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Experimental dissertation for Ph.D degree in

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Native artery recanalization in patients with Critical Limb Ischemia followed bypass failure

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1. Introduction

Peripheral vascular disease (PVD) is a common condition with variable morbidity affecting mostly men and women older than 50 years. Based on incidence rates extrapolated to today's increasingly aging population, PVD affects as many as 10 million people in the United States[1].

Nearly one in four of the approximately 60,000 people screened annually through Legs for Life, a nationwide screening program, is determined to be at moderate to high risk of lower extremity PVD and is referred to their primary care physicians for diagnosis (data collected by the Society of Cardiovascular and Interventional Radiology) [2].

The prevalence of peripheral arterial disease (PAD) continues to increase, with recent data suggesting that almost 30% of patients in at-risk populations have PAD[3].

More than 70 percent of patients experience no change or have an improvement in symptoms after five to 10 years of conservative management[1]. Twenty to 30 percent of patients develop more severe symptoms that require intervention. Fewer than 10 percent of patients require amputation[1].

Critical limb ischemia (CLI), occurring in ~10% of patients with peripheral arterial disease, is a syndrome of persistent and recurring ischemic rest pain requiring regular analgesia for more than two weeks, with o vascular laboratory studies consistent with severe arterial ischemia[4] [Figure1].

Figure 1. A foot wound caused by ischemic rest pain and tissue loss (critical limb ischemia). These wounds typically appear on the distal portion of the foot and require vascular referral.

In most developed countries, the incidence of critical limb ischemia is estimated to be between 50 – 100 per 100.000 every year and leads to pronounced morbidity and mortality as well as to the consumption of many health-care and social-care resources[5].

Patients with critical limb ischemia may also develop ischemic ulcerations and gangrene if prompt revascularization were not to occur. The presence of ischemic ulcerations and/or rest pain reflects such severe ischemia that resting tissue oxygen demands cannot be met.

If not aggressively treated, rest pain will progress to ischemic ulceration, gangrene, loss of motor/sensory function of the limb, and eventually, limb loss.

Because of the occurrence of CLI in patients with PAD, approximately 160,000 amputations are performed annually in the United States[6].

Lower extremity bypass surgery has been considered as a gold standard and a primary indication for treatment of chronic CLI[7]. But, it should be noted that the traditional open surgery bypass is not without significant morbidity and mortality. Hynes N. *et al*. demonstrated that surgery has been shown to be associated with increased mortality (30-day survival of 96% *versus* 100% for angioplasty) and morbidity[8].

Vein harvest site and graft infections, when they occur, can be devastating. Bart E. *et al*. showed that in 276 patients who underwent lower extremity revascularization via open surgical bypass the operative morbidity rate was 21%, largely due to wound complications and infections; with only 45% of patients reported being back to normal within 6 months[9].

Also, many patients with peripheral vascular disease usually have several other co-morbidities, such as heart disease, diabetes and renal failure, which would put them at higher surgical and anaesthetic risk. In addition, some patients may not have an adequate amount of vein to harvest to allow for autologous bypass grafting. *Therefore, these patients became poor candidates for surgical vascular reconstruction and the amputation is often the only option of management*.

The works of Dotter *et al*. [10] and Gruntzig *et al*. [11] revolutioni[illegible] treatment of peripheral vascular disease, heralding the arri[illegible] endovascular treatment techniques such as percutaneous transluminal angioplasty (PTA). Subintimal angioplasty, sometimes described as percutaneous intentional extraluminal recanalization, was first introduced in 1987 to treat femoro-popliteal occlusive disease in intermittent claudication[12]. Since that time, the success of this technique has seen its use extended to treatment of occlusive lesions in the popliteal artery, trifurcation and crural vessels where it has found an important role in the management of critical limb ischemia.

However, most reports on these emerging treatment modalities are lack of high-quality data and the investigation of revascularization strategies for Chronic Lower Limb Ischemia is therefore essential[13].

At our department, limb-salvage angioplasty has been introduced as an alternative-last chance method with the primary goal of achieving limb salvage in selected poor surgical candidates with end-stage arterial occlusive disease and with bypass failure. The purpose of this study was to evaluate the treatment outcomes after limb-salvage PTA/S for poor surgical candidate patients with CLI following occluded bypass and who otherwise would be candidates for primary amputation.

2. Arterial occlusive disease

2.1 Introduction

Atherosclerosis is the leading cause of occlusive arterial disease of the extremities in patients over 40 years old; the highest incidence occurs in the sixth and seventh decades of life. As in patients with atherosclerosis of the coronary and cerebral vasculature, there is an increased prevalence of peripheral atherosclerotic disease in individuals with diabetes mellitus, hypercholesterolemia, hypertension, or hyperhomocysteinemia and in cigarette smokers.

Arterial occlusive disease may be divided into acute and chronic. Peripheral arterial occlusive is commonly staged according to the Rutherford[14] [Table 1] and Fontaine classification into four degrees:

I: Asymptomatic atherosclerotic lesions

II: Intermittent claudication

- a) mild (free walking distance > 100-200 m)
- b) severe (walking distance less than 100m)

III: Rest pain

IV: Trophic changes with necrosis and gangrene

Acute arterial occlusions

These occlusions are due to arterial emboli or acute thrombosis in approximately 90%[15]. Other etiologies are dissections of the arterial wall (traumatic or spontaneous), external compression, spasm (trauma, iatrogenic, drugs) or hemodynamic problems.

