind it and the femoral vein to the medial side of the femur, and, passing downward behind the Adductor longus, ends at the lower third of the thigh in a small branch, which pierces the Adductor magnus, and is distributed on the back of the thigh to the hamstring muscles. The terminal part of the profunda is sometimes named the fourth perforating artery.

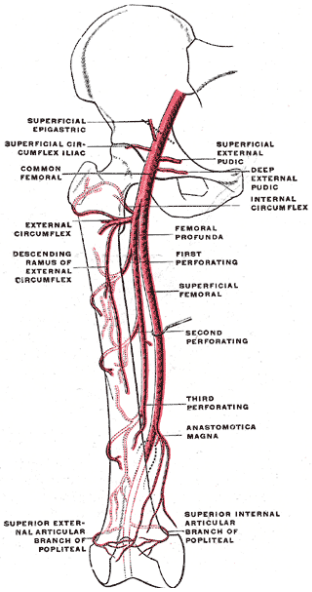


Fig. 3

Scheme of the femoral artery

Popliteal artery

The popliteal artery (Fig. 4) is the continuation of the femoral, and courses through the popliteal fossa. It extends from the opening in the Adductor magnus, at the junction of the middle and lower thirds of the thigh, downward and lateralward to the intercondyloid fossa of the femur, and then vertically downward to the lower border of the Popliteus, where it divides into anterior and posterior tibial arteries.

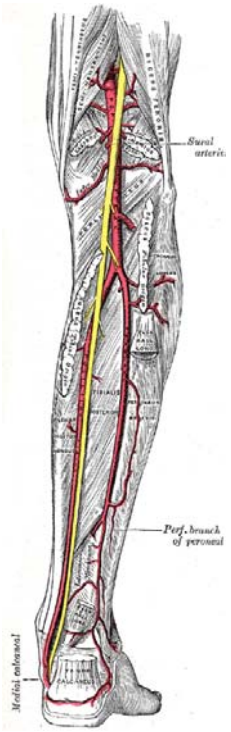


Fig. 4

The popliteal, posterior tibial, and peroneal arteries

Anastomosis around the knee-joint

Around and above the patella, and on the contiguous ends of the femur and tibia, is an intricate net-work of vessels forming a superficial and a deep plexus (Fig. 5). The superficial plexus is situated between the fascia and skin around about the patella, and forms three well-defined arches: one, above the upper border of the patella, in the loose connective tissue over the Quadriceps femoris; the other two, below the level of the patella, are situated in the fat behind the ligamentum patellæ. The deep plexus, which forms a close net-work of vessels, lies on the lower end of the femur and upper end of the tibia around their articular surfaces, and sends numerous offsets into the interior of the joint. The arteries which form this plexus are the two medial and the two lateral genicular branches of the popliteal, the highest genicular, the descending branch of the lateral femoral circumflex, and the anterior recurrent tibial.

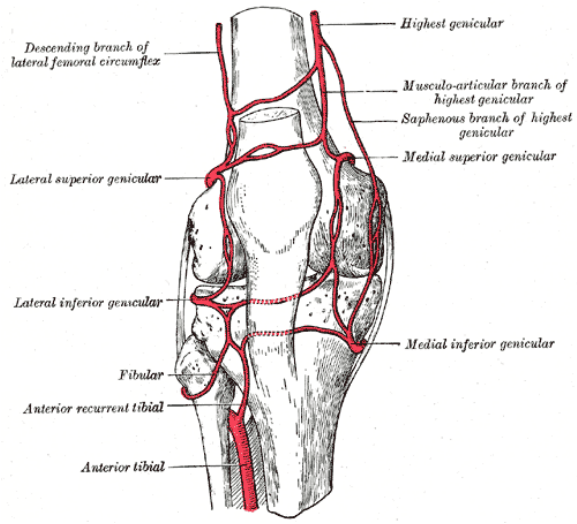


Fig. 5
Circumpatellar anastomosis

Anterior tibial artery

The anterior tibial artery (Fig. 6) commences at the bifurcation of the popliteal, at the lower border of the Popliteus, passes forward between the two heads of the Tibialis posterior, and through the aperture above the upper border of the interosseous membrane, to the deep part of the front of the leg: it here lies close to the medial side of the neck of the fibula. It

then descends on the anterior surface of the interosseous membrane, gradually approaching the tibia; at the lower part of the leg it lies on this bone, and then on the front of the ankle-joint, where it is more superficial, and becomes the dorsalis pedis. The arteria dorsalis pedis, the continuation of the anterior tibial, passes forward from the ankle-joint along the tibial side of the dorsum of the foot to the proximal part of the first intermetatarsal space, where it divides into two branches, the first dorsal metatarsal and the deep plantar.

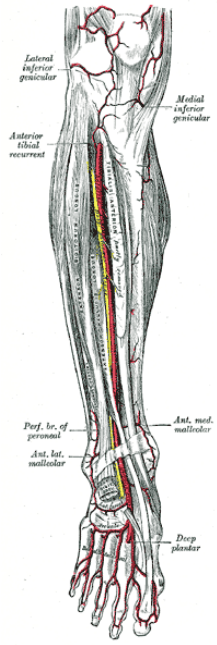


Fig. 6
Anterior tibial and dorsalis pedis arteries

Posterior tibial artery

The posterior tibial artery (Fig. 4) begins at the lower border of the Popliteus, opposite the interval between the tibia and fibula; it extends obliquely downward, and, as it descends, it approaches the tibial side of the leg, lying behind the tibia, and in the lower part of its course is situated midway between the medial malleolus and the medial process of the calcaneal tuberosity. Here it divides beneath the origin of the Adductor hallucis into the medial and lateral plantar arteries (Figs. 7 and 8)

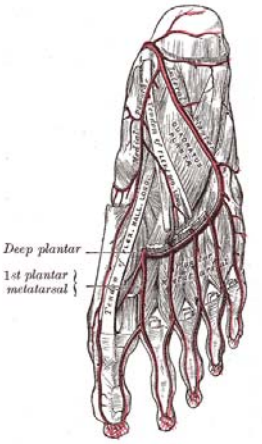


Fig. 7
The plantar arteries.
Deep view

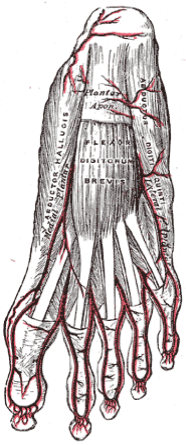


Fig. 8
The plantar arteries.
Superficial view

Peroneal artery

The peroneal artery (a. peronæa) (Fig. 4) is deeply seated on the back of the fibular side of the leg. It arises from the posterior tibial, about 2.5 cm below the lower border of the Popliteus, passes obliquely toward the fibula, and then descends along the medial side of that bone, contained in a fibrous canal between the Tibialis posterior and the Flexor hallucis longus, or in the substance of the latter muscle. It then runs behind the tibiofibular syndesmosis and divides into lateral calcaneal branches which ramify on the lateral and posterior surfaces of the calcaneus (Figs. 7 and 8 – deep and superficial views). It is covered, in the *upper* part of its course, by the Soleus and deep transverse fascia of the leg; *below,* by the Flexor hallucis longus.

PREVALENCE OF PERIPHERAL ARTERIAL DISEASE

Asymptomatic PAD

Total disease prevalence has been evaluated in several epidemiologic studies and is in the range of 3% to 10%, increasing to 15% to 20% in persons over 70 years [2, 3]. The most widely used test to estimate the prevalence of asymptomatic PAD in the leg is the measurement of the ankle-brachial systolic pressure index (ABI). A resting ABI of ≤0.90 is caused by hemodynamically-significant arterial stenosis and is most often used as a hemodynamic definition of PAD. In symptomatic individuals, an ABI ≤0.90 is approximately 95% sensitive in detecting arteriogram-positive PAD and almost 100% specific in identifying healthy individuals. Using this criterion, several studies have looked at symptomatic and asymptomatic PAD patients in the same population. The ratio of the two is independent of age and is usually in the range of 1:3 to 1:4. The Edinburgh Artery Study found that, using duplex scanning, a third of the patients with asymptomatic PAD had a complete occlusion of a major artery to the leg[4]. In autopsies of unselected adults, 15% of men and 5% of women who were asymptomatic, had a 50% or greater stenosis of an artery to the leg. It is interesting to compare this with the finding that 20% to 30% of subjects with complete occlusion of at least one coronary artery on autopsy are asymptomatic. It can be concluded that for every patient with symptomatic PAD there are another three to four subjects with PAD who do not meet the clinical criteria for intermittent claudication (IC).

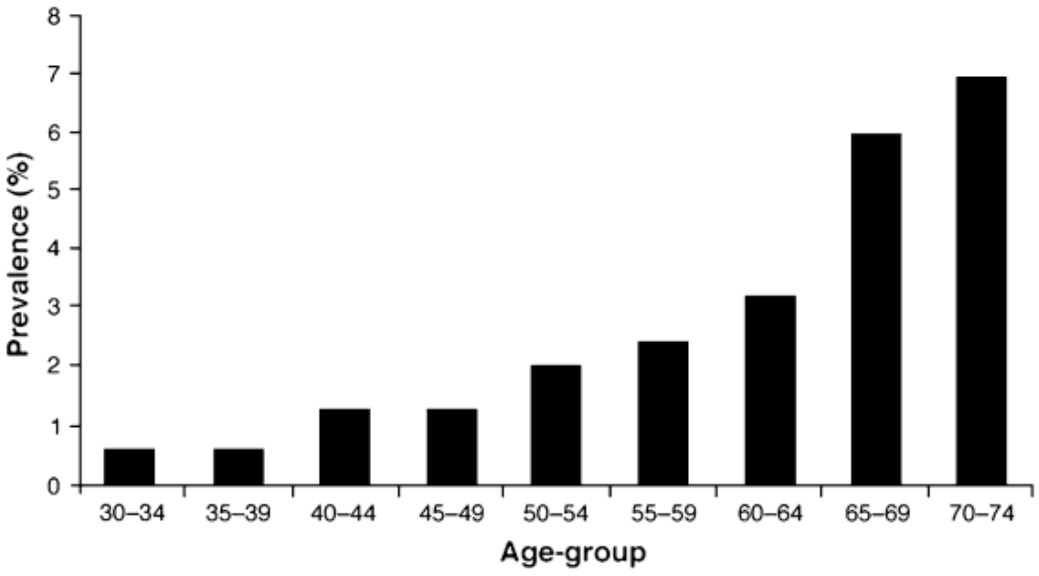
Symptomatic PAD

IC is usually diagnosed by a history of muscular leg pain on exercise that is relieved by a short rest, but it must be remembered that while it is the main symptom of PAD, its measurement does not always predict the presence or absence of PAD. Patients with quite severe PAD may not have IC because other condition limits exercise or they are sedentary. In contrast, some patients with what seems to be IC may not have PAD (for example, spinal stenosis can produce symptoms like IC in the absence of

vascular disease). Likewise, patients with very mild PAD may develop symptoms of IC only when they become very physically active. The prevalence of IC would appear to increase from about 3% in patients aged 40 to 6% in patients aged 60 years. Several large population studies have looked at the prevalence of IC and Figure 9 shows a calculated mean prevalence weighted by study sample size[5]. In the relatively younger age groups, claudication is more common in men but at older ages there is little difference between men and women. A surprising finding in population screening studies is that between 10% and 50% of patients with IC have never consulted a doctor about their symptoms[5].

Fig. 9

Weighted mean prevalence of IC (symptomatic PAD) in large population-based studies



RISK FACTORS AND FACTORS ASSOCIATED WITH PAD

Gender

The prevalence of symptomatic or asymptomatic PAD is slightly greater in men than in women, particularly in the younger age groups. In patients with IC, the ratio of men to women is between 1:1 and 2:1. In some

studies this ratio increases to 3:1 in more severe stages of the disease, such as chronic critical limb ischemia (CLI). Other studies have, however, shown a more equal distribution of PAD between genders and even a predominance of women with CLI.

Age

As mentioned above, there is a striking increase in both the incidence and prevalence of PAD with increasing age (Fig. 9).

Smoking

The relationship between smoking and PAD has been recognized since 1911, and it has been suggested that the association may be even stronger than that between smoking and coronary artery disease (CAD). Furthermore, a diagnosis of PAD is made approximately a decade earlier in smokers than in non-smokers. The severity of PAD tends to increase with the number of cigarettes smoked. Heavy smokers have a four-fold higher risk of developing IC compared with non-smokers. Smoking cessation is associated with a decline in the incidence of IC[5].

Diabetes mellitus

IC is about twice as common among diabetic patients than among non-diabetic patients. In patients with diabetes, for every 1% increase in hemoglobin A1c there is a corresponding 26% increased risk of PAD[6]. Over the last decade, mounting evidence has suggested that insulin resistance plays a key role in a clustering of cardiometabolic risk factors which include hyperglycemia, dyslipidemia, hypertension and obesity. Insulin resistance is a risk factor for PAD even in subjects without diabetes, raising the risk approximately 40% to 50%[7]. PAD in patients with diabetes is more aggressive compared to non-diabetics, with early large vessel involvement coupled with distal symmetrical neuropathy. The need for a major amputation is five- to ten-times higher in diabetics than non-diabetics. This is contributed to by sensory neuropathy and decreased

resistance to infection. Based on these observations PAD screening with an ABI is recommended every 5 years in patients with diabetes[8].

Hypertension

Hypertension is associated with all forms of cardiovascular disease, including PAD. However, the relative risk for developing PAD is less for hypertension than diabetes or smoking.

Dyslipidemia

In the Framingham study, a fasting cholesterol level greater than 7 mmol/L (270 mg/dL) was associated with a doubling of the incidence of IC but the ratio of total to high-density lipoprotein (HDL) cholesterol was the best predictor of occurrence of PAD[9]. There is evidence that treatment of hyperlipidemia reduces both the progression of PAD and the incidence of IC. An association between PAD and hypertriglyceridemia has also been reported and has been shown to be associated with the progression and systemic complications of PAD. Lipoprotein(a) is a significant independent risk factor for PAD.

Inflammatory markers

Some studies have shown that C-reactive protein (CRP) was raised in asymptomatic subjects who in the subsequent five years developed PAD compared to an age-matched control group who remained asymptomatic[10].

Hyperviscosity and hypercoagulable states

Raised hematocrit levels and hyperviscosity have been reported in patients with PAD, possibly as a consequence of smoking. Increased plasma levels of fibrinogen, which is also a risk factor for thrombosis, have been associated with PAD in several studies. Both hyperviscosity and hypercoagulability have also been shown to be markers or risk factors for a poor prognosis[5].

Hyperhomocysteinemia

The prevalence of hyperhomocysteinemia is as high in the vascular disease population, compared with 1% in the general population. It is reported that hyperhomocysteinemia is detected in about 30% of young patients with PAD. The suggestion that hyperhomocysteinemia may be an independent risk factor for atherosclerosis has now been substantiated by several studies. It may be a stronger risk factor for PAD than for CAD[5].

Chronic renal insufficiency

There is an association of renal insufficiency with PAD, with some recent evidence suggesting it may be causal[11].

Figure 10 summarizes the influence or association between some of the above factors and PAD.

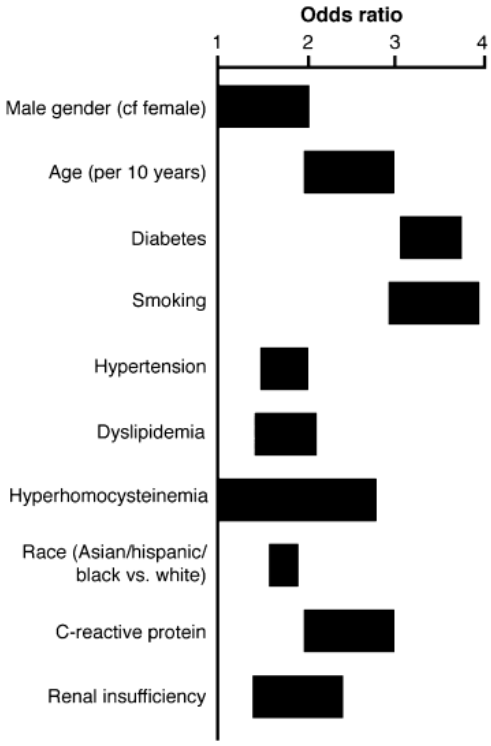


Fig. 10
Approximate range of odds ratios for risk factors for symptomatic peripheral arterial disease

CO-EXISTING VASCULAR DISEASE

Coronary artery disease

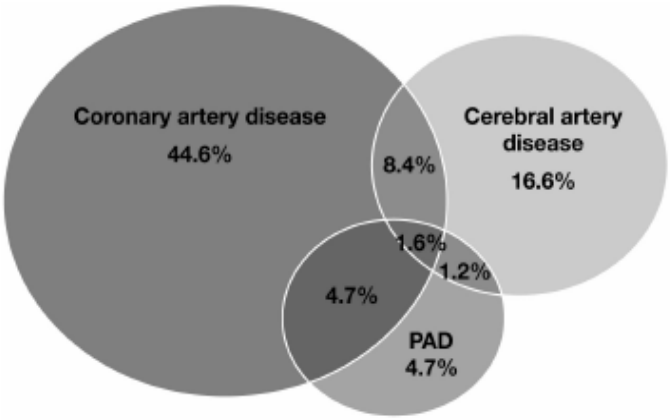
In patients with PAD the prevalence of CAD and cerebral artery disease is 40% to 60%[12]. Not surprisingly, patients with documented CAD are more likely to have PAD. The prevalence of PAD in patients with ischemic heart disease varies in different series from around 10% to 30%. Autopsy studies have shown that patients who die from a myocardial infarction are twice as likely to have a significant stenosis in the iliac and carotid arteries as compared to patients dying from other causes.

Cerebral artery disease

The link between PAD and cerebral artery disease seems to be weaker than that with CAD. By duplex examination, carotid artery disease occurs in 26% to 50% of patients with IC, but only about 5% of patients with PAD will have a history of any cerebrovascular event[13, 14]. Figure 11 shows the overlap in vascular disease affecting coronary, peripheral and cerebrovascular arteries.

Fig. 11

Overlap in vascular disease affecting different territories[13]



Renal artery disease

In patients with PAD, the prevalence of renal artery stenosis of 50% or over ranges from 23% to 42% (in the hypertensive general population is around 3%).

FATE OF THE LEG

Asymptomatic patients

The progression of the underlying PAD to CLI does not depend on the presence or absence of symptoms of IC. Whether symptoms develop or not depends largely on the level of activity of the subject. This is one of the reasons why some patients' initial presentation is with CLI, in the absence of any earlier IC. Functional decline over two years is related to baseline ABI and the nature of the presenting limb symptoms[15].