The majority of *arterial emboli* originate in the left heart (86%) [16]. Other sources are aneurisms and ulcerative plaques of large arteries. Usually the emboli get trapped at arterial bifurcations and causes further thrombosis by apposition or stagnation of blood flow. The most frequent location of arterial emboli is the common femoral artery (46%) [16]. A special form of peripheral embolism is cholesterol embolism caused by showers of cholesterol crystals released from atherosclerosis of the aorta and pelvic vessels which lead to microemboli in digital arteries (Blue toe syndrome).

Acute and subacute arterial thrombosis is caused by atherosclerosis in over 90% [15]. Rarely inflammatory processes, trauma, hematological diseases or interventional procedures are the cause. The clinical signs depend on the location and extend of the thrombosis; however they are generally less severe than with acute embolic diseases.

Chronic arterial occlusive diseases

Chronic arterial occlusive disease leads to progressive stenosis and/or occlusions and is due mainly to obliterative arteriosclerosis. It usually starts after the age of 40 and is dependent on certain risk factors such as smoking, hypertension, hyperlipidemia, diabetes, family history of cardiac or vascular disease, obesity, and sedentary lifestyle. [Figure 2] and [Figure 3]

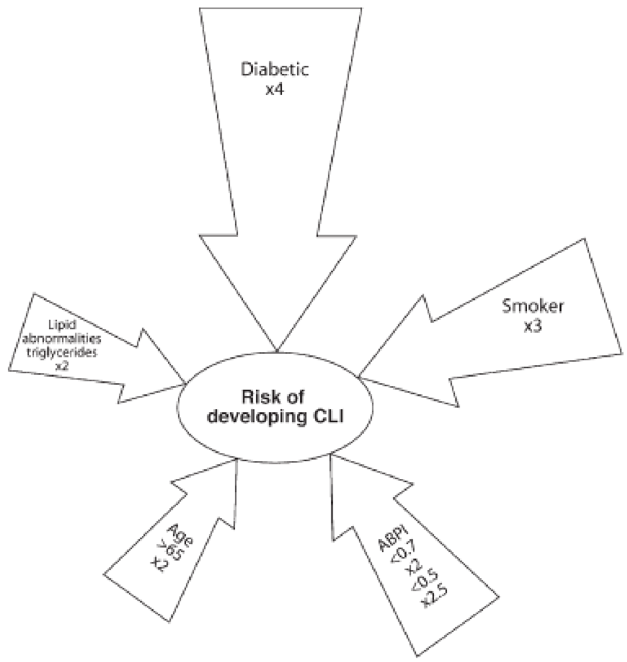


Figure 2. Approximate magnitude of the effect of risk factors on the development of critical limb ischemia in patients with peripheral arterial disease.
CLI – critical limb ischemia.

Segmental lesions causing stenosis or occlusion are usually localized in large and medium-sized vessels. The sites of predilection are the arteries of the pelvis and lower extremities, the origins of the neck vessels and the carotid bifurcation. The pattern of PAD in CLI typically includes stenosis and occlusions in the arterial tree from the superficial femoral artery (SFA) to the pedal arch [17].

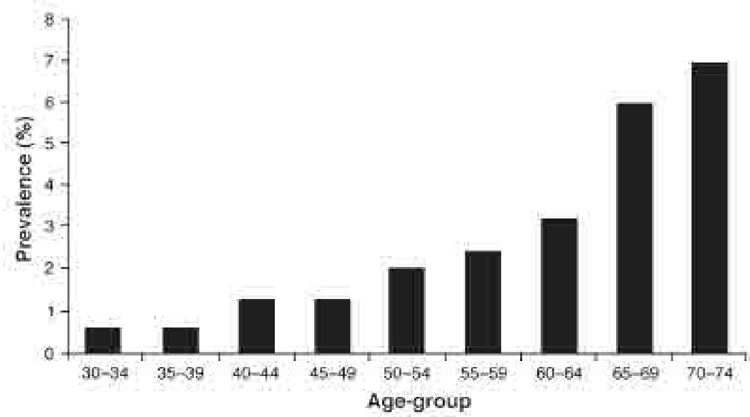


Figure 3. Weighted mean prevalence of intermittent claudication (symptomatic PAD) in large population-based studies.

The pathology of the lesions includes atherosclerotic plaques with calcium deposition, thinning of the media, patchy destruction of muscle and elastic fibers, fragmentation of the internal elastic lamina, and thrombi composed of platelets and fibrin. The primary sites of involvement are the abdominal aorta and iliac arteries (30% of symptomatic patients) [18], superficial femoral artery, especially in the region of the adductor canal, and popliteal arteries (80 to 90% of patients) [18], and the more distal vessels, including the tibial and peroneal arteries (40 to 50% of patients) [18]. Atherosclerotic lesions occur preferentially at arterial branch points, sites of increased turbulence, altered shear stress, and intimal injury. Involvement of the distal vasculature is most common in elderly individuals and patie diabetes mellitus.