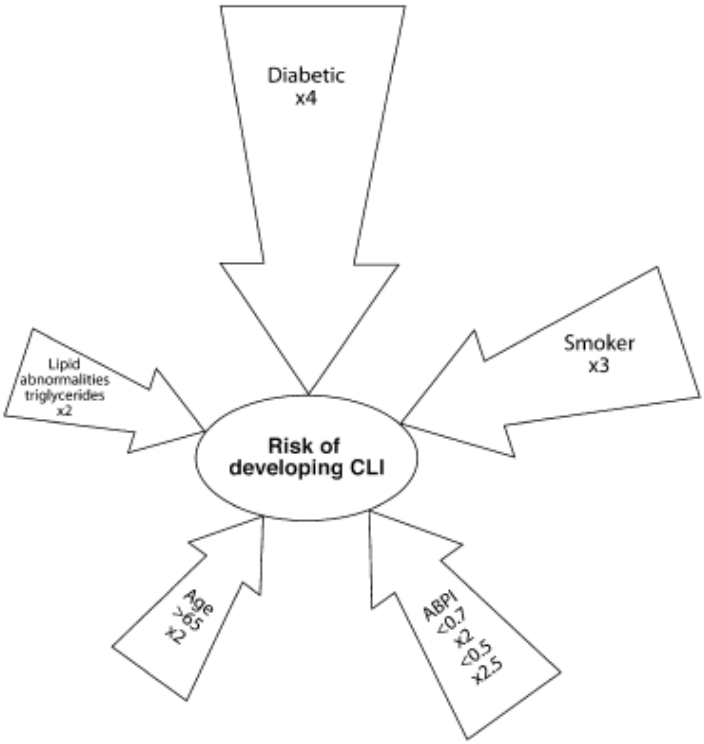
Intermittent claudication

Although PAD is progressive in the pathological sense, its clinical course as far as the leg is concerned is surprisingly stable in most cases, and only about a quarter of patients with IC will ever significantly deteriorate. This symptomatic stabilization may be due to the development of collaterals, metabolic adaptation of ischemic muscle, or the patient altering his gait to favor non-ischemic muscle groups. The remaining 25% of patients with IC deteriorate in terms of clinical stage; this is most frequent during the first year after diagnosis (7%–9%) compared with 2% to 3% per year thereafter. More recent reviews also highlight that major amputation is a relatively rare outcome of claudication, with only 1% to 3.3% of patients with IC needing major amputation over a 5-year period[16, 17]. Although amputation is the major fear of patients told that they have circulatory disease of the legs, they can be assured that this is an unlikely outcome, except in diabetes patients. It has been shown that in patients with IC the best predictor of deterioration of PAD (e.g. need for arterial surgery or major amputation), is an ABI of <0.50 with a hazard ratio of more than 2 compared to patients with an ABI >0.50.

Critical limb ischemia

The only reliable large prospective population studies on the incidence of CLI showed a figure of 220 new cases every year per million population[18]. However, there is indirect evidence from studies looking at the progression of IC, population surveys on prevalence and assumptions based on the major amputation rates. There will be approximately between 500 and 1000 new cases of CLI every year in a European or North American population of 1 million. Risk factors that seem to be associated with the development of CLI are summarized in Figure 12. These factors appear to be independent and are, therefore, probably additive.

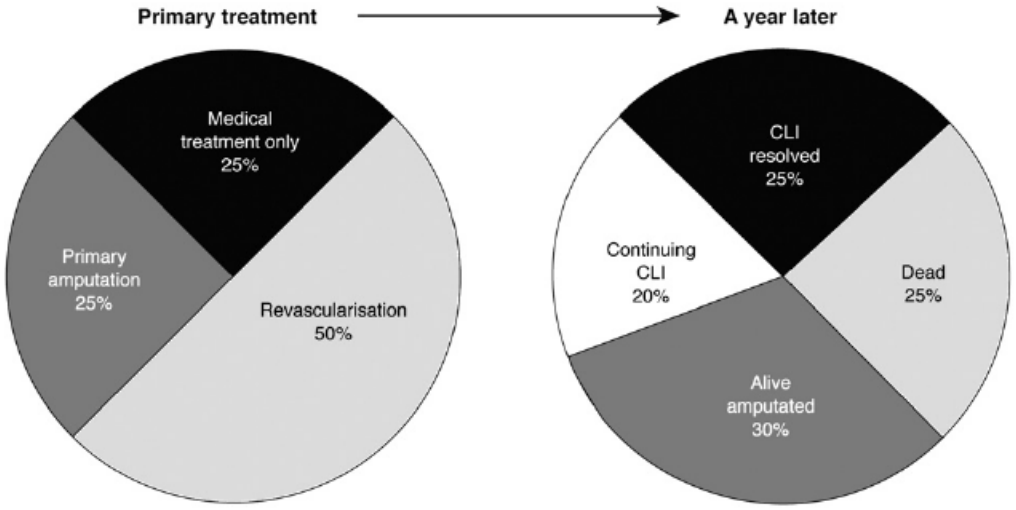
Fig. 12
Approximate magnitude of the effect of risk factors on the development of critical limb ischemia in patients with peripheral arterial disease



Large surveys suggest that approximately half the patients with CLI will undergo some type of revascularization, although in some, particularly active, interventional centers an attempt at reconstruction is reported in as

many as 90% of CLI patients. Figure 13 shows the fate of the patients presenting with chronic CLI.

Fig. 13
Fate of the patients presenting with chronic critical leg ischemia

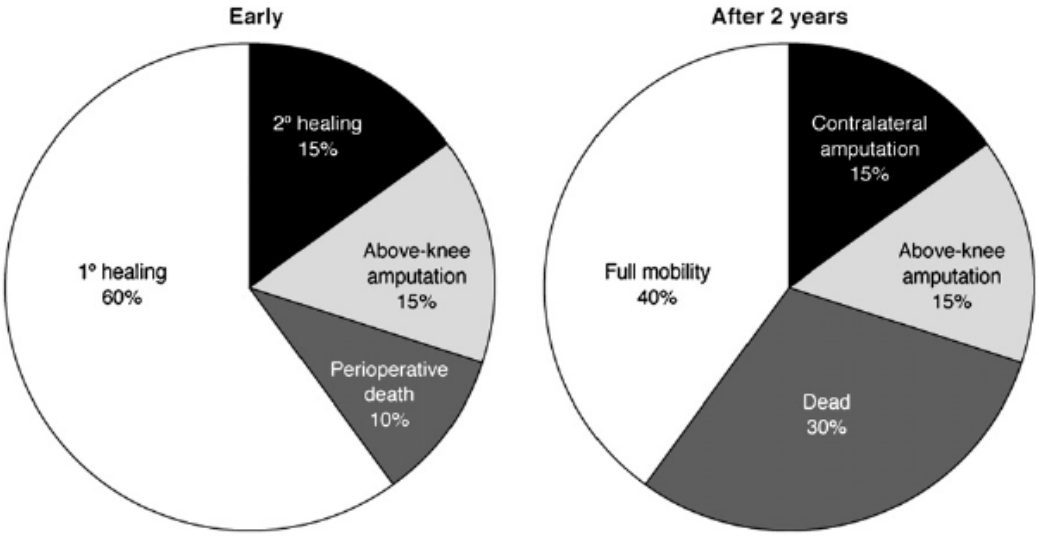


There are some data from multicenter, closely monitored trials of pharmacotherapy for CLI that refer to 6 months' follow-up and relate to a subgroup of patients who are unreconstructable or in whom attempts at reconstruction have failed. The results for this subgroup reveal that approximately 40% will lose their leg within 6 months, and up to 20% will die.

Amputation

Increased availability and use of endovascular and surgical interventions have resulted in a significant decrease in amputation for CLI. The concept that all patients who require an amputation have steadily progressed through increasingly severe claudication to rest pain, ulcers and, ultimately, amputation, is incorrect. It has been shown that more than half of patients having a below-knee major amputation for ischemic disease had no symptoms of leg ischemia whatsoever as recently as 6 months previously[19]. Figure 14 describes the fate of the patient with below-knee amputation.

Fig.14
Fate of the patient with below-knee amputation



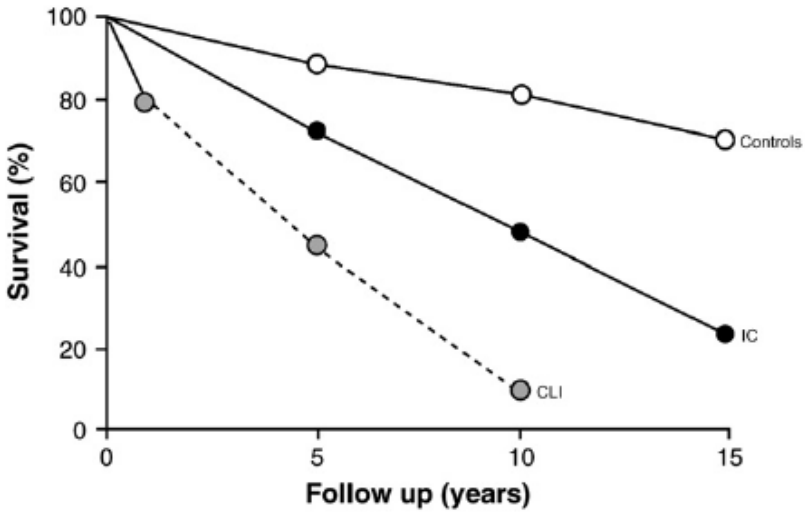
FATE OF THE PATIENT

Asymptomatic and claudicating PAD patients

The annual overall major cardiovascular event rate (myocardial infarction, ischemic stroke and vascular death) is approximately 5%-7%. Excluding those with CLI, patients with PAD have a 2% to 3% annual incidence of non-fatal myocardial infarction and their risk of angina is about two- to three- times higher than that of an age-matched population. CAD is by far the most common cause of death among patients with PAD (40%–60%), with cerebral artery disease accounting for 10% to 20% of deaths. Other vascular events, mostly ruptured aortic aneurysm, cause approximately 10% of deaths. Thus, only 20% to 30% of patients with PAD die of non-cardiovascular causes. Figure 15 summarizes the results from all studies comparing mortality rates of claudicating patients with those of an age-matched control population[5].

Fig. 15

Survival of patients with peripheral arterial disease



Severity of PAD and survival

Patients with chronic CLI have a 20% mortality in the first year after presentation, and the little long-term data that exists suggests that mortality continues at the same rate (Fig.15). There is a strong correlation between ABI, as a measure of the severity of the PAD, and mortality[20]. ABI is also a good predictor of non-fatal and fatal cardiovascular events as well as total mortality, in an unselected general population[4].

MANAGEMENT OF CARDIOVASCULAR RISK FACTORS AND CO-EXISTING DISEASE

Identifying the PAD patient in the population

The initial clinical assessment for PAD is a history and physical examination. A history of intermittent claudication is useful in raising the suspicion of PAD, but significantly underestimates the true prevalence of PAD. In contrast, palpable pedal pulses on examination have a negative predictive value of over 90% that may rule out the diagnosis in many cases. In contrast, a pulse abnormality significantly overestimates the true prevalence of PAD. Thus, objective testing is warranted in all patients

suspected of having PAD. The primary non-invasive screening test for PAD is the ABI. An abnormal ABI identifies a high-risk population that needs aggressive risk factor modification and antiplatelet therapy.

Modification of atherosclerotic risk factors

As highlighted above, patients with PAD typically have multiple cardiovascular risk factors, which need to be modified to reduce the risk for cardiovascular events[5].

Smoking cessation

Smoking is associated with a marked increased risk for peripheral atherosclerosis. The number of pack years is associated with disease severity, an increased risk of amputation, peripheral graft occlusion and mortality[21].

Weight reduction

Patients who are overweight (body mass index [BMI] 25–30) or who are obese (BMI >30) should receive counseling for weight reduction by inducing negative caloric balance with reduction of calorie intake, carbohydrate restriction and increased exercise.

Hyperlipidemia

Independent risk factors for PAD include elevated levels of total cholesterol, low-density lipoprotein (LDL) cholesterol, triglycerides, and lipoprotein(a). Factors that are protective for the development of PAD are elevated high-density lipoprotein (HDL) cholesterol and apolipoprotein (a-1) levels.

Hypertension

Hypertension is associated with a two- to three-fold increased risk for PAD.

Diabetes

Diabetes increases the risk of PAD approximately three- to four-fold, and the risk of claudication two-fold. Diabetes is also associated with peripheral neuropathy and decreased resistance to infection, which leads

to an increased risk of foot ulcers and foot infections. Several studies of both type 1 and type 2 diabetes have shown that aggressive blood-glucose lowering can prevent microvascular complications (particularly retinopathy and nephropathy); this has not been demonstrated for PAD, primarily because the studies conducted to date examining glycemic control in diabetes were neither designed nor powered to examine PAD endpoints[22, 23].

Homocysteine

An elevated plasma homocysteine level is an independent risk factor for PAD.

Inflammation

Markers of inflammation have been associated with the development of atherosclerosis and cardiovascular events. In particular, C-reactive protein is independently associated with PAD.

Antiplatelet drug therapy

Patients with cardiovascular disease realize a 25% odds reduction in subsequent cardiovascular events with the use of aspirin/acetylsalicylic acid [24]. Nevertheless, no statistically significant reduction in cardiovascular events was observed in PAD patients who did not have other evidence of vascular disease in other territories[25, 26]. Antiplatelet drugs are clearly indicated in the overall management of PAD, although the efficacy of aspirin/ASA is uniformly shown only when PAD and cardiovascular disease coexist[27]. Ticlopidine has been evaluated in several trials in patients with PAD, and has been reported to reduce the risk of myocardial infarction, stroke and vascular death[28]. However, the clinical usefulness of ticlopidine is limited by side effects such as neutropenia and thrombocytopenia. Clopidogrel was shown to be effective in the symptomatic PAD population to reduce the risk of myocardial infarction, stroke and vascular death. The overall benefit in this particular group was a 24% relative risk reduction over the use of aspirin/ASA[29]. Clopidogrel has a safety profile similar to aspirin/ASA, with only rare reports of thrombocytopenia. Patients undergoing surgical procedures are at

increased risk of bleeding when taking anti-thrombotics including heparins, aspirin/ASA or clopidogrel. Thus, temporary cessation of these drugs should be individualized based on the type of surgery to reduce bleeding risks.

INTERMITTENT CLAUDICATION (IC)

Definition of IC and limb symptoms

In patients with PAD, the classical symptom is IC, which is muscle discomfort in the lower limb, reproducibly produced by exercise and relieved by rest within 10 minutes. Patients may describe muscle fatigue, aching or cramping on exertion that is relieved by rest. The symptoms are most commonly localized to the calf, but may also affect the thigh or buttocks. Typical claudication occurs in up to one-third of all patients with PAD. Importantly, patients without classical claudication also have walking limitations that may be associated with atypical or no limb symptoms[30]. Typical claudication symptoms may not occur in patients who have co-morbidities that prevent sufficient activity to produce limb symptoms (i.e. congestive heart failure, severe pulmonary disease, musculoskeletal disease) or in patients who are so deconditioned that exercise is not performed. Patients with IC have normal blood flow at rest and, therefore, have no limb symptoms at rest. With exercise, occlusive lesions in the arterial supply of the leg muscles limits the increase in blood flow, resulting in a mismatch between oxygen supply and muscle metabolic demand that is associated with the symptom of claudication. Acquired metabolic abnormalities in the muscle of the lower extremity also contribute to the reduced exercise performance in PAD.

Physical examination

Key components of the general examination include measurement of blood pressure in both arms, assessment of cardiac murmurs, gallops or arrhythmias, and palpation for an abdominal aortic aneurysm. Less specific aspects of the physical examination for PAD include changes in

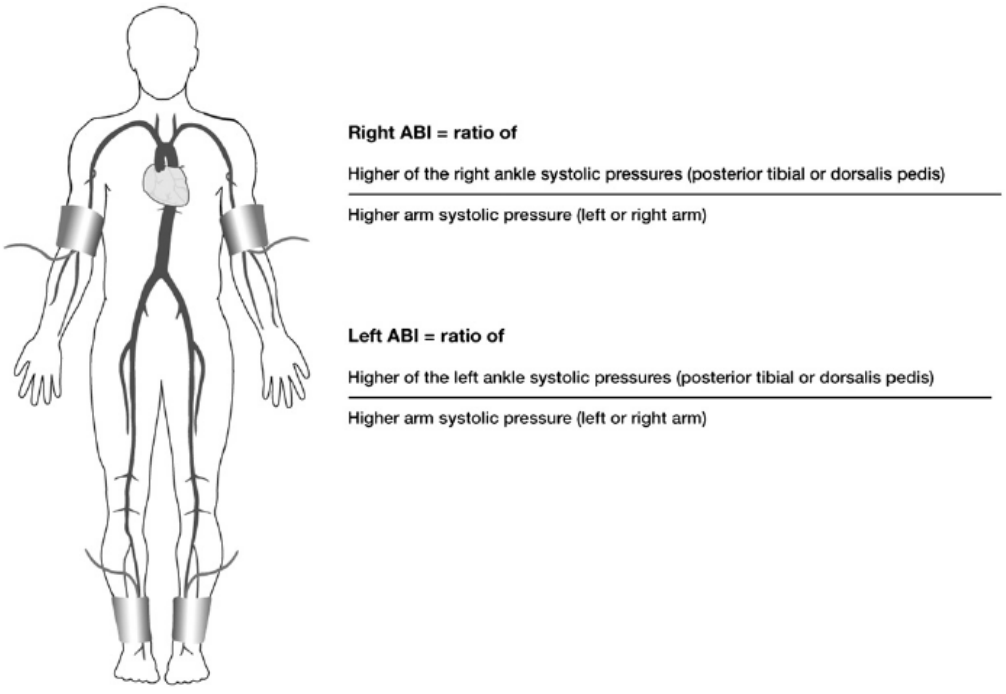
color and temperature of the skin of the feet, muscle atrophy from inability to exercise, decreased hair growth and hypertrophied, slow-growing nails. The presence of a bruit in the region of the carotid, aorta or femoral arteries may arise from turbulence and suggest significant arterial disease. However, the absence of a bruit does not exclude arterial disease. The specific peripheral vascular examination requires palpation of the radial, ulnar, brachial, carotid, femoral, popliteal, dorsalis pedis and posterior tibial artery pulses. The posterior tibial artery is palpated at the medial malleolus. In a small number of healthy adults, the dorsalis pedis pulse on the dorsum of the foot may be absent due to branching of the anterior tibial artery at the level of the ankle. In this situation, the distal aspect of the anterior tibial artery may be detected and assessed at the ankle. Also, a terminal branch of the peroneal artery may be palpated at the lateral malleolus. An especially prominent pulse at the femoral and/or popliteal location should raise the suspicion of an aneurysm. A diminished or absent femoral pulse suggests aorto-iliac artery occlusive disease. In contrast, a normal femoral, but absent pedal, pulse suggests significant arterial disease in the leg with preserved inflow. Pulses should be assessed in both legs and pulse abnormalities correlated with leg symptoms to determine the lateralization of the disease. Patients with an isolated occlusion of an internal iliac (hypogastric) artery may have normal femoral and pedal pulses at rest and after exercise, but buttocks claudication (and impotence in males). Similar symptoms may occur in patients with stenosis of the common or external iliac artery. These patients may also have normal pulses at rest, but loss of the pedal pulses after exercise. Despite the utility of the pulse examination, the finding of absent pedal pulses tends to over-diagnose PAD, whereas if the symptom of classic claudication is used to identify PAD, it will lead to a significant under-diagnosis of PAD[31]. Thus, PAD must be confirmed in suspected patients with non-invasive testing using the ankle-brachial index, or other hemodynamic or imaging studies.