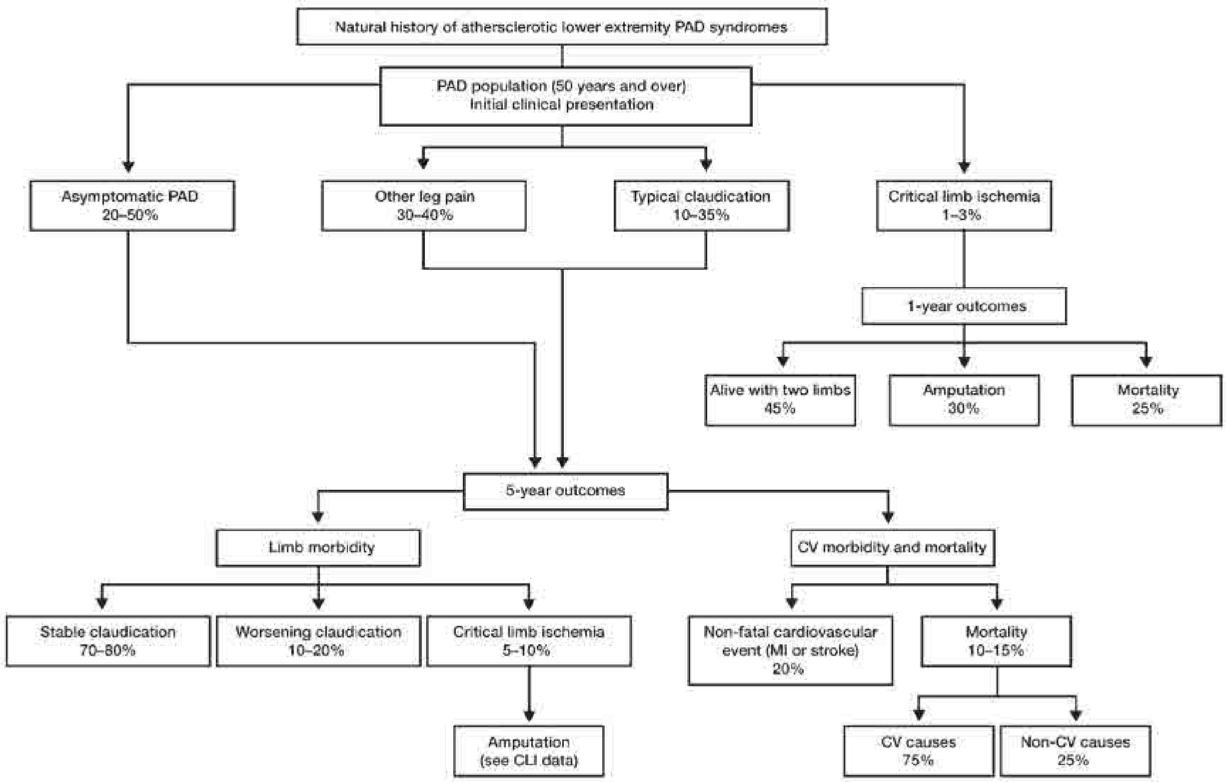


Figure 4. Fate of the claudicant over 5 years (adapted from ACC/AHA guidelines [19]). PAD – peripheral arterial disease; CLI – critical limb ischemia; CV – cardiovascular; MI – myocardial infarction.

In diabetes, the small arteries of the calf and feet are particularly involved and there is often combined disease in the femoral, popliteal and calf arteries as well as changes in the deep femoral artery.

In most cases, the presence of PAD is a sign of systemic atherosclerosis, which puts these patients at high risk of stroke, myocardial infarction, and cardiovascular death. Patients with symptomatic PAD have a 30% risk of death within five years, increasing to almost 50% within 10 years and are 60% more likely to die from a heart attack and 12% more like ischemic stroke [20].

2.2 The pathogenesis of arterial occlusive disease

Atherosclerosis

Atherosclerosis is the leading cause of death and disability in the developed world. Despite our familiarity with this disease, some of its fundamental characteristics remain poorly recognized and understood. Although many generalized or systemic risk factors predispose to its development, atherosclerosis affects various regions of the circulation preferentially and yields distinct clinical manifestations depending on the particular circulatory bed affected. Atherosclerosis of the coronary arteries commonly causes myocardial infarction and angina pectoris. Atherosclerosis of the arteries supplying the central nervous system frequently provokes strokes and transient cerebral ischemia. In the peripheral circulation, atherosclerosis causes intermittent claudication and gangrene and can jeopardize limb viability. Indeed, atherosclerotic lesions often form at branching points of arteries, regions of disturbed blood flow.

Atherogenesis in humans typically occurs over a period of many years, usually many decades. Growth of atherosclerotic plaques probably does not occur in a smooth linear fashion, but rather discontinuously, with periods of relative quiescence punctuated by periods of rapid evolution. [Figure 5] After a generally prolonged "silent" period, atherosclerosis may become clinically manifest. [Figure 6] The clinical expressions of atherosclerosis [illegible]
chronic, as in the development of stable, effort-induced angina pecto

predictable and reproducible intermittent claudication. Alternatively, a much more dramatic *acute* clinical event such as myocardial infarction, a cerebrovascular accident, or sudden cardiac death may first herald the presence of atherosclerosis. Other individuals may never experience clinical manifestations of arterial disease despite the presence of widespread atherosclerosis demonstrated post mortem.

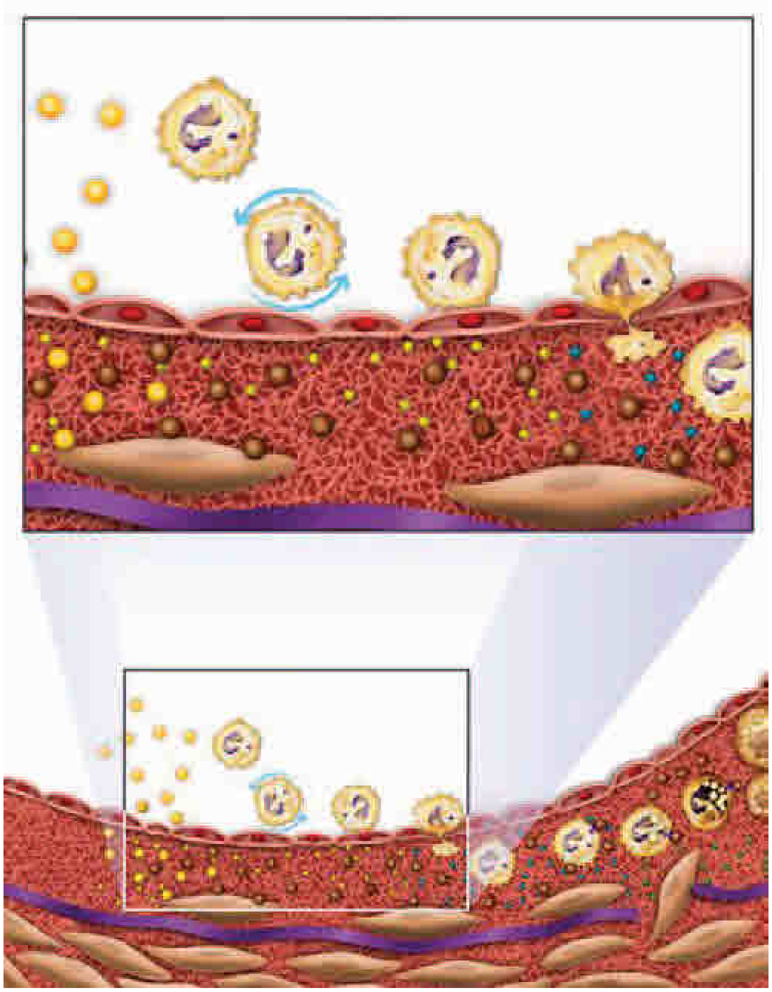


Figure 5. Cross-sectional view of an artery depicting steps in development of an atheroma, from left to right.

At the figure 5 the *upper panel* shows a detail of the boxed area below. The endothelial monolayer overlying the intima contacts blood. Hypercholesterolemia promotes accumulation of LDL particles (light spheres) in the intima. The lipoprotein particles often associate with constituents of the extracellular matrix, notably proteoglycans. Sequestration within the intima separates lipoproteins from some plasma antioxidants and favors oxidative modification. Such modified lipoprotein particles (darker spheres) may trigger a local inflammatory response responsible for signaling subsequent steps in lesion formation. The augmented expression of various adhesion molecules for leukocytes recruits monocytes to the site of a nascent arterial lesion. Once adherent, some white blood cells will migrate into the intima. The directed migration of leukocytes probably depends on chemoattractant factors including modified lipoprotein particles themselves and chemoattractant cytokines depicted by the smaller spheres, such as the chemokine macrophage chemoattractant protein 1 produced by vascular wall cells in response to modified lipoproteins. Leukocytes in the evolving fatty streak can divide and exhibit augmented expression of receptors for modified lipoproteins (scavenger receptors). These mononuclear phagocytes ingest lipids and become foam cells, represented by a cytoplasm filled with lipid droplets. As the fatty streak evolves into a more complicated atherosclerotic lesion, smooth-muscle cells migrate from the media (*bottom of lower* through the internal elastic membrane (*solid wavy line*), and acc within the expanding intima where they lay down extracellular matrix that forms the bulk of the advanced lesion (*bottom panel*, *right-hand side*).

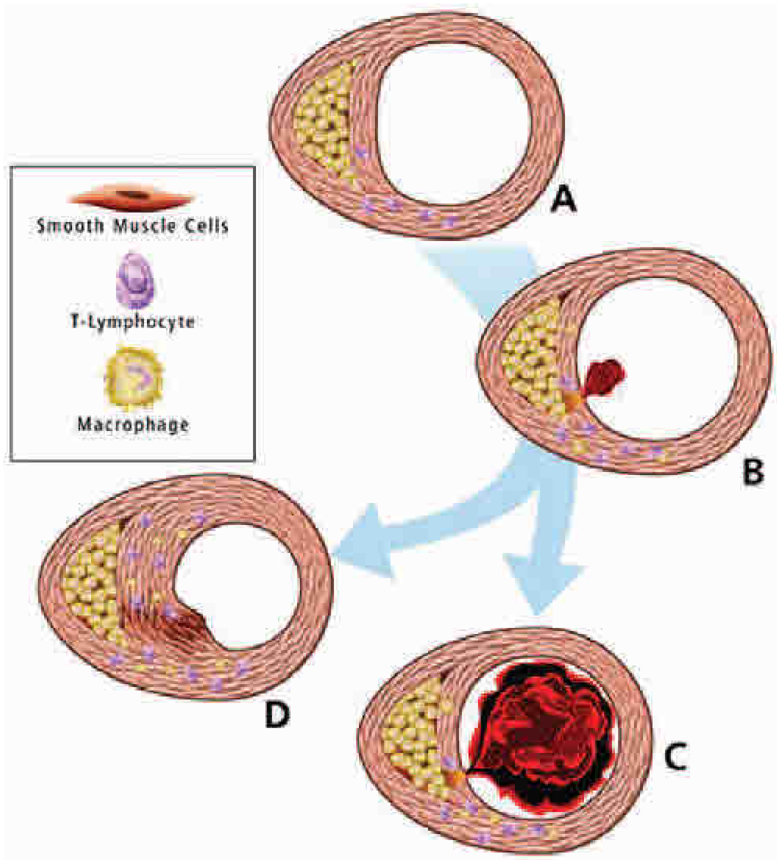


Figure 6. Plaque rupture, thrombosis, and healing.