DIAGNOSTIC EVALUATION OF PATIENTS WITH PAD

Ankle pressure measurements (ankle-brachial index)

Measuring the pressure in the ankle arteries has become a standard part of the initial evaluation of patients with suspected PAD. A common method of measurement uses a 10–12 cm sphygmomanometer cuff placed just above the ankle and a Doppler instrument used to measure the systolic pressure of the posterior tibial and dorsalis pedis arteries of each leg (Figure 16). These pressures are then normalized to the higher brachial pressure of either arm to form the anklebrachial index (ABI). The index leg is often defined as the leg with the lower ABI.

Fig.16
Measurement of the ABI



The ABI provides considerable information, and it can serve as an aid in differential diagnosis: patients with exercise-related leg pain of non-vascular causes will have a normal ankle pressure at rest and after exercise. In patients with PAD who do not have classic claudication a reduced ABI is highly associated with reduced limb function. This is defined as reduced walking speed and/or a shortened walking distance

during a timed 6-minute walk. From a systemic perspective, a reduced ABI is a potent predictor of the risk of future cardiovascular events. This risk is related to the degree of reduction of the ABI and is independent of other standard risk factors. In some patients with diabetes, renal insufficiency, or other diseases that cause vascular calcification, the tibial vessels at the ankle become non-compressible. This leads to a false elevation of the ankle pressure. These patients typically have an ABI >1.40 and, in some of these patients, the Doppler signal at the ankle cannot be obliterated even at cuff pressures of 300 mmHg. In these patients additional non-invasive diagnostic testing should be performed, as toe systolic pressures, pulse volume recordings, transcutaneous oxygen measurements or vascular imaging (most commonly with duplex ultrasound). When any of these tests is abnormal, a diagnosis of PAD can be reliably made[5].

Exercise testing to establish the diagnosis of PAD

Patients with claudication who have an isolated iliac stenosis may have no pressure decrease across the stenosis at rest and, therefore, a normal ABI at rest. However, with exercise the increase inflow velocity will make such lesions hemodynamically significant, inducing a decrease in the ABI that can be detected in the immediate recovery period. The procedure requires an initial measurement of the ABI at rest. The patient is then asked to walk (typically on a treadmill at 3.2 km/h, 10%–12% grade) until claudication pain occurs (or a maximum of 5 minutes), following which the ankle pressure is again measured. A decrease in ABI of 15%–20% would be diagnostic of PAD[5].

TREATMENT OF INTERMITTENT CLAUDICATION

Overall strategy

The treatment goals are to relieve symptoms, improve exercise performance and daily functional abilities[32]. The initial approach to the treatment of limb symptoms should focus on structured exercise and, in selected patients, pharmacotherapy to treat the exercise limitation of

claudication (risk factor modification and antiplatelet therapies are indicated to decrease the risk of cardiovascular events and improve survival). Failure to respond to exercise and/or drug therapy would lead to the next level which is to consider limb revascularization. However, in patients in whom a proximal lesion is suspected (findings of buttocks claudication, reduced or absent femoral pulse) the patient could be considered for revascularization without initially undergoing extensive medical therapy.

Exercise rehabilitation

The predictors of response to the training program include achieving a high level of claudication pain during the training sessions and 6 months or longer of formal training and walking exercise. The mechanisms of response to exercise training include improvements in walking efficiency, endothelial function and metabolic adaptations in skeletal muscle[33, 34]. The exercise prescription should be based on exercise sessions that are held three times a week, beginning with 30 minutes of training but then increasing to approximately 1 hour per session. During the exercise session, treadmill exercise is performed at a speed and grade that will induce claudication within 3–5 minutes. The patient should stop walking when claudication pain is considered moderate. The patient will then rest until claudication has abated, after which the patient should resume walking until moderate claudication discomfort recurs. This cycle of exercise and rest should be at least 35 minutes at the start of the program and increase to 50 minutes as the patient becomes comfortable with the exercise sessions. In subsequent visits, the speed or grade of the treadmill is increased if the patient is able to walk for 10 minutes or longer at the lower workload without reaching moderate claudication pain.

Pharmacotherapy for intermittent claudication

A number of types of drugs have been promoted for symptom relief, with varying levels of evidence to support their use. Finally, current drug

therapy options do not provide the same degree of benefit as does a supervised exercise program or successful revascularization[35].

Drugs with evidence of clinical utility in claudication

Cilostazol

Cilostazol is a phosphodiesterase III inhibitor with vasodilator, metabolic and antiplatelet activity. A metaanalysis of six randomized, controlled trials demonstrated that the net benefit of cilostazol over placebo in the primary endpoint of peak treadmill performance ranged from 50–70 meters depending on the type of treadmill test performed[36]. Cilostazol treatment also resulted in a significant overall improvement in the quality of life measures. Side effects included headache, diarrhea, and palpitations. An overall safety analysis of 2702 patients revealed that the rates of serious cardiovascular events, and all-cause and cardiovascular mortality was similar between drug and placebo groups[37]. However, since the drug is in the phosphodiesterase III inhibitor class of drugs, it should not be given to patients with any evidence of congestive heart failure because of a theoretical concern for increased risk of mortality. This drug has the best overall evidence for treatment benefit in patients with claudication.

Naftidrofuryl

Naftidrofuryl is a 5-hydroxytryptamine type 2 antagonist and may improve muscle metabolism, and reduce erythrocyte and platelet aggregation. In many studies, naftidrofuryl significantly increased pain-free walking compared with placebo and showed benefits on treadmill performance and quality of life at 6-12 months[38-41]. Side effects were minor (mostly mild gastrointestinal disorders) and not different to placebo.

Drugs with supporting evidence of clinical utility in claudication

Carnitine and Propionyl-L-Carnitine

Claudication is not simply the result of reduced blood flow, and alterations in skeletal muscle metabolism are part of the pathophysiology of the disease. L-carnitine and propionyl-L-carnitine interact with skeletal muscle

oxidative metabolism, and these drugs are associated with improved treadmill performance[42, 43]. The drug also improved quality of life and had minimal side effects as compared with placebo.

Lipid lowering drugs

Patients with PAD have endothelial and metabolic abnormalities secondary to their atherosclerosis, which may be improved with statin therapy. Since current results are preliminary, several positive trials suggest that further study is warranted[44, 45].

Drugs with insufficient evidence of clinical utility in claudication

Pentoxifylline

Pentoxifylline lowers fibrinogen levels, improves red cell and white cell deformability and thus lowers blood viscosity. Several meta-analyses have concluded that the drug is associated with modest increases in treadmill walking distance over placebo, but the overall clinical benefits were questionable[46-48].

Antithrombotic agents

ASA and clopidogrel reduce the risk of cardiovascular events in patients with PAD. However, no studies have shown a benefit of antiplatelet or anticoagulant drugs in the treatment of claudication[49].

Vasodilators

Examples include drugs that inhibit the sympathetic nervous system (alpha blockers), direct-acting vasodilators (papaverine), beta2-adrenergic agonists (nylidrin), calcium channel blockers (nifedipine) and angiotensin-converting enzyme inhibitors. These drugs have not been shown to have clinical efficacy in randomized, controlled trials[50].

L-Arginine

L-arginine has the ability to enhance endothelium-derived nitric oxide and, thus, improve endothelial function. Further studies are needed to determine if this treatment would have benefit and no unacceptable risk[51].

Acyl coenzyme A-cholesterol acyltransferase inhibitors

Drugs in this class may reduce cholesterol accumulation in arterial plaque, thus affecting the natural history of atherosclerosis. A study with avasimibe in claudication demonstrated no clear evidence of efficacy and possible adverse effects on low-density lipoprotein cholesterol levels[52].

5-Hydroxytryptamine antagonists

Ketanserin is a selective serotonin (S2) antagonist that lowers blood viscosity and also has vasodilator and antiplatelet properties. Controlled trials of this drug have shown it not to be effective in treating claudication[53].

Prostaglandins

Prostaglandins have been used in several studies in patients with critical leg ischemia with some success in wound healing and limb preservation. In patients with claudication, prostaglandin E1 (PGE1) has been best studied. Intravenous administration of a prodrug of PGE1 showed positive effects on treadmill performance[54], but the overall evidence does not support the use of this drug class for claudication.

Buflomedil

Buflomedil has an alpha-1 and -2 adrenolytic effects that result in vasodilatation. This drug has antiplatelet effects, results in improvements in red cell deformability and weakly antagonizes calcium channels. Two relatively small studies have shown marginally positive effects on treadmill performance[55, 56], but evidence is insufficient to support the use of this agent at this time.

Defibrotide

Defibrotide is a polydeoxyribonucleotide drug with antithrombotic and hemorheological properties. Several small studies suggest a clinical benefit, but larger trials would be necessary to better understand the clinical benefits and any risks of therapy[57].

Future treatments for claudication

Vascular endothelial growth factor (VEGF) and basic fibroblast growth factor (bFGF) are mitogenic agents that stimulate the development of new vessels. When bFGF protein was given intra-arterially, patients with claudication had an improvement in exercise performance[58]. Newer applications deliver the agent as gene therapy in a viral vector given intra-muscularly. Unfortunately, initial studies have not been positive with VEGF[59]. Therefore, more studies will be needed to address the overall efficacy of angiogenic factors in the treatment of claudication.

CRITICAL LIMB ISCHEMIA (CLI)

Definitions

CLI is a manifestation of PAD that describes patients with typical chronic ischemic rest pain (Table 1) or patients with ischemic skin lesions, either ulcers or gangrene[5]. The term CLI should only be used in relation to patients with chronic ischemic disease, defined as the presence of symptoms for more than 2 weeks. CLI populations are difficult to study, with large numbers of patients lost to follow-up or dying in longitudinal studies, leading to incomplete data sets.

Table 1. Classification of PAD: Fontaine´s stages and Rutherford´s categories

Fontaine		Rutherford		
Stage	**Clinical**	**Grade**	**Category**	**Clinical**
I	Asymptomatic	0	0	Asymptomatic
IIa	Mild claudication	I	1	Mild claudication
IIb	Moderate to severe claudication	I	2	Moderate claudication
		I	3	Severe claudication
III	Ischemic rest pain	II	4	Ischemic rest pain
IV	Ulceration or gangrene	III	5	Minor tissue loss
		III	6	Major tissue loss

The diagnosis of CLI should be confirmed by the ABI, toe systolic pressure or transcutaneous oxygen tension. Ischemic rest pain most commonly occurs below an ankle pressure of 50 mmHg or a toe pressure less than 30 mmHg. Some ulcers are entirely ischemic in etiology; others initially have other causes (e.g. traumatic, venous, or neuropathic) but will not heal because of the severity of the underlying PAD. Healing requires an inflammatory response and additional perfusion above that required for supporting intact skin and underlying tissues. The ankle and toe pressure levels needed for healing are, therefore, higher than the pressures found in ischemic rest pain. For patients with ulcers or gangrene, the presence of CLI is suggested by an ankle pressure less than 70 mmHg or a toe systolic pressure less than 50 mmHg. Nevertheless, there is not complete consensus regarding the vascular hemodynamic parameters required to make the diagnosis of CLI.

Patients presumed at risk for critical limb ischemia

A subgroup of PAD patients fall outside the definition of either claudication or CLI. These patients have severe PAD with low perfusion pressures and low ankle systolic pressures, but are asymptomatic. They are usually sedentary and, therefore, do not claudicate, or they may have diabetes

with neuropathy and reduced pain perception. These patients are presumed vulnerable to develop clinical CLI. The natural history of this subgroup of severe PAD is not well characterized, but outcomes of excess mortality and amputation would be expected. The term 'chronic subclinical ischemia' has been ascribed to this subgroup. Natural history studies of claudication document that few patients progress to CLI. Many patients who present with CLI are asymptomatic prior to its development[60]. However, research in this area is lacking, understandably, for patients who are asymptomatic and can only be detected by more routine ABI testing.

Prognosis

CLI confers a prognosis of high risk for limb loss and for fatal and non-fatal vascular events, myocardial infarction and stroke (TASC). In general, the prognosis is much worse than that of patients with IC. Observational studies of patients with CLI who are not candidates for revascularization suggest that a year after the onset of CLI, only about half the patients will be alive without a major amputation, although some of these may still have rest pain, gangrene or ulcers. Approximately 25% will have died and 25% will have required a major amputation. Their prognosis is in many ways similar to that of some malignancies. The diagnosis of CLI thus predicts a poor prognosis for life and limb. Patients should have aggressive modification of their cardiovascular risk factors and should be prescribed antiplatelet drugs. Ultimately, much of the care of CLI patients is palliative in nature, an issue that is very important when considering revascularization or amputation.

CLINICAL PRESENTATION AND EVALUATION IN CLI

Pain

CLI is dominated by pedal pain (except in diabetic patients, where superficial pain sensation may be altered and they may experience only deep ischemic pain, such as calf claudication and ischemic rest pain). In most cases, the pedal pain is intolerably severe; it may respond to foot

dependency, but otherwise responds only to opiates. The pain is caused by ischemia, areas of tissue loss, ischemic neuropathy or a combination of these; it occurs or worsens with reduction of perfusion pressure. In most cases, walking capacity is very severely impaired, with walking often becoming almost impossible. Ischemic rest pain most typically occurs at night (when the limb is no longer in a dependent position) but in severe cases can be continuous. The pain is localized in the distal part of the foot or in the vicinity of an ischemic ulcer or gangrenous toe. The pain often wakes the patients at night and forces them to rub the foot, get up, or take a short walk around the room. Partial relief may be obtained by the dependent position, whereas elevation and cold increase the severity of the pain. Often, patients sleep with their ischemic leg dangling over the side of the bed, or sitting in an armchair; as a consequence ankle and foot edema develop. In severe cases, sleep becomes impossible because pain sets in after only a short period of supine rest, causing in many patients a progressive further decline of their general physical and psychological condition. Ischemic rest pain is often accompanied by pain caused by peripheral ischemic neuropathy. This results in severe, sharp, shooting pain that does not necessarily follow the anatomic distribution of the nerves but usually is most pronounced at the distal part of the extremity. The pain often occurs at night, with episodes lasting minutes to hours but with constant diffuse pain remaining in between.

Ulcer and gangrene

Patients with CLI may also present with ischemic ulcers or gangrene. It is important to note that some patients may progress through rest pain into tissue loss. However, in many patients, notably those with diabetic neuropathy, the initial presentation is with a neuro-ischemic ulcer or gangrene. Gangrene usually affects the digits or, in a bedridden patient, the heel (as this is a pressure point). In severe cases, gangrene may involve the distal parts of the forefoot. It is usually initiated by a minor local trauma. Gangrenous tissue, if not infected, can form an eschar, shrink and eventually mummify and, if the underlying circulation is adequate enough

(or has been made adequate enough by treatment) to support the process, spontaneous amputation may follow. In contrast to the focal and proximal atherosclerotic lesions of PAD found typically in other high-risk patients, in patients with CLI and diabetes the occlusive lesions are more likely to be more diffuse and distally located, particularly in infrageniculate arteries. Importantly, PAD in patients with diabetes is usually accompanied by peripheral neuropathy with impaired sensory feedback, enabling the silent progression of the ischemic process. Thus, a patient with diabetes and severe, asymptomatic PAD could also have a 'pivotal event' that leads acutely to an ischemic ulcer and a limb-threatening situation. A common example is the use of new, tight or ill fitting shoes in a patient with neuropathy. Thus, an asymptomatic, usually undiagnosed patient can lapse, apparently abruptly, into CLI. By identifying a patient with sub-clinical disease and instituting preventive measures, it may be possible to avoid CLI or at least prompt early referral if the patient develops CLI.

MACROCIRCULATORY PATHOPHYSIOLOGY IN CLI

Arterial segment involvement

CLI occurs when arterial lesions impair blood flow to such an extent that the nutritive requirements of the tissues cannot be met. This is usually caused by multilevel arterial occlusive disease[61]. In some cases, the hemodynamic consequences of arterial lesions may be compounded by a decreased cardiac output. CLI is considered to be the result of multisegment arterial occlusive disease in most cases.

- Patients with diffuse multisegment disease, both supra and infrainguinal are significant management problems, as proximal revascularizations may not remain patent due to lack of arterial outflow without additional infrainguinal procedures. Should a major amputation be required, the risk of non-healing is considerable due to proximal occlusive disease

- In patients with diabetes, arteries proximal to the knee joint are often spared or moderately diseased, and the majority of occlusions occur at the tibial peroneal trunk and distally. Often, the peroneal artery and the dorsalis pedis artery are open beyond these occlusions and serve as potential distal targets for a bypass

Skin microcirculation

Patients with CLI develop microcirculatory defects including endothelial dysfunction, altered hemorheology and white blood cell activation and inflammation. The normal function of the skin microcirculation can be considered in regard to two aspects: a complex microvascular flow regulatory system and a series of defense mechanisms. In CLI, there is a maldistribution of the skin microcirculation in addition to a reduction in total blood flow. The importance of the local microcirculatory response in individual patients with CLI is suggested by the wide overlap in ankle or toe blood pressure, which assesses the macrocirculation, in patients with and without CLI. Capillary microscopy studies have confirmed a heterogeneous distribution of skin microcirculatory flow. This is also accompanied by a reduction in tcPO2[62]. In summary, although PAD is the underlying and principal defect in patients with CLI, the low tissue perfusion pressure sets up a number of complex local microcirculatory responses, which may contribute to rest pain and trophic changes. Many of these processes can be viewed as an inappropriate response of the microcirculatory flow regulatory mechanism and its normal defense mechanisms. Therefore, although the primary aim of treatment must be the correction of the PAD, attempts to manipulate and normalize the microcirculatory changes pharmacologically may enhance the results of revascularization and may be one option in patients in whom revascularization is impossible or has failed.

INVESTIGATIONS OF CLI

Physical examination

A first step is to document the location and quality of the pulses. Other less specific findings may include hair loss, muscle atrophy, atrophy of subcutaneous tissues and skin and appendages, dry fissured skin, discoloration and dependant hyperemia. In patients with ulcers there may be other etiologies besides arterial disease. Swelling is usually only a feature when there is active infection or rest pain that prevents patients from elevating their foot in bed at night.