At the figure 6: ***A.*** Arterial remodeling during atherogenesis. During the initial part of the life history of an atheroma, growth is often outward, preserving the caliber of lumen. This phenomenon of "compensatory enlargement" accounts in part for the tendency of coronary arteriography to underestimate the degree of atherosclerosis. ***B.*** Rupture of the plaque's fibrous cap causes thrombosis. Physical disruption of the atheros plaque commonly causes arterial thrombosis by allowing blood cc factors to contact thrombogenic collagen found in the arterial extracellular matrix and tissue factor produced by macrophage-derived foam cells in the lipid core of lesions. In this manner, sites of plaque rupture form the nidus for thrombi. The normal artery wall possesses several fibrinolytic or antithrombotic mechanisms that tend to resist thrombosis and lyse clots that begin to form in situ. Such antithrombotic or thrombolytic molecules include thrombomodulin, tissue and urokinase-type plasminogen activators, heparin sulfate proteoglycans, prostacyclin, and nitric oxide. ***C.*** When the clot overwhelms the endogenous fibrinolytic mechanisms, it may propagate and lead to arterial occlusion. The consequences of this occlusion depend on the degree of existing collateral vessels. In a patient with chronic multivessel, occlusive coronary artery disease, collateral channels have often formed. In such circumstances, even a total arterial occlusion may not lead to myocardial infarction, or it may produce an unexpectedly modest or a non-ST segment elevation infarct because of collateral flow. In the patient with less advanced disease and without substantial stenotic lesions to provide a stimulus to collateral vessel formation, sudden plaque rupture and arterial occlusion commonly produces ST-segment elevation infarction. These are the types of patients who may present with myocardial infarction or sudden death as a first manifestation of coronary atherosclerosis. In some cases, the thrombus may lyse or organize into a mural thrombus without occlu vessel. Such instances may be clinically silent. ***D.*** The subsequent th induced fibrosis and healing causes a fibroproliferative response that can lead to a more fibrous lesion, one that can produce an eccentric plaque that causes a hemodynamically significant stenosis. In this way, a nonocclusive mural thrombus, even if clinically silent or causing unstable angina rather than infarction can provoke a healing response that can promote lesion fibrosis and luminal encroachment. Such a sequence of events may convert a "vulnerable" atheroma with a thin fibrous cap prone to rupture into a more "stable" fibrous plaque with a reinforced cap. Angioplasty of unstable coronary lesions may "stabilize" the lesions by a similar mechanism, producing a wound followed by healing.

Diabetes mellitus aggravates atherogenesis. In addition to the well-known microvascular complications of diabetes, macrovascular disease such as atherosclerosis causes a great deal of excess mortality in the diabetic population. Diabetes-associated dyslipidemias strongly promote atherogenesis. In particular, the constellation of insulin resistance, high triglycerides, and low HDL, often in association with the central adiposity and hypertension frequently seen in type 2 diabetic patients, seems to accelerate atherogenesis potently. As noted above, hyperglycemia may promote the nonenzymatic glycation of LDL. LDL modified in this manner, like oxidatively modified LDL, may signal many of the initial e atherogenesis. Triglyceride rich lipoprotein particles, often elevated in poorly controlled diabetic patients, also accentuate atherogenesis.

Lp(a) (often pronounced "lipoprotein little a" to distinguish it from apolipoprotein AI and others found in HDL) provides a potential link between hemostasis and blood lipids. The Lp(a) particle consists of an apoprotein (a) molecule bound by a sulfhydryl link to the apolipoprotein B moiety of an LDL particle. Apoprotein (a) has homology with plasminogen and may inhibit fibrinolysis by competing with plasminogen. Other risk factors for atherosclerosis related to blood clotting include elevated levels of fibrinogen or of the inhibitor of fibrinolysis, plasminogen-activator inhibitor 1 (PAI-1).

The relationship between *tobacco use* and atherosclerosis also remains poorly understood. The rapid reduction in risk for cardiac events after cessation of cigarette smoking implies that tobacco may promote thrombosis or some other determinant of plaque stability as well as contribute to the evolution of the atherosclerotic lesion itself. For example, tobacco smokers have elevated fibrinogen levels, a variable associated with increased atherosclerosis and acute cardiovascular events.

2.3 Clinical Evaluation

Fewer than 50% of patients with PAD are symptomatic, though many have a slow or impaired gait [18]. The most common *symptom* is intermittent claudication, which is defined as a pain, ache, cramp, numbness, or a sense of fatigue in the muscles; it occurs during exercise and is relieved by rest. The site of claudication is distal to the location of the occlusive lesion. For example, buttock, hip, and thigh discomfort occur in patients with aortoiliac disease (*Leriche syndrome*), whereas calf claudication develops in patients with femoral-popliteal disease.