Specifical investigations

- General investigations of atherosclerotic disease
- Confirmation of the diagnosis and quantification of the arterial flow:
  - ✓ Ankle pressure – In patients with ischemic ulcers the ankle pressure is typically 50–70 mmHg, and in patients with ischemic rest pain typically 30–50 mmHg
  - ✓ Toe pressures – should include toe pressures in diabetic patients (critical level <50 mmHg)
  - ✓ tcPO2 (critical level <30 mmHg)
  - ✓ Investigation of microcirculation (usually used as a research tool) – A combination of tests may be indicated due to the poor sensitivity and specificity of the single test.
    - Capillaroscopy
    - Fluorescence videomicroscopy
    - Laser Doppler fluxometry
- Anatomic (Imaging techniques: angiography, duplex ultrasound, computed tomographic angiography and magnetic resonance angiography)

PREVENTION OF CLI

Risk factors associated with the foot

Patients with atherosclerotic PAD, Buerger's disease, diabetes and any other condition that can cause a loss of protective sensation to the foot or interferes with wound healing are at risk of developing ulcerations and a future amputation. Persons with diabetes are at a higher risk for developing lower extremity complications. A thorough foot examination will assist in identifying those patients who are at risk. Once an individual is classified as high risk, a visual foot inspection should be performed at every visit and referral to a foot care specialist for further assessment is recommended.

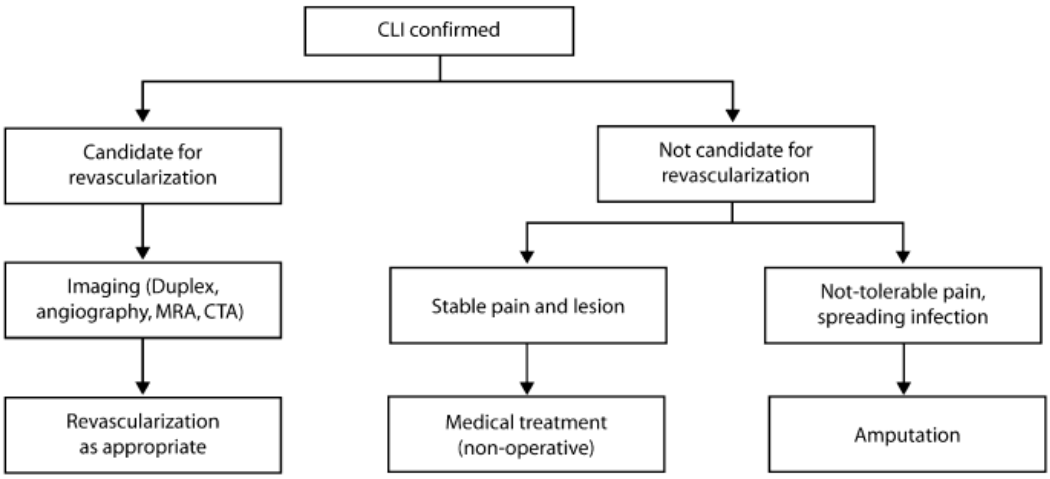
The role of peripheral neuropathy

Loss of protective sensation or peripheral neuropathy places the patient at a higher risk for developing foot related complications. Foot deformities may be the result of motor neuropathy. Therefore, recognition of structural deformities, or altered biomechanics as well as limited joint mobility identify the patient as high risk. Footwear should be inspected to determine if it provides adequate support and protection for the foot. Preventive foot care strategies for patients at risk of developing foot complications is essential for limb preservation. Patients should be educated on the importance of self-care of the feet, including proper foot care and footwear assessment. Early detection of foot problems and early intervention may decrease the frequency and severity of lower extremity complications. Therefore, patients should be performing daily foot inspections at home.

TREATMENT OF CLI

Overall strategy (Fig. 17)

Fig. 17
Algorithm for treatment of the patient with critical limb ischemia (CLI)
(MRA – magnetic resonance angiography; CTA – computed tomographic angiography)



The primary goals of the treatment of CLI are to relieve ischemic pain, heal neuro-ischemic ulcers, prevent limb loss, improve patient function and quality of life and prolong survival. A primary outcome would be amputation-free survival. In order to achieve these outcomes, most patients will ultimately need a revascularization procedure requiring referral to a vascular specialist. Other components of treatment of patients with CLI are medical interventions to control pain and infection in the ischemic leg, prevention of progression of the systemic atherosclerosis, and optimization of cardiac and respiratory function. For some CLI patients with severe co-morbidities or a very limited chance of successful revascularization, a primary amputation may be the most appropriate treatment. Cardiovascular risk factor control is mandatory in CLI patients as well as in all PAD patients[5].

Pain control

Pain management is essential in improving function and quality of life. The hallmark of CLI is ischemic rest pain and painful ulceration. Pain is usually located to skin and possibly bone structures. Ideally, relief of pain is achieved by reperfusion of the extremity. However, while planning the revascularization, adequate pain control must be a goal of management in all patients. Furthermore, in patients for whom revascularization is not an option, narcotic pain relief is commonly needed. Initial attempts at pain relief should include the use of acetaminophen/paracetamol or nonsteroidal anti-inflammatory medications, although the latter are rarely effective and narcotic medications are frequently required. Control of pain is usually more effective if analgesia is given regularly rather than on demand. Placing the affected limb in the dependent position provides partial relief of ischemic pain in some patients. Patients with CLI are often depressed and pain control can be improved by use of antidepressant medications.

Revascularization

Intervention is indicated to salvage a useful and pain-free extremity. The treatment chosen depends upon the pre-morbid condition of the patient and the extremity as well as estimating the risk of intervention based on co-morbid conditions and the expected patency and durability of the reconstruction. In CLI, multi-level disease is frequently encountered. Adequate inflow must be established prior to improvement in the outflow. After revascularization, ulcer healing may require adjunctive treatments that may be best achieved in collaboration between the vascular specialist and specialists in foot care.

Management of ulcers

The management of the patient with CLI and foot ulcers illustrates the need for a multidisciplinary approach to the treatment of CLI patients. These patients should be treated according to the following principles.

Restoration of perfusion

The successful treatment of a foot ulcer rests with the possibility of increasing the perfusion to the foot. A revascularization procedure should be considered if clear signs of CLI are present or if healing does not occur in a neuro-ischemic ulcer despite optimal off-loading, treatment of infection, if present, and intensive wound care. After revascularization, local wound care and possibly foot salvage procedures must be considered.

Local ulcer care and pressure relief

Prior to a revascularization procedure the ulcer can be treated with non-adherent gauze and should be off-loaded if there is an increase in pressure or shear stress. Off-loading can be achieved by several methods including shoe modifications, orthotics and casting techniques[8, 63, 64] depending on the localization of the ulcer and the severity of the ischemia. Once perfusion is improved adequate off-loading becomes more important as the increase in blood flow may not compensate for the repetitive tissue trauma due to poorly fitted shoes. The local treatment of a revascularized foot ulcer can be carried out in many fashions and a multitude of products exist. Basic principles of wound care include: removing necrotic/fibrotic tissue from the ulcer, keeping a moist wound environment and eliminating infection.

Treatment of infection

Local infection is a severe complication of a neuroischemic ulcer, as it tends to run a more severe course and should be treated urgently. Signs of systemic toxicity, such as fever or elevated C-reactive protein, are uncommon. The infection should be identified as early as possible and its level of involvement assessed and aggressively treated. Severe foot infections in diabetic patients are usually polymicrobial with gram positive cocci, gram negative rods and anaerobic organisms[65]. Empiric antibiotic treatment should be initiated immediately. Broad spectrum antibiotic therapy can be adjusted once the causative microorganisms are

determined and results of the culture sensitivity have been obtained. A growing concern is the rise in the incidence of multidrug-resistant *Staphylococcus aureus*, which is up to 30% in some studies[66]. Management of a deep infection usually also includes drainage and debridement of necrotic tissue. Antibiotic therapy is believed to be important in the prevention of further spreading of infection in patients with CLI. Once the acute infection is under control, a revascularization procedure can be performed in a second stage.

Salvage procedures

Limb salvage after revascularization is defined as preservation of some or all of the foot. An attempt at a foot salvage procedure should take place after a revascularization procedure has been performed if possible. A waiting period of at least 3 days has been suggested, this allows for sufficient time for the restoration of perfusion and for demarcation to occur. Salvage procedures can be divided into two categories. The first category involves amputation of some part of the foot. Table 2 shows the different levels of local foot amputations.

Table 2. Different levels of local foot amputations

Digit (partial or total)
Ray (digit and metatarsal)
Midfoot (transmetatarsal; tarso-metatarsal; transverse tarsal)
Symes (ankle)

The natural history of a minor foot amputation should be considered when choosing the appropriate level of amputation in order to account for the subsequent changes in mechanical force and pressure on the foot. For example, a hallux or partial first ray amputation increases the resultant vector of force on the second ray (through metatarsal shaft). This increase in force traversing through the second ray can cause a contracture of the second toe, leading to an increased pressure at both the sub metatarsal head area and the distal pulp of the toe. These changes in pressure require appropriate shoe and insole modifications to avoid foot

complications. A high percentage of patients with a great toe and/or first ray amputation go on to have a second amputation either on the same foot or the contra-lateral foot. Amputation of the lateral toes and rays (fourth and fifth digits) does not cause the same increase in mechanical force and pressure. When multiple medial rays are involved or the ischemia is proximal to the metatarsal heads, but distal to the tarso-metatarsal joint, a mid foot amputation should be considered. A trans-metatarsal amputation provides a stump adequate for walking with minimal shoe and innersole modifications.

The second category of foot salvage involves the debridement of the wounds, including excision of bone. These procedures permit the foot to keep its general outward appearance intact, while disturbing the internal architecture that is causing the increased pressure. Foot salvage procedures, short of amputation, that can be used in the revascularized foot include exostectomy, arthroplasty, metatarsal head excision and calcanectomy.

Diabetes control and treatment of co-morbidity

As in all patients with diabetes, those with concomitant CLI should have optimization of glycemic control. Diabetic patients with a neuro-ischemic foot ulcer frequently have a poor health status. Factors that can negatively affect wound healing such as cardiac failure or poor nutritional status should be evaluated and treated appropriately.

Amputation

Major amputation (above the ankle) in CLI is necessary and indicated when there is overwhelming infection that threatens the patient's life, when rest pain cannot be controlled, or when extensive necrosis has destroyed the foot. Using these criteria, the number of major limb amputations should be limited. Primary amputation is defined as amputation of the ischemic lower extremity without an antecedent attempt at revascularization. Amputation is considered as primary therapy for lower limb ischemia only

in selected cases. Revascularization of the lower extremity remains the treatment of choice for most patients with significant arterial occlusive disease. Unreconstructable vascular disease has become the most common indication for secondary amputation, accounting for nearly 60% of patients. Secondary amputation is indicated when vascular intervention is no longer possible or when the limb continues to deteriorate despite the presence of a patent reconstruction. Persistent infection despite aggressive vascular reconstruction is the second most common diagnosis. Many amputations can be prevented and limbs preserved through a multi-armed, limb-salvage treatment of ischemic necrosis with antibiotics, revascularization and staged wound closure that may necessitate the use of microvascular muscle flaps to cover major tissue defects. On the other hand, and very importantly, amputation may offer an expedient return to a useful quality of life, especially if a prolonged course of treatment is anticipated with little likelihood of healing. Non-ambulatory elderly patients with CLI represent a particularly challenging group. These patients frequently have flexion contractures that form from the prolonged withdrawal response to the pain. Aggressive vascular reconstruction does not provide these patients with a stable and useful limb, and primary amputation is a reasonable option[67]. Therefore, the important issue is to identify a subgroup of CLI patients better served by an amputation than attempts of revascularization. Technical aspects, foot wound healing issues and co-morbidities of the patients should be considered. The goal of amputation is to obtain primary healing of the lower extremity at the most distal level possible. Preservation of the knee joint and a significant length of the tibia permits the use of lightweight prostheses, minimizes the energy of ambulation, and enables older or more frail patients to walk independently[68]. Clinical determination of the amputation level results in uninterrupted primary healing of the below-knee stump in around 80% and the above-knee stump in around 90% of cases[69]. Measurement of tcPO2 combined with clinical determination may be of value to predict healing at various levels of amputation[70].

Amputations have variable outcome and more risk with higher proximal amputations. A major amputation that is above the foot will require a prosthesis. Meticulous technique is essential to ensure a well-formed and well-perfused stump with soft tissue covering the transected end of the bone. A return to independent ambulation is the ultimate challenge for patients undergoing major amputation of the lower extremity. Patients with a well-healed below-knee amputation stump have a greater likelihood of independent ambulation with a prosthesis than those with an above-knee amputation, who have a less than 50% chance of independent ambulation.

Pharmacotherapy for CLI

When open or endovascular intervention is not technically possible or has failed, the question arises as to whether pharmacological treatment is an option[35]. Pharmacotherapy is more likely to be successful in patients who were asymptomatic before developing their foot lesion and in those with shallow foot lesions where the level of ischemia is close to the margin.

Prostanoids

Prostanoids prevent platelet and leukocyte activation and protect the vascular endothelium, which could play a role in the management of CLI. These drugs are administered parenterally over several weeks. Side effects include flushing, headache, and hypotension of a transient nature. Prediction of response is, however, difficult and prostanoids are rarely used due to these facts.

Vasodilators

Direct-acting vasodilators are of no value, as they will primarily increase blood flow to non-ischemic areas.

Antiplatelet drugs

Although long-term treatment may reduce progression of femoral atherosclerosis and exert a beneficial effect on the patency of peripheral by-passes[71], there is no evidence that these drugs would improve

outcomes in CLI. However, as in all patients with PAD, antiplatelet drugs do reduce the risk of systemic vascular events.

Anticoagulants

Unfractionated heparin is frequently used as prophylaxis and as adjuvant treatment to vascular procedures, but has not been tried for symptoms of CLI. Two studies have looked at low molecular weight heparin (LMWH) in CLI patients with ulcers. These were negative trials. Vitamin K antagonists have not been tried for the treatment of symptoms of CLI. Defibrinating agents have not been shown to improve healing of ischemic ulcers or to reduce the number of amputations.

Vasoactive drugs

Naftidrofuryl was not effective in reducing the symptoms of CLI[72]. Pentoxifylline was evaluated in two placebo controlled studies in patients with CLI, with inconclusive results[73, 74].

Other treatments

Hyperbaric oxygen

A review[75] concluded that hyperbaric therapy significantly reduced the risk of major amputation in patients with diabetic ulcers. However, the results should be interpreted with caution because of methodological shortcomings. Nonetheless, hyperbaric oxygen may be considered in selected patients with ischemic ulcers who have not responded to, or are not candidates for, revascularization.

Spinal cord stimulation

A review[76] of six studies including patients with CLI concluded that spinal cord stimulation was significantly better than conservative treatment in improving limb salvage in patients without any option to vascular reconstruction.

REVASCULARIZATION IN CLI

Localization of disease

The determination of the best method of revascularization for treatment of symptomatic PAD is based upon the balance between risk of a specific intervention and the degree and durability of the improvement that can be expected from this intervention. Adequate inflow and appropriate outflow are required to keep the revascularized segment functioning. The location and morphology of the disease must be characterized prior to carrying out any revascularization to determine the most appropriate intervention. In a situation where a proximal stenosis is of questionable hemodynamic significance, pressure measurements across it to determine its significance (criteria: threshold peak systolic difference 5–10 mmHg pre-vasodilatation and 10–15 mmHg post-vasodilatation) may be made. A recent development is direct flow measurements using a thermodilution catheter rather than pressure gradients. Hyperemic duplex scanning has also been suggested.

In general, the outcomes of revascularization depend upon the extent of the disease in the subjacent arterial tree (inflow, outflow and the size and length of the diseased segment), the degree of systemic disease (co-morbid conditions that may affect life expectancy and influence graft patency) and the type of procedure performed.

The endovascular techniques for the treatment of patients with lower extremity ischemia include balloon angioplasty, stents, stent-grafts and plaque debulking procedures.

Surgical options include autogenous or synthetic bypass, endarterectomy or an intra-operative hybrid procedure. Outcomes of revascularization procedures depend on anatomic as well as clinical factors. Patency following percutaneous transluminal angioplasty (PTA) is highest for lesions in the common iliac artery and progressively decreases for lesions

in more distal vessels. Anatomic factors that affect the patency include severity of disease in run off arteries, length of the stenosis/occlusion and the number of lesions treated. Clinical variables impacting the outcome also include diabetes, renal failure, smoking and the severity of ischemia.

Classification of lesions

In TASC classification 'A' lesions represent those which yield excellent results from, and should be treated by, endovascular means; 'B' lesions offer sufficiently good results with endovascular methods that this approach is still preferred first, unless an open revascularization is required for other associated lesions in the same anatomic area; 'C' lesions produce superior enough long-term results with open revascularization that endovascular methods should be used only in patients at high risk for open repair; and 'D' lesions do not yield good enough results with endovascular methods to justify them as primary treatment. Finally it must be understood that most PAD requiring intervention is characterized by more than one lesion, at more than one level, so these schemes are limited by the necessity to focus on individual lesions. Figures 18 and 19 reports TASC classification of aorto-iliac and femoro-popliteal lesions[5].