Symptoms are far more common in the lower than in the upper extremities because of the higher incidence of obstructive lesions in the former region. In patients with severe arterial occlusive disease, critical limb ischemia may develop. Patients will complain of aching pain in the feet or toes while at rest, non healing ulcers on the leg or foot, cold legs or feet, and skin color changes of the legs or feet (particularly dependent rubor). Frequently, these symptoms occur at night when the legs are horizontal and improve when the legs are in a dependent position. With severe ischemia, rest pain may be persistent.

Table 1. Clinical Categories of Limb Ischemia. The Rutherford – Becker Classification

Grade	*Category*	*Clinical Description*	*Objective Criteria*
0	0	Asymptomatic	Normal TM/stress test
I	1	Mild Claudication	Completes TM exercise; ankle pressure (AP) after exercise < 50 mmHg but > 25 mmHg less than BP
	2	Moderate Claudication	Between Categories 1 and 3
	3	Severe Claudication	Cannot complete treadmill exercise and AP after exercise < 50mmHg
II	4	Ischemic Rest Pain	Resting AP < 40 mmHg, flat or barely pulsatile ankle or metatarsal PVR Toe pressure (TP) < 30 mm Hg
III	5	Minor tissue loss – nonhealing ulcer, focal gangrene with diffuse pedal edema	Resting AP < 60 mmHg, ankle or metatarsal PVR flat or barely pulsatile < 40 mmHg
	6	Major tissue loss-extending above TM level	Same as category 5

Table 2. The following chart defines the ischemic rest pain of patients without skin lesions and the presence of ulcers or gangrene

Leriche-Fontaine Classification			
STAGES	***SYMPTOMS***	***PATHOPHYSIOLOGY***	***PATHOPHYSIOLOGY CLASSIFICATIONS***
Stage I	Asymptomatic or effort pain	Relative hypoxia	Silent arteriopathy
Stage IIA	Effort pain/pain-free walking distance > 200 m	Relative hypoxia	Stabilized arteriopathy, non-invalidant Claudication
Stage II B	Pain-free walking distance < 200 m	Relative hypoxia	Instable arteriopathy, invalidant Claudication
Stage III A	Rest pain, ankle arterial pressure > 50 mm Hg	Cutaneous hypoxia, tissue acidosis, ischemic neuritis	Instable arteriopathy, invalidant claudication
Stage III B	Rest pain, ankle arterial pressure < 50 mm Hg	Cutaneous hypoxia, tissue acidosis, ischemic neuritis	Instable arteriopathy, invalidant claudication
Stage IV	Trophic lesions, necrosis or gangrene	Cutaneous hypoxia, tissue acidosis, necrosis	Evolutive arte

SOURCE: NOV

2.4 Diagnosis

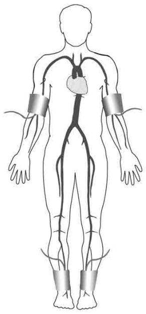
With the rapidly evolving field of endovascular revascularization for peripheral arterial disease, along with improving surgical techniques and medical therapies, an accurate diagnosis must be made. This begins with a thorough historical review of symptoms and a comprehensive physical examination. Important physical findings of PAD include decreased or absent pulses distal to the obstruction, the presence of bruits over the narrowed artery, and muscle atrophy. With more severe disease, hair loss, thickened nails, smooth and shiny skin, reduced skin temperature, and pallor or cyanosis are frequent physical signs. In addition, ulcers or gangrene may occur. Elevation of the legs and repeated flexing of the calf muscles produce pallor of the soles of the feet, whereas rubor, secondary to reactive hyperemia, may develop when the legs are dependent. The time required for rubor to develop or for the veins in the foot to fill when the patient's legs are transferred from an elevated to a dependent position is related to the severity of the ischemia and the presence of collateral vessels. Patients with severe ischemia may develop peripheral edema because they keep their legs in a dependent position much of the time. Ischemic neuritis can result in numbness and hyporeflexia.

Noninvasive Testing

The history and physical examination are usually sufficient to establish the diagnosis of PAD. An objective assessment of the severity of disease is obtained by noninvasive techniques. These include digital pulse volume recordings, Doppler flow velocity waveform analysis, duplex ultrasonography (which combines B-mode imaging and pulse-wave Doppler examination), segmental pressure measurements, transcutaneous oxymetry, stress testing (usually using a treadmill), and tests of reactive hyperemia. In the presence of significant PAD, the volume displacement in the leg is decreased with each pulse, and the Doppler velocity contour becomes progressively flatter. Duplex ultrasonography is often useful in detecting stenotic lesions in native arteries and bypass grafts.

Ankle-Brachial Index

One of the most useful objective parameters to assess lower extremity arterial perfusion is the ankle brachial index (ABI), a test that can be performed in the physician's office, and requires a blood pressure apparatus and a hand held continuous wave Doppler probe. This test compares the blood pressure obtained with the hand-held Doppler in the dorsalis pedis or posterior tibial artery (whichever is higher) to the blood pressure in the higher of the two brachial pressures. This study screens for hemodynamically significant disease and helps define its severity. Generally, an ABI considered normal, > 0.4-< 0.9 reflects mild to moderate PAD, an suggests severe lower extremity arterial disease. In general terms, however, there is direct relationship between a low ABI and progressive symptoms:



ABI	Severity of PAD
> 0.9	Normal
> 0.7 - ≤ 0.9	Mild
> 0.4 - ≤ 0.7	Moderate
≤ 0.4	Severe

Figure 7. Measurement of the ABI. ABI – ankle-brachial index

Indexes less than 0.20 are associated with ischemic or gangrenous extremities. In diabetic patients with heavily calcified vessels, the arteries are frequently noncompressible. This results in an artifactually elevated ankle pressure, which can cause underestimation of disease severity. In these patients, toe pressure determinations more accurately reflect perfusion [21].

Treadmill testing allows the physician to assess functional limitations objectively. Decline of the ankle-brachial systolic pressure ratio immediately after exercise may provide further support for the diagnosis of PAD in patients with equivocal symptoms and findings on examination. Exercise testing also allows simultaneous evaluation for the presence of coronary artery disease.

Arteriography

Arteriography is of major value in localizing an obstruction and visualizing the distal arterial tree. It also assists in distinguishing patie

will benefit more from percutaneous treatment than from embolec open revascularization procedures. In limb-threatening ischemia, an important consideration is whether the delay in performing formal angiography in an angiographic suite can be tolerated. Angiography makes the most sense when catheter-based treatment is an option.

Other imaging techniques

Computed tomographic angiography/Magnetic resonance angiography

Computed tomographic angiography (CTA) and magnetic resonance angiography (MRA) may also be used in the setting of CLI to diagnose and delineate the extent of disease. MR imaging of the vasculature can be cumbersome and time-consuming which may delay treatment. The advantages of CTA include its speed, convenience and ability for cross-sectional imaging of the vessel. The main disadvantage of CTA is its dependence on iodinated contrast media. In patients with CLI who may also require catheter angiography and intervention, this added load of contrast might increase the risk of renal injury to the patient.

Magnetic resonance angiography (MRA) and conventional contrast angiography should not be used for routine diagnostic testing but are performed prior to potential revascularization [22]. [Figure 8] Either test is useful in defining the anatomy to assist operative planning and is also indicated if nonsurgical interventions are being considered, such as percutaneous transluminal angioplasty (PTA) or trombolysis. Studi suggested that magnetic resonance angiography has diagnostic accuracy comparable to that of contrast angiography [22].

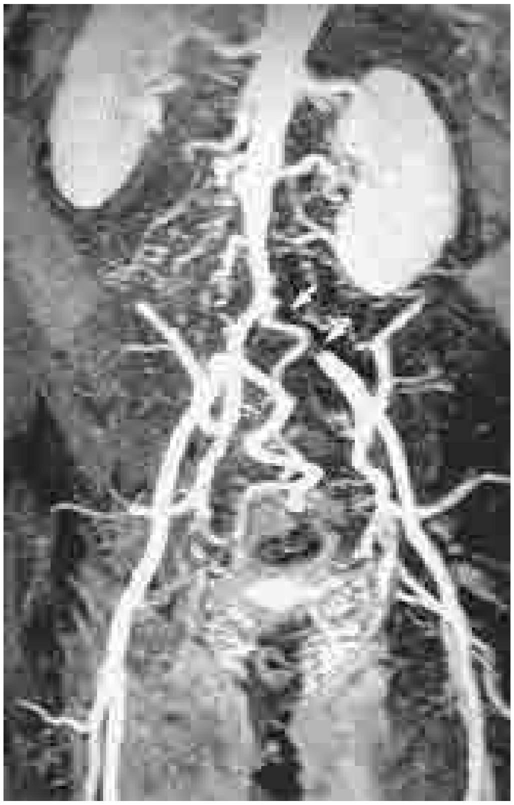


Figure 8. Abdominal magnetic resonance angiography.
Distal abdominal aortic and bilateral common iliac artery occlusions appear as signal voids *(arrows denote left common iliac occlusion)*. The tortuous vessel that courses over the area of right common iliac signal void is an enlarged inferior mesenteric artery, a collateral pathway supplying the external iliac artery via the internal iliac artery.

Prognosis

The natural history of patients with PAD is influenced primarily by the extent of coexisting coronary artery and cerebral vascular disease. Studies using coronary angiography have estimated that approximately one-half of patients with symptomatic PAD also have significant coronary artery disease. Life-table analysis has indicated that patients with claudication have a 70% 5-year and a 50% 10-year survival rate[18]. Most deaths are either sudden or secondary to myocardial infarction. The likelihood of symptomatic progression of PAD appears less than the chance of succumbing to coronary artery disease. Approximately 70% of nondiabetic patients who present with mild to moderate claudication remain symptomatically stable or improve [18]. Deterioration is likely to occur in the remainder, with approximately 10% of the group ultimately undergoing amputation. The prognosis is worse in patients who continue to smoke cigarettes or who have diabetes mellitus. [Figure 9] Figure 10 provides an estimate of the primary treatment of these patients globally and their status a

year later [23].

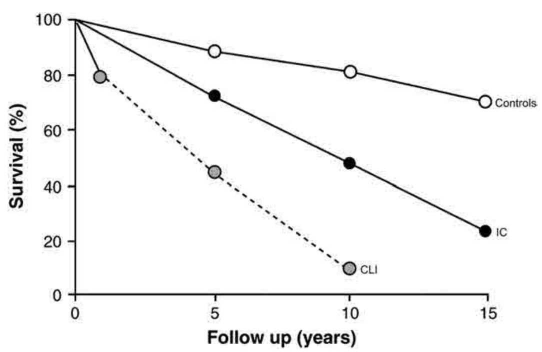


Figure 9. Survival of patients with peripheral arterial disease. IC – intermittent claudication; CLI – critical limb ischemia[23].