Fig. 18

TASC classification of aorto-iliac lesions (CIA – common iliac artery; EIA – external iliac artery; CFA – common femoral artery; AAA – abdominal aortic aneurysm)

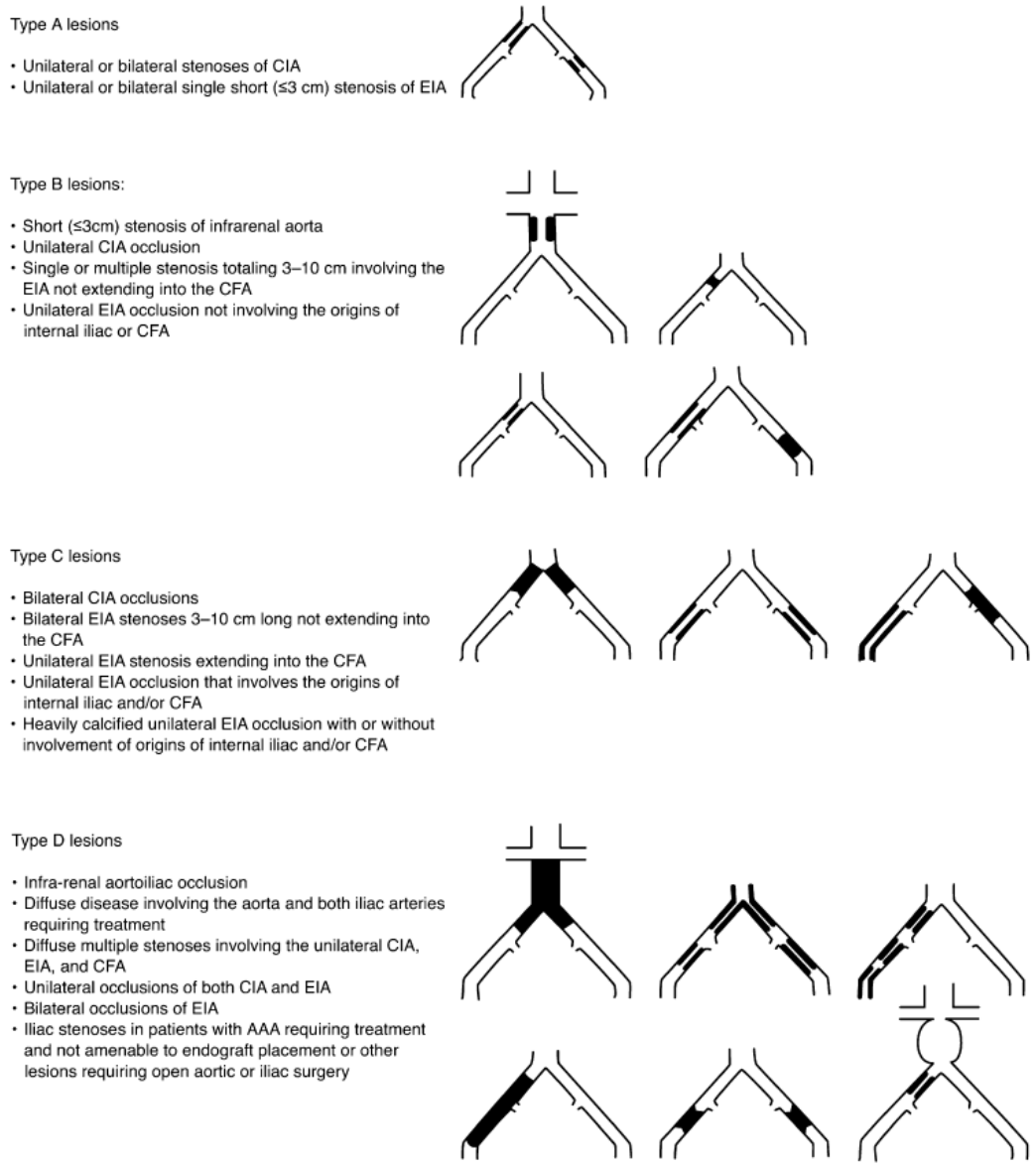
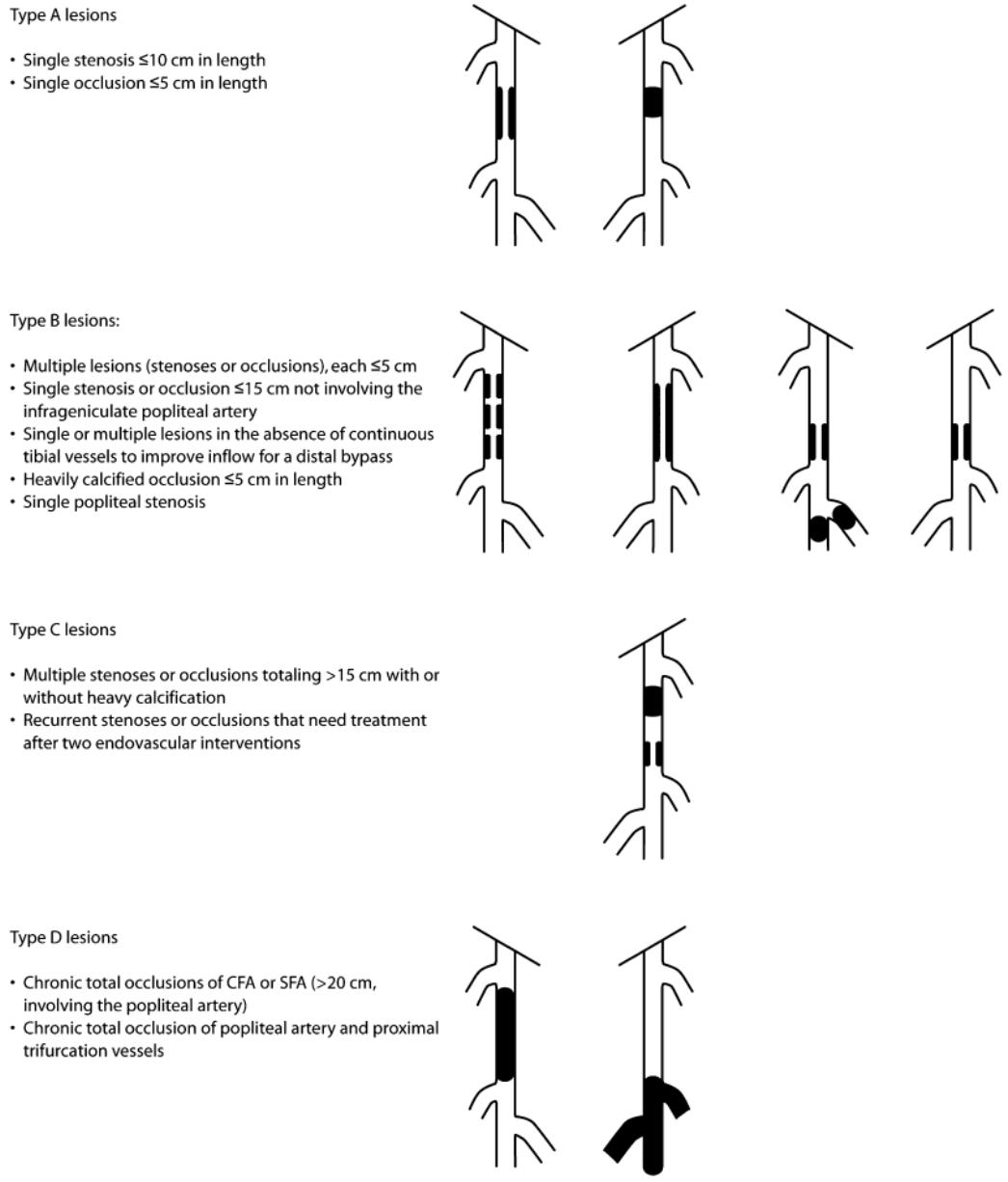


Fig. 19

TASC classification of femoral popliteal lesions (CFA – common femoral artery; SFA – superficial femoral artery)



AORTOILIAC (SUPRA INGUINAL) REVASCULARIZATION

Endovascular treatment of aorto-iliac occlusive disease

Although aorto-bifemoral bypass appears to have better long-term patency than the currently available endovascular strategies for diffuse aorto-iliac occlusive disease, the risks of surgery are significantly greater than the

risks of an endovascular approach, in terms of not only mortality but also major morbidity and delay in return to normal activities. Therefore, the assessment of the patient's general condition and anatomy of the diseased segment(s) become central in deciding which approach is warranted. The technical and initial clinical success of PTA of iliac stenoses exceeds 90% in all reports in the literature and approaches 100% for focal iliac lesions. The technical success rate of recanalization of long segment iliac occlusions is 80%–85% with or without additional fibrinolysis. Recent device developments geared towards treatment of total occlusions, however, have substantially improved the technical success rate of recanalization[77]. Factors negatively affecting the patency of such interventions include quality of run-off vessels, severity of ischemia and length of diseased segments. Female gender has also been suggested to decrease patency of external iliac artery stents[78].

Choice of primary stent placement versus primary angioplasty followed by selective stent placement (provisional stenting) was addressed in a prospective randomized, multicenter study[79]. Results showed that PTA with provisional stenting had a similar outcome to primary stenting with 2-year reintervention rates of 7% and 4%, respectively, for PTA and primary stenting (not significant). The 5-year outcomes of the groups were also similar with 82% and 80% of the treated iliac artery segments remaining free of revascularization procedures after a mean follow-up of 5.6±1.3 years[80]. A meta-analysis by Bosch and Hunink compared the results of aortoiliac PTA versus aortoiliac stenting including 2116 patients with sufficient detail to allow stratification over subgroups with various risk levels for long-term patency[81]. Technical success was higher for stenting, whereas complication rates and 30-day mortality rates did not differ significantly. The outcome of two different self-expanding stents (Nitinol SMART stent and Wallstent) for the treatment of iliac artery lesions was compared in a multicenter prospective randomized trial[82]. The 1-year primary patencies were 94.7% and 91.1% (not significant), respectively,

with similar complication and symptomatic improvement rates regardless of the type of stent.

Surgical treatment of aorto-iliac occlusive disease

Bilateral surgical bypass from the infra-renal abdominal aorta to both femoral arteries is usually recommended for diffuse disease throughout the aortoiliac segment (Fig. 20). The aorta may be approached via a transperitoneal or retroperitoneal approach and interest is increasing in laparoscopic approach. Younger patients (<50 years of age) with lower primary and secondary patency have a greater need for secondary bypass[83]. Table 3 summarizes the patency at 5 and 10 years after aortobifemoral by pass[84].

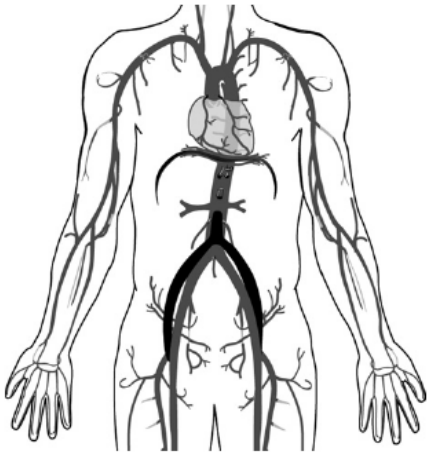


Fig. 20
Bilateral bypass from infra renal abdominal aorta to both femoral arteries

Table 3. Patency at 5 and 10 years after aortobifemoral bypass

	5-year % patency (range)		10-year %patency (range)	
Indication	Claudication	CLI	Claudication	CLI
Limb based	91 (90–94)	87 (80–88)	86 (85–92)	81 (78–83)
Patient based	85 (85–89)	80 (72–82)	79 (70–85)	72 (61–76)
CLI – critical limb ischemia				

In some situations, when an abdominal approach is to be avoided due to anatomic considerations or cardiac and/or pulmonary risks, a modified retroperitoneal approach or a unilateral bypass with a femoro-femoral

crossover may be used. Consideration should be given to using an axillo (bi) femoral (Fig. 21) or cross-over femoral (Fig. 22) bypass in patients with increased comorbidities, making a transabdominal approach less desirable. Patency rates depend upon the indication for the reconstruction and the justification for the unilateral bypass (normal inflow artery versus high surgical risk). In some cases, patency of unilateral bypass can be supplemented by endovascular means. The thoracic aorta has also been used as an inflow artery. Mean patency rates at 5 years after extra-anatomic bypass range from 50% to 75%.

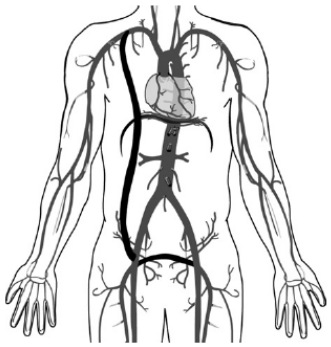


Fig. 21
Axillo (bi) femoral bypass

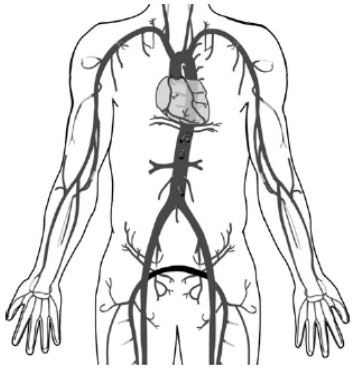


Fig. 22
Cross-over femoral bypass

INFRAINGUINAL REVASCULARIZATION

Endovascular treatment of infrainguinal arterial occlusive disease

Endovascular treatment of infrainguinal disease in patients with IC is an established treatment modality. The low morbidity and mortality of endovascular techniques such as PTA makes it the preferred choice of

treatment in limited disease such as stenoses/occlusions up to 10 cm in length. The technical and clinical success rate of PTA of femoro-popliteal artery stenoses in all series exceeds 95%[85]. Device developments such as hydrophilic guide wires and technical developments, such as subintimal recanalization, provide high recanalization rates in total occlusions of more than 85%[24]. The technique of subintimal angioplasty is not as dependent on length, but rather on the presence of normal vessel above and below the occlusion to allow access[86]. Table 4 summarizes pooled results of femoral popliteal dilatations[85, 87-89].

Table 4. Pooled results of femoral popliteal dilatations

	1-year % patency (range)	3-year % patency (range)	5-year % patency (range)
PTA: stenosis	77 (78–80)	61 (55–68)	55 (52–62)
PTA: occlusion	65 (55–71)	48 (40–55)	42 (33–51)
PTA + stent: stenosis	75 (73–79)	66 (64–70)	
PTA + stent: occlusion	73 (69–75)	64 (59–67)	

Risk factors for recurrence were analyzed by multivariate stepwise backward regression analyses in various studies. Clinical stage of disease (IC versus CLI), length of lesion and outflow disease were most commonly found as independent risk factors for restenoses. A study by Schillinger of 172 patients successfully undergoing PTA of the superficial femoral and popliteal arteries observed that 6-month patency rates were related to hs-CRP levels at baseline and at 48 hours after intervention[90]. There is general agreement that for acute failure of PTA of an SFA lesion, stent placement is indicated. A recent randomized trial has demonstrated significantly higher primary patency rates of stenting vs. PTA of femoro-popliteal artery lesions TASC A and B at 1-year follow up[91]. Randomized trials comparing PTA versus bypass surgery (BP) in infrainguinal arterial obstructive disease are almost nonexistent. However, Wolf *et al.* published a multicenter, prospective randomized trial comparing PTA with BP in 263

men who had iliac, femoral or popliteal artery obstruction[92]. This study of patients randomly assigned to BP or PTA showed no significant difference in outcomes during a median follow-up of 4 years (survival, patency and limb salvage). Another randomized study of 452 patients demonstrated no difference in amputation-free survival at 6 months; however, surgery was somewhat more expensive[93]. Medical treatment after PTA and stent placement is recommended to prevent early failure because of thrombosis at the site of intervention. Standard therapy is heparinization during the intervention to increase activated clotting time to 200–250 seconds. After PTA and stenting of femoropopliteal arteries, a life-long antiplatelet medication is recommended to promote patency (acetylsalicylic acid or clopidogrel). Life-long antiplatelet therapy is also recommended to prevent cardiovascular events. Much of the supporting evidence for periprocedural antiplatelet and adjuvant therapy is extrapolated from that related to the coronary circulation.

Endovascular treatment of infrapopliteal occlusive disease

Endovascular procedures below the popliteal artery are usually indicated for limb salvage and there are no data comparing endovascular procedures to bypass surgery for IC in this region. Angioplasty of a short anterior or posterior tibial artery stenosis may be performed in conjunction with popliteal or femoral angioplasty. Use of this technique is usually not indicated in patients with IC. There is increasing evidence to support a recommendation for angioplasty in patients with CLI and infrapopliteal artery occlusion where in-line flow to the foot can be re-established and where there is medical co-morbidity. In the case of infrapopliteal angioplasty, technical success may approach 90% with resultant clinical success of approximately 70% in some series of patients with CLI. Salvage rates are reported as being slightly higher. Predictors of successful outcome include a shorter length of occlusion and a lesser number of vessels treated. The complication rate (2.4%–17% depending upon the definition) can usually be treated by endovascular or surgical techniques and a failed angioplasty does not preclude subsequent bypass.

Surgical treatment of infrainguinal occlusive disease

In the case of multilevel disease, the adequacy of inflow must be assessed anatomically or with pressure measurements and occlusive disease treated prior to proceeding with an outflow procedure. In some situations, a combined approach with dilatation of proximal lesions and bypassing of distal lesions should be performed. A recent study has shown a trend towards increasingly complex bypass grafts (composite and spliced vein) to more distal arteries in patients with greater comorbidities, such as diabetes, renal failure and coronary artery disease; however, mortality rates have remained constant[94].

Bypass

Infrainguinal bypass procedures (Figs. 23-24) need to arise from a patent and uncompromised inflow artery although the actual level (common femoral artery versus superficial femoral or popliteal artery) does not correlate with patency. If the infrainguinal bypass is constructed following an inflow procedure, patency is improved by making the proximal anastomosis to a native artery rather than the inflow graft[95]. The quality of the outflow artery is a more important determinant of patency than the actual level where the distal anastomosis is performed. A distal vessel of the best quality should be used for the distal anastomosis. There is no objective evidence to preferentially select either tibial or peroneal artery, since they are typically of equal caliber. The results of femoral crural bypass have not been subjected to meta-analysis. Five-year assisted patency rates are reported in table 5.

Table 5. Five-year patency following femoral popliteal bypass[84]

PTFE: polytetrafluoroethylene graft

	Claudication	CLI
Vein	80	66
Above-knee PTFE	75	47
Below-knee PTFE	65	65

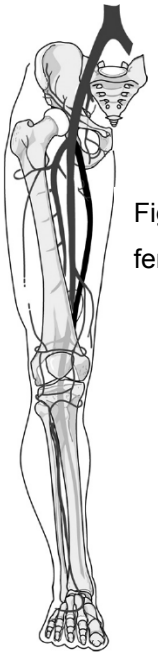


Figure 23 Above-knee femoral popliteal bypass

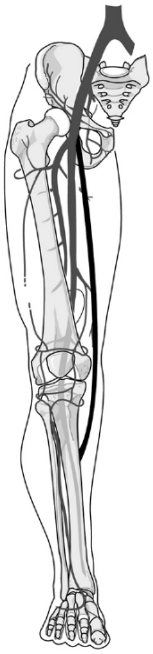


Figure 24 Femoral tibial bypass

AIM OF THE STUDY

PTA has revolutionized the management of PAD. Even in the setting of CLI, broadly similar outcomes have been obtained when PTA and bypass surgery are compared. With PTA, local anesthesia can be used, hospital stay is shorter, and morbidity and mortality rates may be lower. Moreover, the best results may be achieved when the revascularization with PTA is a part of a strategy of integrated care that begins with the initial clinical evaluation by the vascular specialist, follows the patient after the restoration of an adequate blood flow, leads to the healing of the ischemic skin lesion, and finally takes measures to prevent or minimize a further worsening of the disease. Aim of this study was to assess the feasibility of this strategy of integrated care and to evaluate the mid-term results, mainly in terms of mortality, limb salvage (LS), progression of disease (DP), and need of further revascularizations.

METHODS

Between January 2007 and June 2008, a total of 215 patients (265 critical arterial lesions in 265 limbs) underwent elective PTA for symptomatic PAD in one single centre (Clinique Pasteur – Toulouse – France). The present study included 105 patients treated for CLI, with 137 critical arterial lesions in 137 limbs. All patients were referred to our centre for signs and symptoms consistent with CLI and were subsequently evaluated by an expert vascular specialist by means of an accurate physical examination, with general investigation of atherosclerotic disease and a duplex ultrasound to obtain the quantification of the arterial flow, and the confirmation of the diagnosis. Patients were then jointly evaluated by vascular specialist, interventional cardiologist and a vascular surgeon: a diagnostic angiography was performed if indicated by the results of non-invasive assessment, and the decision to perform PTA instead of surgery was considered on the basis of a suitable anatomy, the technical feasibility of the procedure, the presence of comorbidities (in particular co-existing coronary or cerebrovascular disease, chronic renal insufficiency and neurologic alterations), a high surgical risk and the patient's preference.

Arterial lesions were codified according to TASC classification of aorto-iliac and femoral-popliteal lesions (Figs. 18-19). To better evaluate the impact on survival and the restenosis rates according to the level of the disease, the arterial tree was also categorized into three groups: the aorta and iliac arteries (A-I), the common femoral, superficial femoral, and profunda femoral arteries (Fem), and the popliteal and tibial arteries (Pop-Tib). PTA was performed using mostly the femoral approach, choosing the anterograde puncture for more distal and complex lesions. Indications for stent placement were significant residual stenosis, flow-limiting dissections, or elastic recoil after PTA. Antiplatelet therapy was started at least 24 hours before the procedure with aspirin (100 mg/day) and a loading dose of 300 mg of clopidogrel. After the procedure, all patients were prescribed lifelong aspirin (75-100 mg/day) or clopidogrel (75mg/day), and, for stent placement, dual antiplatelet therapy of aspirin+clopidogrel (at least 1 month) was recommended. In case of previous oral anticoagulant treatment, single antiplatelet therapy (aspirin or clopidogrel) was prescribed, also after stent placement. All treated patients were carefully followed after their discharge by regular office visits in a peculiar medical facility called “wound healing centre”, where the active collaboration between the vascular specialist and specialists in foot care allowed to achieve the best results in terms of cicatrization and subsequent prevention of the worsening of the disease. Clinical follow-up of at least three months was then obtained for all patients by office visit or direct telephone call. Periodical non-invasive assessment with duplex ultrasound was systematically performed at 1, 3 and 6 months. All angiographic controls were ischemia-driven.

Definitions

CLI was defined as chronic ischemic rest pain with presence of non-healing ulceration or gangrene attributable to objectively proven arterial occlusive disease. Procedural success was defined as restoration of a normal blood flow (TIMI 3) with a residual stenosis <30%. Creatinine clearance < 60 ml/min defined a significant renal disease. Target lesion

revascularization (TLR) was defined as any revascularization (PTA or bypass surgery) performed to treat a >50% luminal narrowing at the lesion site or in the 5-mm distal or proximal segments adjacent to the lesion. DP was defined as new lesion in a different site. LS was defined as the preservation of the affected limb with no need for amputation above the metatarsal level (minor amputation).

Statistical analysis

Data are presented as frequencies with percentages and mean ± standard deviation (SD). Differences between groups were assessed using chi-square for categorical variables and Student t-test for continuous ones. Event- free survival curves were generated by the Kaplan-Meier method. A multivariable Cox proportional hazard model was created to identify independent predictors of mortality, TLR, DP and LS. All the variables that showed, at the univariate analysis, a significant difference between groups, with a p-value <0.1, were entered in the Cox regression model, to evaluate their independent role in predicting events during the follow-up. Results were reported as odds ratios, together with associated 95% confidence intervals. Statistical analyses were performed using SPSS 15.0 for Windows (SPSS Inc., Chicago, IL, USA).

RESULTS

Clinical characteristics and biological data

One-hundred-five patients with a total of 137 peripheral arterial lesions in 137 limbs underwent elective PTA for CLI. The mean age was 77±10 years, 59 patients (56.2%) were males and 58 (55.2%) were diabetic, 42 of them (40%) with insulin-requiring diabetes. Mean HbA1c was 6.9±1.2% and signs of diabetic neuropathy were present in 31/58 diabetic patients (53.4%). Forty-eight patients (45.7%) were smokers or former smokers. Eighty-nine patients (84.8%) were hypertensive, 57 (54.3%) had dyslipidemia, and 71 (67.6%) had significant renal disease. Two patients (1.9%) had end-stage renal failure, requiring dialysis three times per week.

Seven (6.7%) patients had a previous PTA and 10 (9.5%) a previous peripheral graft. History of coronary artery disease (CAD) was present in 35 (33.3%) patients and history of cardiac heart failure (CHF) in 28 (26.7%). Mean left ventricular ejection fraction (LVEF) was 56±10%. Concerning other co-existing vascular disease, carotid artery stenosis≥70% was present in 13 patients (12.4%), and abdominal aortic aneurysm≥3 cm in 5 patients (4.8%). Indication to clinical evaluation and subsequent revascularization with PTA was rest pain with non-healing ulcer in 96 patients (91.4%) and with gangrene in 9 patients (8.6%). All patients were in Fontaine stage IV. As to biological data, mean Hct value was 36±5%, mean CRP 41±59 mg/l, mean fibrinogen 4.4±1.2 g/l and mean pro-BNP 2343±4278 pg/ml. Table 6 summarizes clinical and biological characteristics of the studied population.

Table 6. Clinical and biological characteristics of the studied population

Variables	**Mean ± SD or Frequency (%)**
N patients	105
Age (years)	77±10
Male sex	59 (56.2)
Diabetes	58 (55.2)
IDDM	42 (40)
Diabetic neuropathy	31/58 (53.4)
Smoking habit	48 (45.7)
Hypertension	89 (84.8)
Dyslipidemia	57 (54.3)
Previous peripheral graft	10 (9.5)
Previous PTA	7 (6.7)
Carotid disease (≥70%)	13 (12.4)
Abdominal aortic aneurysm (≥3 cm)	5 (4.8)
History of CAD	35 (33.3)
History of CHF	28 (26.7)
LVEF (%)	56±10
Renal disease (CrCl<60 ml/min)	71 (67.6)
End-stage renal failure	2 (1.9)
Indication	
Rest pain with non-healing ulcer	96 (91.4)
Rest pain with gangrene	9 (8.6)
Fontaine stage	
IV	105 (100)
Hct (%)	36±5
CRP (mg/l)	41±59

Fibrinogen (g/l)	4.4±1.2
Creatinine (µmol/l)	115±66
HbA1c (%)	6.9±1.2
pro-BNP (pg/ml)	2343±4278
CrCl (ml/min)	50±23

Hemodynamic and procedural parameters

One-hundred-thirty-seven lesions were treated, in 137 affected limbs. Mean lesion diameter was 5.3±1.7 mm and mean lesion length was 55±32 mm. Five lesions (3.6%) were included in A-I group, 60 (43.8%) in Fem group, and 68 (49.6%) in Pop-Tib group. In four cases (2.9%) PTA concerned lesions in previous grafts. Concerning TASC classification, lesions were mostly type B3 (98 cases - 71.5%) i.e. single or multiple stenosis totaling 3-10 cm involving the external iliac artery (EIA) not extending into the common femoral artery (CFA), for aorto-iliac lesions, and single or multiple lesions in the absence of continuous tibial vessels to improve inflow for a distal bypass, for femoral popliteal lesions. Nineteen lesions (13.9%) were type C1, i.e. bilateral common iliac artery occlusions, for aorto-iliac lesions, and multiple stenoses or occlusions totaling >15 cm with or without heavy calcification, for femoral-popliteal lesions. A total of 77 (56.2%) occlusion were treated: the popliteal-tibial segment was involved in 40/77 cases (51.9%) and the femoral segment in 32/77 (41.6%). Femoral access was used to treat 131 lesions (95.6%) with a 6F sheath in 107 cases (78.1%) and an anterograde approach in 57 (41.6%). Balloon angioplasty was performed in 127 (92.7%) lesions and stent implantation was required in 81 lesions (59.1%), mostly with a self-expanding stent (74/81 – 91.4%). Mean stent diameter was 6±1.4 mm and mean stent length was 69±44 mm. Subintimal angioplasty was performed to treat occlusions in 46/77 cases (59.7%). Closure device were used in only 35 cases (25.5%), due to the diffuse and calcified arterial disease in this peculiar subset of patients. Table 7 describes in detail the hemodynamic characteristics of the arterial lesions and the procedural parameters.

Table 7. Hemodynamic characteristics of the arterial lesions and procedural parameters

Variables	Mean ± SD or Frequency (%)
N lesions	137
ABI	0.4±0.1
TASC classification	
a2	2 (1.5)
b1	5 (3.6)
b2	3 (2.2)
b3	98 (71.5)
b5	1 (0.7)
c1	19 (13.9)
c2	6 (4.4)
c3	1 (0.7)
d2	2 (1.5)
Aorto-iliac PTA	5 (3.6)
Femoral PTA	60 (43.8)
Popliteal-Tibial PTA	68 (49.6)
Previous grafts PTA	4 (2.9)
Total occlusion treated	77 (56.2)
Aorto-iliac	3/77 (3.9)
Femoral	32/77 (41.6)
Popliteal-Tibial	40/77 (51.9)
Bypass	2/77 (2.6)
Occlusion with procedural success	67/77 (87)
Abdominal aorta lesions	0
Iliac artery	
Critical lesion	6 (4.4)
Occlusion	2 (1.5)
Common femoral	
Critical lesion	6 (4.4)
Occlusion	1 (0.7)
Superficial femoral	
Critical lesion	36 (26.3)
Occlusion	27 (19.7)
Profunda femoral	
Critical lesion	5 (3.6)
Occlusion	0
Popliteal	
Critical lesion	20 (14.6)
Occlusion	18 (13.1)
Tibio-peroneal trunk	
Critical lesion	8 (5.8)
Occlusion	8 (5.8)
Peroneal	
Critical lesion	15 (10.9)
Occlusion	16 (11.7)
Anterior tibial	
Critical lesion	13 (9.5)
Occlusion	23 (16.8)

Posterior tibial	
Critical lesion	3 (2.2)
Occlusion	19 (13.9)
Previous grafts	
Critical lesion	4 (2.9)
Occlusion	3 (2.2)
Femoral access	131 (95.6)
Humeral access	4 (2.9)
Graft access	2 (1.5)
French size	
6 F	107 (78.1)
7 F	30 (21.9)
Retrograde access	80 (58.4)
Anterograde access	57 (41.6)
% stenosis	91±9
Lesion diameter	5.3±1.7
Lesion length	55±32
Balloon angioplasty	127 (92.7)
Stent implantation	81 (59.1)
Stent type	
Self-expanding stent	74 (91.4)
Balloon-expandable stent	7 (8.6)
Stent diameter	6±1.4
Stent length	69±44
Stents number (per lesion)	0.8±0.8
Subintimal angioplasty	46/77 (59.7)
Endografts	0
Thrombolythic therapy	2
Atherectomy	0
Closure device	
Manual compression	102 (74.5)
Angioseal	11 (8)
Starclose	24 (17.5)

Peri-procedural and in-hospital follow-up

Procedural success was achieved in 125 lesions (91.2%). As to total occlusions, 67/77 (87%) were treated with an immediate success. There were 3 (2.2%) procedural complications and 2 in-hospital death (1.9%). The mean hospital stay was 5.3±4.7 days. Fourteen patients (13.3%) had in-hospital complications with 2 non-fatal myocardial infarction (MI), 4 hemorrhagic complications needing transfusion, 3 cases of acute renal failure and 2 local complications needing surgical repair. As predictable, patients with critical pre-procedural conditions usually had more than one in-hospital complication. At discharge, 101 patients (96.2%) were on ASA, 92 (87.6%) were on clopidogrel, 14 (13.3%) were on warfarin, and 88

(83.8%) had dual antiplatelet therapy. Table 8 summarizes peri-procedural and in-hospital follow-up data.

Table 8. Peri-procedural and in-hospital follow-up

Variables	Mean ± SD or Frequency (%)
N lesions	137
Immediate procedural success	125 (91.2)
Procedural complications	3 (2.2)
Hematoma	1 (0.7)
AV fistula	2 (1.5)
In-hosp death	2 (1.9)
Patients with in-hospital complications	14 (13.3)
Type of in-hospital complications	
Thrombosis	3 (2.2)
Embolism	1 (0.7)
Hematoma	8 (5.8)
False aneurysm	2 (1.5)
AV fistula	1 (0.7)
Haemorrhage	5 (3.6)
Need of transfusion	4 (2.9)
Need of surgery	2 (1.5)
Non-fatal MI	2 (1.5)
Acute renal failure	3 (2.2)
Hospital stay	5.3±4.7
Therapy at discharge (patients)	
Warfarin	14 (13.3)
ASA	101 (96.2)
Clopidogrel	92 (87.6)
ASA + Clopidogrel	88 (83.8)
ASA + Clopidogrel + Warfarin	3 (2.9)

Mid-term follow-up

Clinical follow-up was available for 100% of patients over a mean of 304±161 days. At follow-up, 26 patients (24.8%) had died, 20 (19%) of them for cardiovascular causes. Twelve patients (11.4%) were amputated, and 7 of them (58.3%) were still alive. LS was achieved in 124 (90.5%) limbs. Restenosis was present in 14 lesions (10.2%) and DP was found in 19 lesions (13.9%). TLR was performed in 12 lesions (8.8%): 10 (7.3%) repeated PTA and 2 (1.5%) bypass surgery. DP was treated with PTA in 2 cases (1.5%), with bypass surgery in 3 cases (2.2%), in 1 case (0.7%)

with thromboendarterectomy, and with medical therapy in the remaining 13 cases (9.5%). TLR and DP were associated in 3 cases (2.2%). Nineteen patients (18.1%) reported symptoms of IC, and continuing CLI with persistence of tissue necrosis was found in 15 patients (14.3%), in 9 (8.6%) cases with co-existing infection. Dual antiplatelet therapy was not discontinued in 39 (37.1%) patients, and 5 patients experienced hemorrhagic complications. Data on mid-term follow-up are summarized in Table 9.

Table 9. Mid-term follow-up

Variables	**Mean ± SD or Frequency (%)**
Follow-up (days)	304±161
Angiographic control (symptoms driven)	28 (20.4)
All cause mortality	26 (24.8)
Cardiac mortality	20 (19)
Amputated patients	12 (11.4)
Claudication	19 (18.1)
Tissue necrosis	15 (14.3)
Infection	9 (8.6)
Angor	2 (1.9)
MI	3 (2.9)
PCI	1 (1)
Stroke	2 (1.9)
Hemorrhage	5 (4.8)
Antithrombotic therapy	11 (10.5)
ASA	77 (73.3)
Clopidogrel	52 (49.5)
ASA + Clopidogrel	39 (37.1)
Total lesions treated	**137**
Limb salvage	124 (90.5)
Restenosis	14 (10.2)
Embolic occlusion	1 (0.7)
Disease progression	19 (13.9)
TLR	12 (8.8)
Treatment of restenosis and disease progression	
re-PTA	10 (7.3)
Medical therapy	14 (10.2)
Bypass	4 (2.9)
TEA	1 (0.7)

Mortality

Mortality was associated with history of cardiac heart failure (46.2% vs 20.3%, p=0.01), lower LVEF (50%±11 vs 58%±8, p<0.05), higher plasmatic levels of fibrinogen (5±1.1 g/l vs 4.1±1.1 g/l, p<0.05) and pro-BNP (11420±25316 pg/ml vs 1176±1875 pg/ml, p<0.05), and a PTA performed on the femoral artery (69.2% vs 45.6%, p=0.04). Independent predictors of mortality were LVEF < 60% (OR 19; 95% C.I. 2.5-45; p=0.04) and a level of plasma fibrinogen ≥ 4.3 g/l (OR 27; 95% C.I. 2.1-40; p=0.01). The two cut-off values were chosen on the basis of mean values of each parameter. Table 10 and 11 show the results of univariate and multivariate analysis, concerning mortality. KM curve on cumulative survival of the studied population is presented in Figure 25.

Table 10. Differences between groups, according to mid-term survival (only p values <0.1 were reported)

Variables	**Dead** Mean ± SD or Frequency (%)	**Alive** Mean ± SD or Frequency (%)	**p value**
N of patients	26 (25)	79 (75)	
History of CHF	12 (46.2)	16 (20.3)	0.01
LVEF (%)	50±11	58±8	<0.05
Renal disease (CrCl<60 ml/min)	21 (80.8)	50 (63.3)	0.09
Fibrinogen (g/l)	5±1.1	4.1±1.1	<0.05
pro-BNP (pg/ml)	11420±25316	1176±1875	<0.05
Femoral PTA	18 (69.2)	36 (45.6)	0.036
Popliteal-Tibial occlusion	4 (15.4)	26 (32.9)	0.086
Immediate procedural success	21 (80.8)	74 (93.7)	0.052

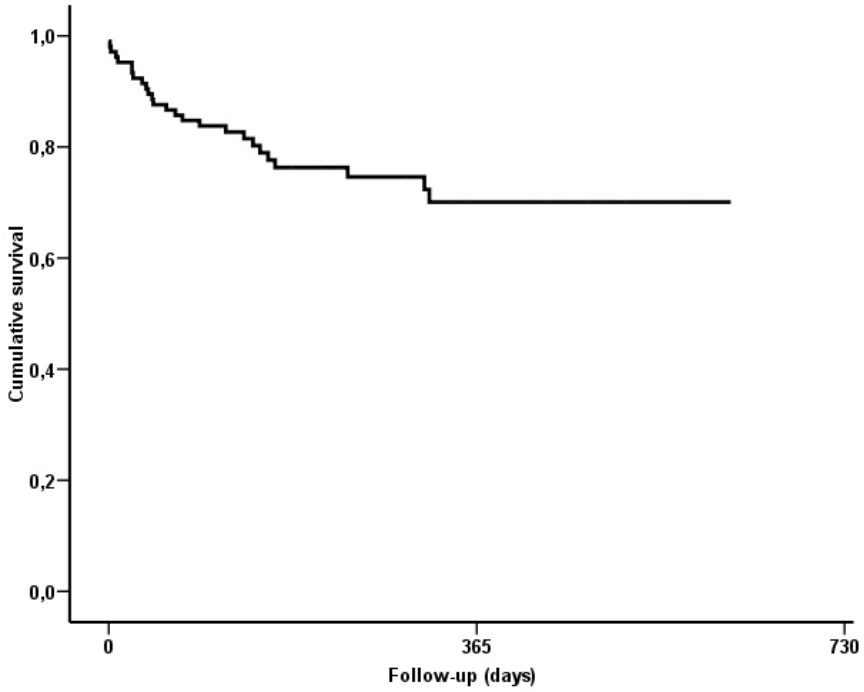
Table 11. Multivariate Cox analysis, showing predictors of mortality

Mortality

Variables	**OR**	**95%C.I.**	**p value**
Renal disease	5.1	0.8-32	0.08
LVEF < 60%	19.2	2.5-45	0.04
Fibrinogen ≥ 4.3 g/l	27.3	2.1-40	0.01

Fig. 25

Cumulative survival of the studied population



TLR and DP

TLR was associated with smoking habit (75% vs 42.4%, p=0.03), dyslipidemia (83.3% vs 48.8%, p=0.02), a previous peripheral graft (33.3% vs 8%, p=0.006) and higher plasmatic levels of pro-BNP 14095±36802 pg/ml vs 2435±4438 pg/ml, p<0.05). Finally, TLR was not associated to the use of subintimal technique (8.3% in TLR group vs 36% in no-TLR group). At multivariate analysis, no parameter showed and independent role in predicting TLR. Table 12 reports univariate analysis as to TLR.

DP was associated with a higher prevalence of CAD (63.2% vs 32.2%, p=0.009), the presence of a significant renal disease (89.5% vs 65.3%, p=0.03) and placement of shorter stents (41±28 vs 73±45, p<0.05). At multivariate analysis, no independent predictors of DP were found, and renal disease showed only a trend toward a predicting role (OR 3.9, 95% C.I. 0.9-17, p=0.07). Table 13 reports univariate analysis as to DP.

KM curves according to survival-free from TLR and from DP are presented in Figure 26 and 27.

Table 12. Differences between groups, according to TLR presence (only p values <0.1 were reported)

Variables	**No TLR** Mean ± SD or Frequency (%)	**TLR** Mean ± SD or Frequency (%)	**p value**
N of lesions treated	125 (91.2)	12 (8.8)	
Smoking habit	53 (42.4)	9 (75)	0.03
Dyslipidemia	61 (48.8)	10 (83.3)	0.02
Previous peripheral graft	10 (8)	4 (33.3)	0.006
Subintimal angioplasty	45 (36)	1 (8.3)	0.05
pro-BNP (pg/ml)	2435±4438	14095±36802	<0.05

Fig. 26

Survival free from TLR

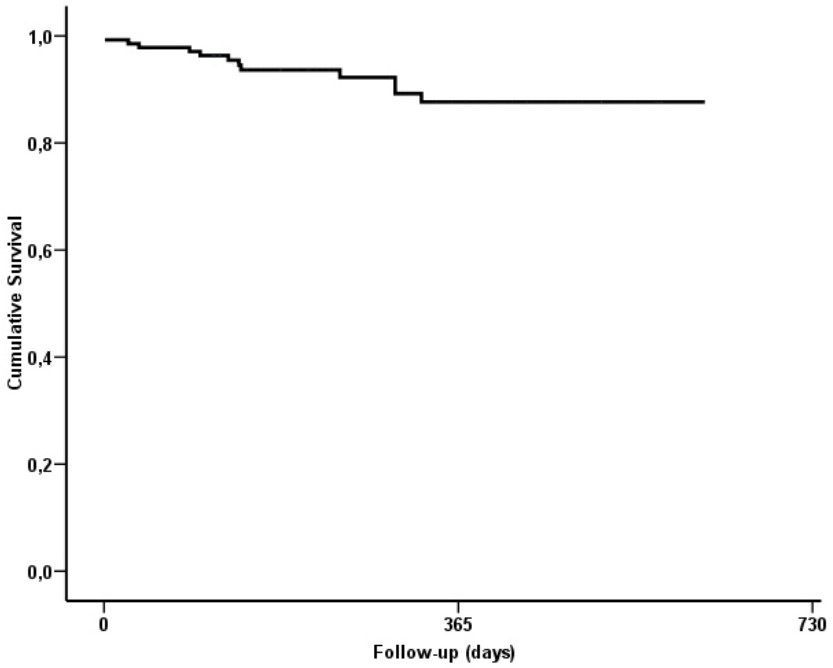
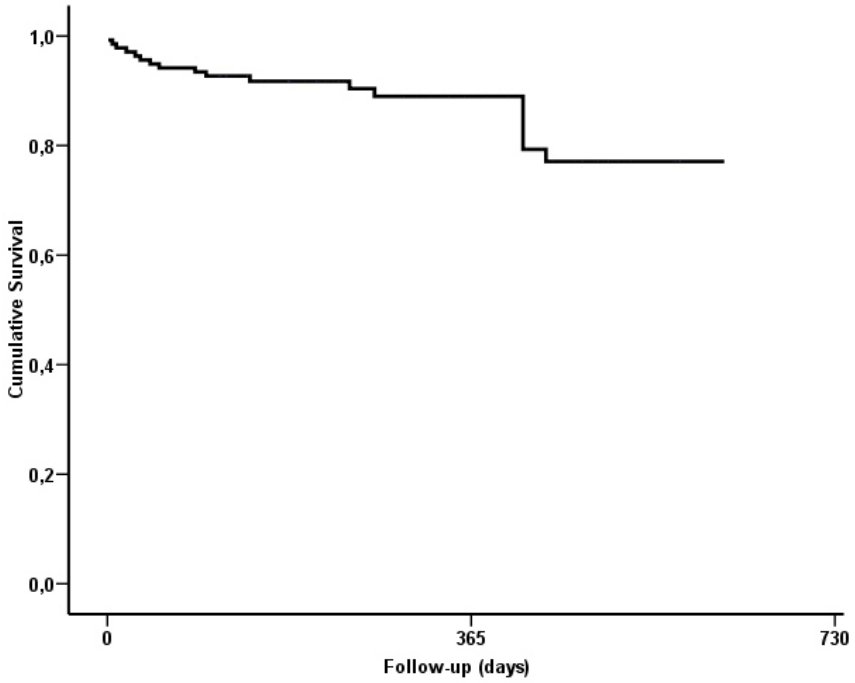


Table 13. Differences between groups, according to DP presence (only p values <0.1 were reported)

Variables	No DP Mean ± SD or Frequency (%)	DP Mean ± SD or Frequency (%)	p value
CAD	38 (32.2)	12 (63.2)	0.009
Renal disease	77 (65.3)	17 (89.5)	0.03
Stent length	73±45	41±28	<0.05

Fig. 27

Survival free from disease progression



Limb salvage

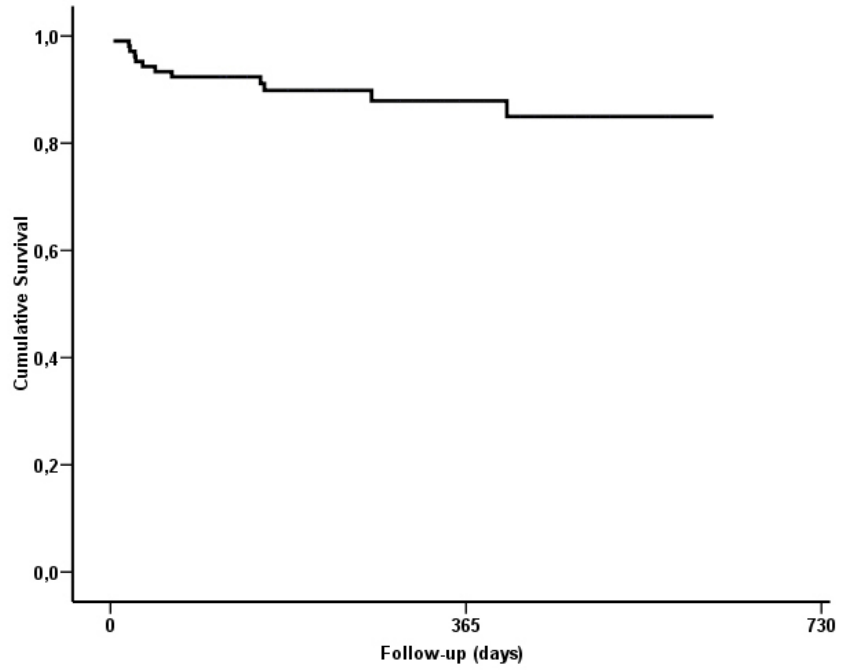
LS was associated with lower plasmatic levels of CRP (27.9±46.4 vs 59.6±41.4, p<0.05). No parameter had a predictive role on LS at multivariate analysis. Table 14 reports univariate analysis for LS. Figure 28 presents KM curve, according to survival free from amputation.

Table 14. Differences between groups, according to limb salvage (only p values <0.1 were reported)

Variables	No limb salvage Mean ± SD or Frequency (%)	Limb salvage Mean ± SD or Frequency (%)	p value
N of patients	12 (11.4)	93 (88.6)	
Indication			0.03
Rest pain with non-healing ulcer	9 (75)	87 (93.5)	
Rest pain with gangrene	3 (25)	6 (6.5)	
CRP (mg/l)	59.6±41.4	27.9±46.4	<0.05

Fig. 28

Survival free from amputation



DISCUSSION

Feasibility

Similar to other series[96, 97], our study showed that endovascular option for the treatment of PAD appears safe, with high procedural success (91%), low-procedure-related complication rate (2%), and a mean hospital stay less than 6 days. Moreover, PTA do not require general anesthesia, can be safely performed as a day-case procedure[98], and is less aggressive

than surgery, with comparable outcomes and a decreasing rate of major amputation[97]. The incorporation of subintimal angioplasty into current practice has also permitted to significantly change the treatment of arterial occlusions[99-102], providing most patients with limb salvage and freedom from surgical bypass at least at mid-term[103]. Our experience shows favorable in-hospital outcomes, particularly a low rate of major cardiovascular events (1.5%) and hemorrhagic complications (1.5%). Reported in-hospital complication rates range from 3 to 9%, depending on the heterogeneity of risk profile[96, 104]. These observations are relevant in a population with a mean age of nearly 80 years, where all patients presented with non-healing ulcer or gangrene, 68% of patients had significant renal disease, and mean pro-BNP value was > 2000 pg/ml. Comparing to other studies[96, 104, 105], the higher mean age and the greater prevalence of renal disease identify a very fragile population at high surgical risk, for which endovascular treatment represents the hope to avoid amputation, and improve functional status and quality of life. To support endovascular option also in very critical conditions, a recent study stated that PTA is feasible and effective also in dialysis patients with PAD, and should be preferred to other more invasive interventions[106].

Mortality

Although a mortality rate of 25% is not negligible, it is in step with the high risk population of our study. A lower LVEF, a history of CHF, as in another study[104], and higher pro-BNP levels were strongly associated with mortality and, as already known for patients with CLI, mostly of our patients die for cardiovascular causes (19%). Mortality was also associated with higher levels of plasma fibrinogen (reflecting the inflammatory status and the co-existence of ulcer infection, that represents a marker of PAD severity), and with the presence of the disease at the femoral level, probably due to the more proximal involvement of the arterial tree. Independent predictors of mortality were an LVEF < 60% and a level of plasma fibrinogen ≥ 4.3 g/l. The presence of significant renal disease also showed a trend toward a significant role in favouring

mortality. Patients with the highest risk profile are those with reduced left ventricular function (mostly related to CAD) and significant inflammatory and infective status, that also underlines a more active and aggressive atherosclerotic disease.

Restenosis, TLR and DP

Angiographic control were not systematically planned but performed only in the presence of persistent CLI with evidence of restenosis or significant progression of the disease at duplex ultrasound. The restenosis rate was low (10%) with a TLR of 9%. More important was the progression of the disease (14%), as expected in this evolutive pathology. TLR was associated with classical risk factors as smoking habit and dyslipidemia, higher pro-BNP levels and the presence of a previous peripheral graft that is expression of an already diffused disease, mostly with a poor distal runoff[107]. DP was associated with renal disease and CAD, which are markers of advanced and aggressive disease. The relation between shorter stents and more frequent DP may suggest that an extensive treatment of the lesion does not necessarily lead to restenosis and may, on the other side, reduce DP. A recent meta-analysis of infrapopliteal angioplasty for CLI[108] reports that the durability of PTA is limited compared with bypass surgery. Nevertheless, for this kind of patients, the main result is not to avoid restenosis and DP, but to restore a normal blood flow (sometimes as a “temporary bypass”) for the time that is necessary to provide wound healing and limb salvage, favouring the treatment of infections where needed.

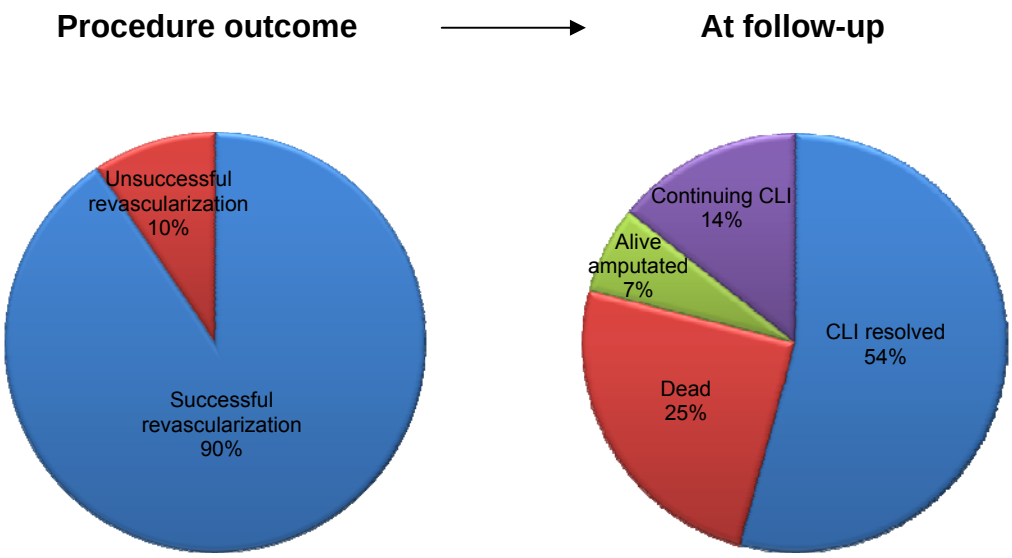
Limb salvage

Immediate procedural success was obtained in 125 limbs, and LS was achieved in 124 limbs. LS was associated with lower CRP levels, confirming that ulcer infection in PAD, expressed by CRP elevation, represents a powerful marker for amputation risk[109]. In this high risk population, only 12 patients were amputated and 7 of them are still alive. CLI was completely resolved in 54% of patients. This impressive result,

confirmed in other studies[96, 105, 110], underlines the efficacy of endovascular procedure that has to be regarded as the first line revascularization strategy in all cases of CLI[104]. LS, improvement in functional outcomes[111] and improvement in quality of life[112, 113] must be the main targets to achieve, in these patients with very high risk of amputation and, therefore, mortality. Moreover, salvage with repeat PTA can be accomplished, if necessary, in most patients, and, concerning the superficial femoral artery, also the early-failure after PTA alters the distal target in only 30% of patients if open bypass is planned[114]. Figure 29 reports the fate of the patients presenting with CLI in our study.

Fig.29

Fate of patients with CLI in our study



The concept of "integrated care"

There is no way to achieve the best results in terms of patient care, if the endovascular treatment is not conceived as a part of a planned strategy (Fig. 30), aimed at following the patient in every step of his healing process[115]. This model of integrated care[116, 117] started at the very first clinical observation by the general practitioner[118], in presence of signs or symptoms suggestive of PAD. The patient was then referred to the vascular specialist that confirmed the diagnosis and, jointly with the

interventional cardiologist and the vascular surgeon, evaluated feasibility and modality of the revascularization procedure. At the same time, the patient was investigated for co-existing vascular disease, trying also to modify his risk factors for cardiovascular events, especially diabetes[119], with optimal medical treatment. After the discharge, the patient was followed, once a week or more, by regular office visits in the "wound care unit", where the vascular specialist, with the aid of other specialists if needed, took care of ulcer, leading to healing with the improvement of the patient status. If no revascularization was possible or when the limb continued to deteriorate despite the presence of a patent reconstruction or in the case of persistent infection despite aggressive vascular reconstruction, the amputation became the only choice, aimed at obtaining the healing of the lower extremity at the most distal level possible. As the other patients, amputated patients were carefully followed after the surgical intervention: in this subgroup of patients is very important not to lose the contact, due to the risk for the patients to let himself go and to sink into depression.

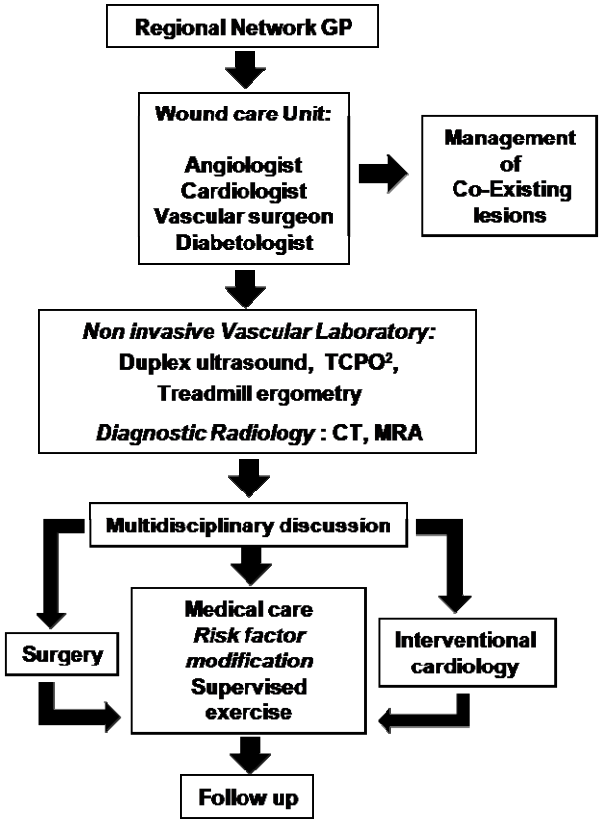


Fig.30
The integrated care model

A PATIENT CASE

Eighty year old woman, with hypertension, dyslipidemia and non-insulin-dependent-diabetes as risk factors. Previous femoro-tibial graft. She was referred to our centre for chronic rest pain with non-healing ulcer at the right leg (Fig. 31), and persistent fever (39°C) not-responding to antibiotic therapy. Duplex ultrasound revealed an occlusion of femoro-tibial graft.

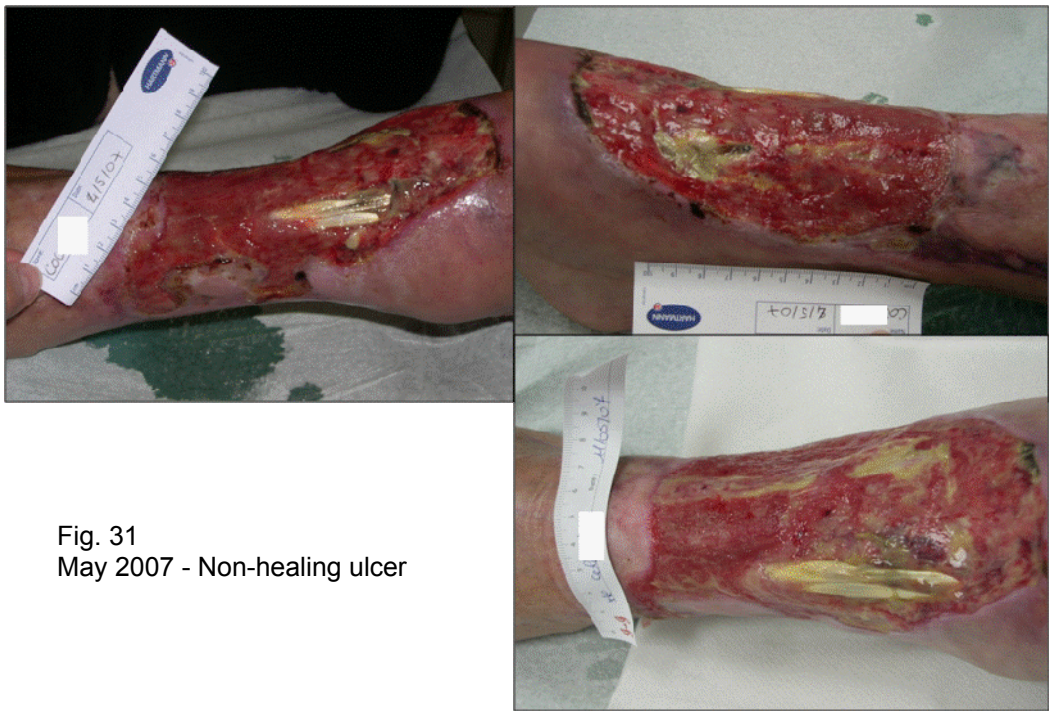


Fig. 31
May 2007 - Non-healing ulcer

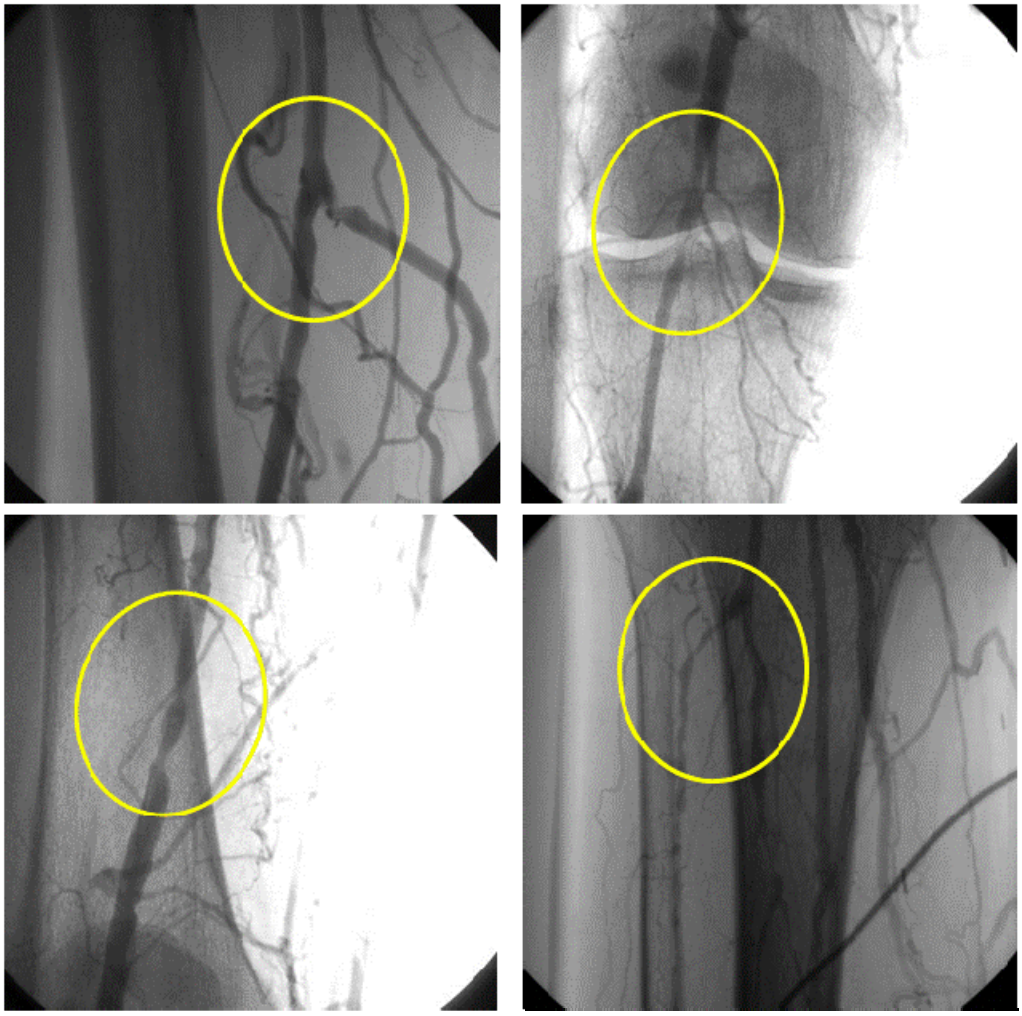
Angiography showed subocclusive lesion at the proximal anastomosis of the graft, with critical femoro-popliteal lesions and critical lesion at posterior tibial artery toward the plantar arch (Fig. 32).

Fig. 32

Baseline angiograms

a) proximal graft anastomosis

b) popliteal artery

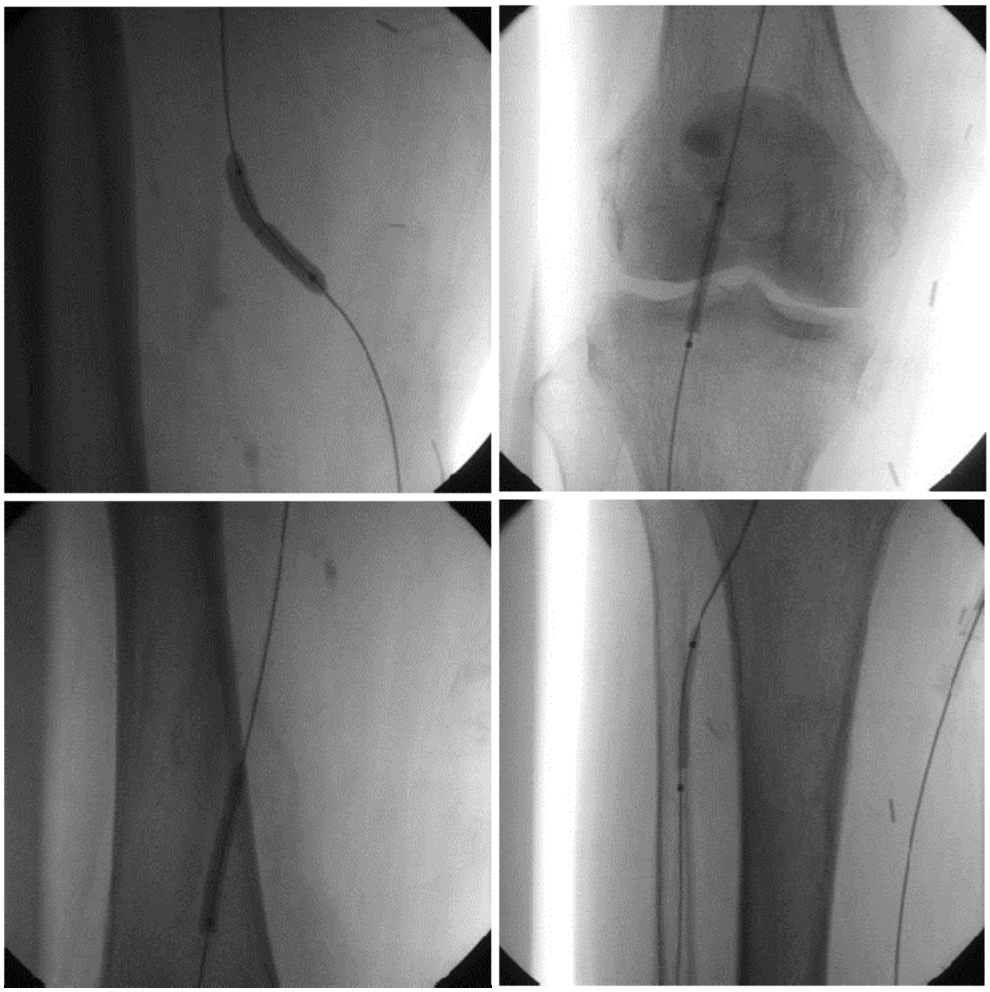


c) superficial femoral artery

d) tibial posterior artery

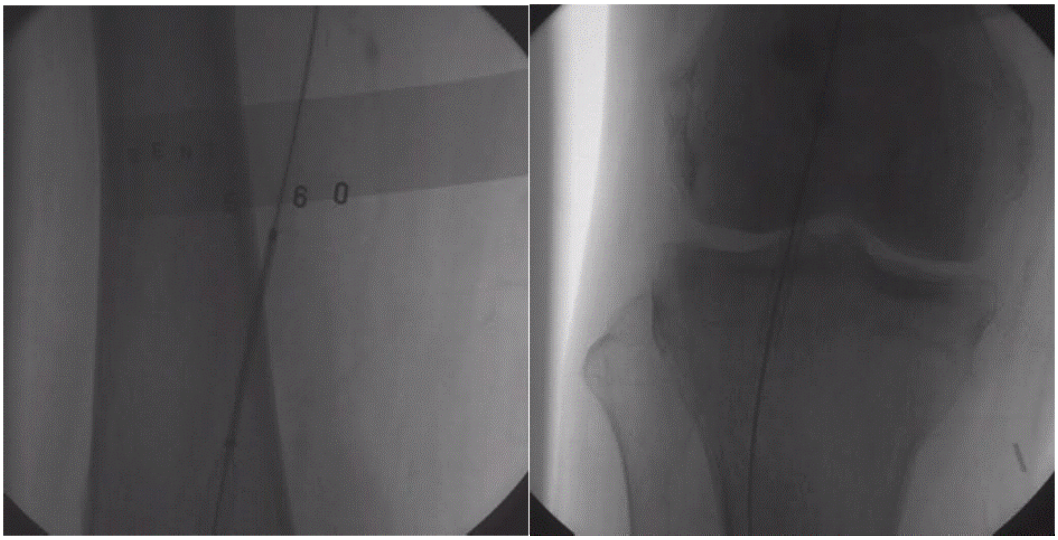
All lesions were treated with PTA with balloon (Fig. 33).

Fig. 33
PTA of the four lesions



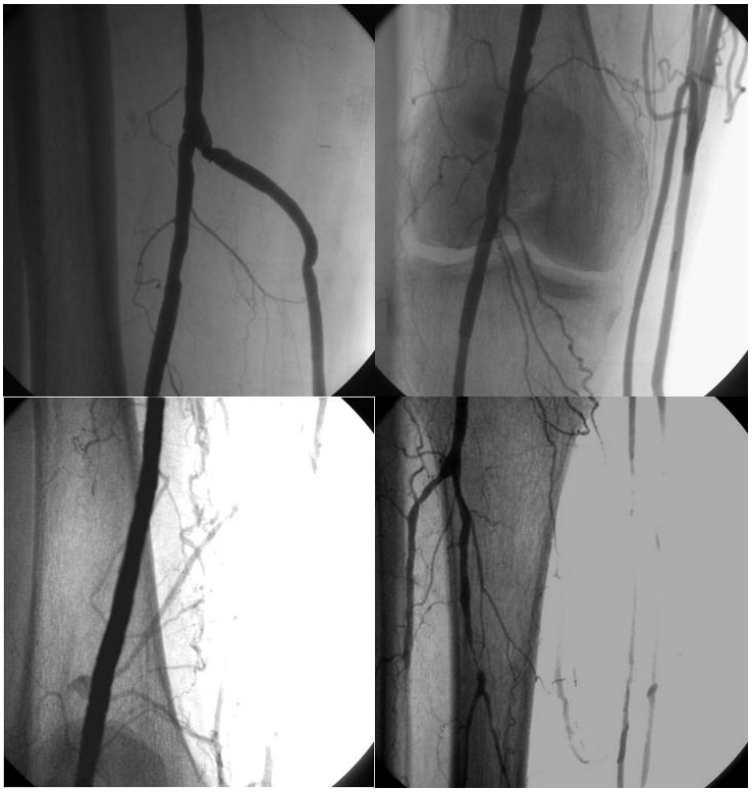
Femoro-popliteal lesions were treated with subsequent stent placement (Fig. 34); graft lesion and lesion on posterior tibial artery were treated only with balloon dilatation.

Fig. 34
Stenting of femoro-popliteal lesions



Final angiograms showed satisfactory results in terms of restoration of perfusion (Fig. 35).

Fig. 35
Final angiographic result



The patient had immediate improvement after the procedure: rest pain disappeared, cicatrization started and fever disappeared after 72 hours of antibiotic therapy. Improvement and healing process during the follow-up was impressive (Figs. 36-39).

Fig. 36

Follow-up at 2 months (July 2007)

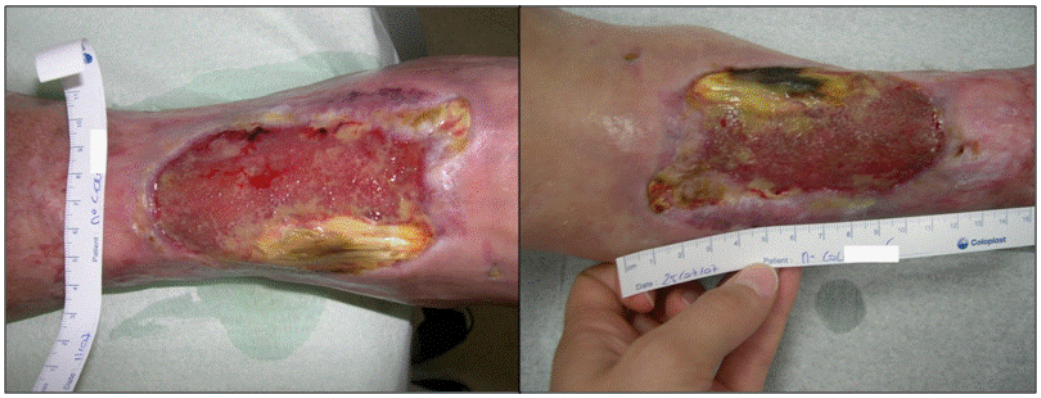


Fig. 37

Follow-up at 7 months (December 2007)

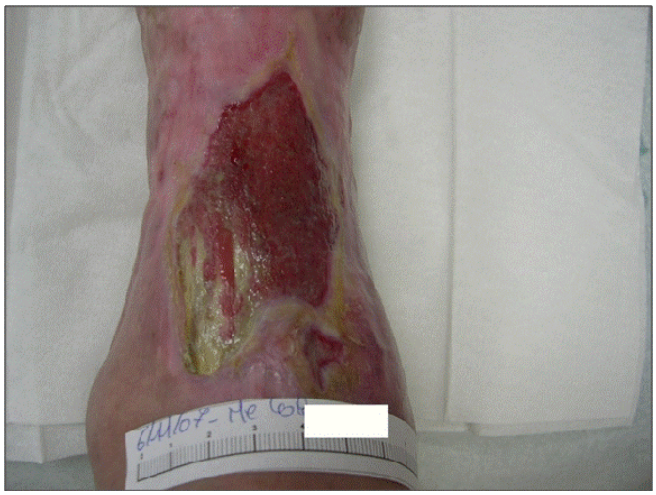


Fig. 38

Follow-up at 11 months (April 2008)

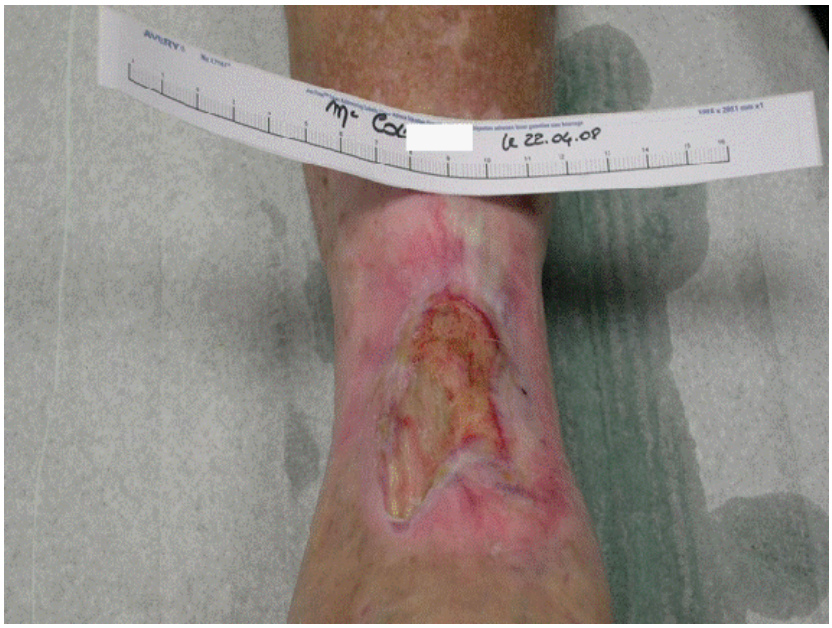
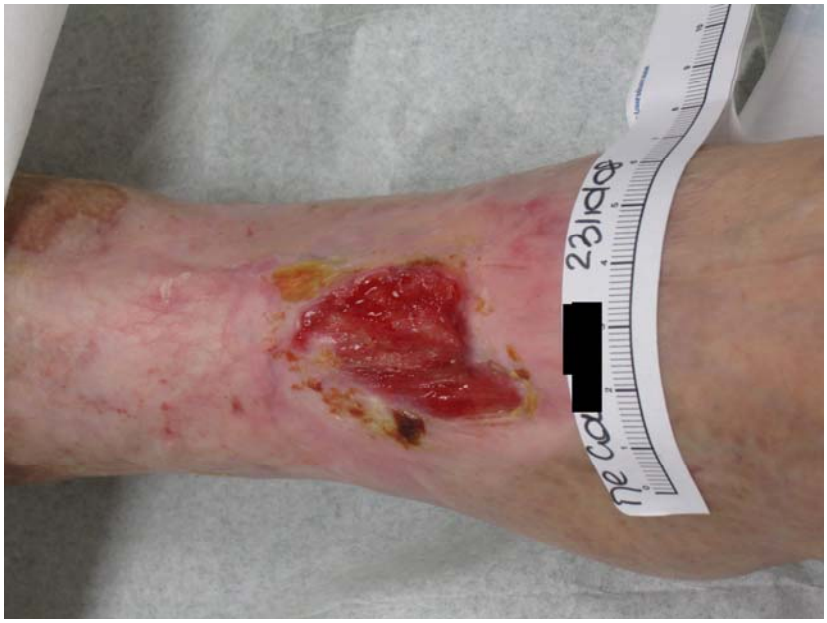


Fig. 39

Follow-up at 17 months (October 2008)



CONCLUSIONS

PTA in the treatment of CLI is safe, with favourable in-hospital and mid-term outcomes, especially when considered as a part of a strategy of integrated care. Despite its high mortality rate, partly due to the mean age of the population and the presence of significant comorbidities, the high rate of LS and the low TLR rate underline the role of this reperfusion strategy even in a subset of fragile patients with severe and diffused PAD. Although secondary intervention is often necessary to maintain patency, it would be appropriate to use PTA as initial therapy for chronic femoro-popliteal occlusive disease, regardless of clinical classification at presentation or TASC category of lesion severity. Moreover, this data confirms that patients with severe arterial disease are prone to die mostly due to cardiac causes and that inflammatory and infection markers, as fibrinogen and CRP levels, may be useful in the pre-procedural risk stratification. Recent advances and newer technologies[120] as novel angioplasty balloon[121], the use of glycoprotein IIb/IIIa inhibitors[122], nitinol stents[123], stent grafts, the use of drug eluting stents[124, 125], rotational atherectomy devices[126], cutting balloon PTA[127], excimer laser-assisted PTA[128], crioplasty[129], devices for crossing total occlusions, true-lumen re-entry devices, thrombectomy catheters, embolic protection devices and gene therapy[130], will significantly improve the immediate angiographic results and mid- and long-term clinical outcomes of PTA procedures. Finally, revascularization has to be considered just a phase of patient treatment, and only a multidisciplinary team, working in a “wound care unit”, may allow an overall and effective management of patients with CLI.

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