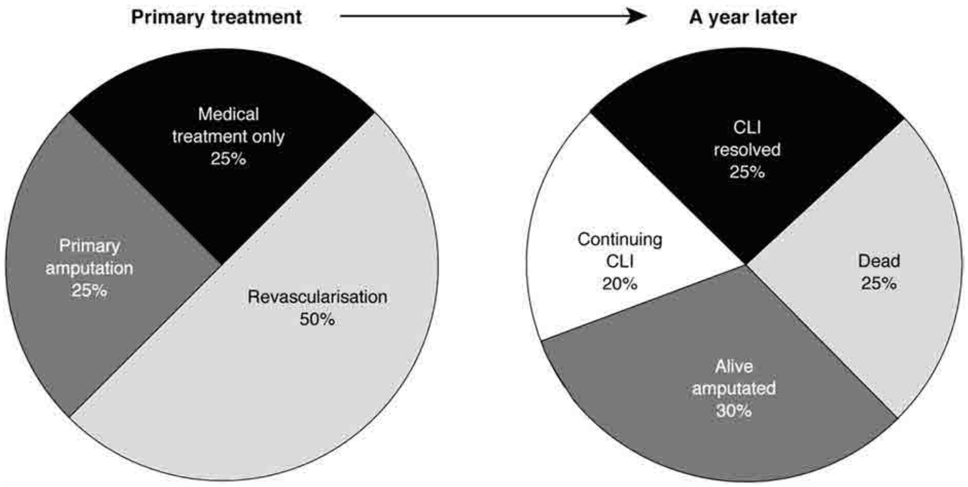


Figure 10. Fate of the patients presenting with chronic critical leg ischemia. CLI–critical limb ischemia[23].

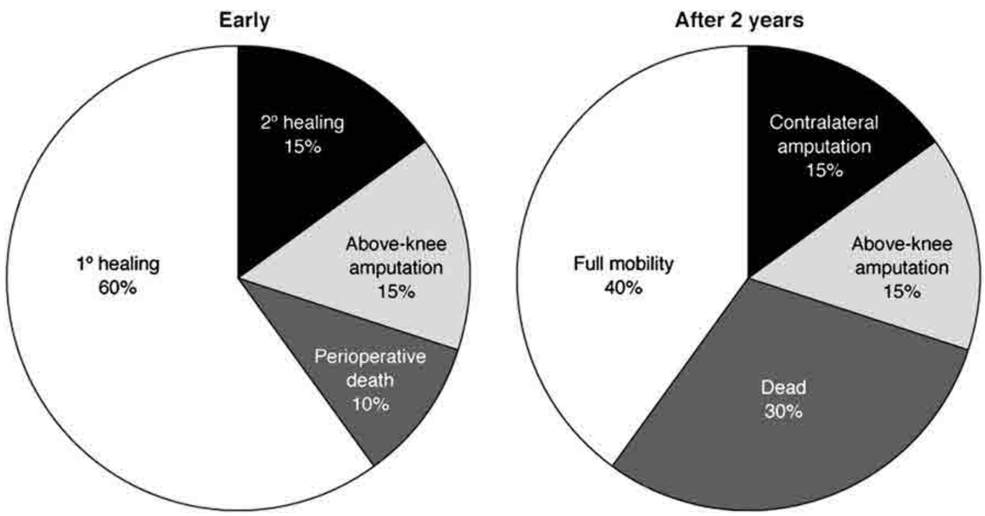


Figure 11. Fate of the patient with below-knee amputation[23].

The incidence of major amputations from large population or nation-wide data varies from 120 to 500/million/year. The ratio of below-knee to above-knee amputations in large surveys is around 1:1. Only about 60% of below-knee amputations heal by primary intention, 15% heal after secondary procedures and 15% need to be converted to an above-knee level. 10% die in the peri-operative period. The dismal 1- to 2-year prognosis is summa Figure 11[23].

2.5 Treatment

Therapeutic options include supportive measures, pharmacologic treatment, nonoperative interventions, and surgery. Supportive measures include meticulous care of the feet, which should be kept clean and protected against excessive drying with moisturizing creams. Well-fitting and protective shoes are advised to reduce trauma. Sandals and shoes made of synthetic materials that do not "breathe" should be avoided. Elastic support hose should be avoided, as they reduce blood flow to the skin. In patients with ischemia at rest, shock blocks under the head of the bed together with a canopy over the feet may improve perfusion pressure and ameliorate some of the rest pain.

Treatment of associated factors that contribute to the development of atherosclerosis should be initiated. The importance of discontinuing cigarette smoking cannot be overemphasized. The physician must assume a major role in this life-style modification. It is important to control blood pressure in hypertensive patients but to avoid hypotensive levels. Treatment of hypercholesterolemia is advocated, although reduction in cholesterol levels has not been shown unequivocally to reverse peripheral atherosclerotic lesions. However, it has been shown to prevent or to slow progression of the disease and to improve survival in patients with atherosclerosis. Patients with claudication should also be encouraged to exercise regularly progressively more strenuous levels. Supervised exercise training p may improve muscle efficiency and prolong walking distance. Patients also should be advised to walk for 30 to 45 min daily, stopping at the onset of claudication and resting until the symptoms resolve before resuming ambulation.

Pharmacologic Management

This form of treatment of patients with PAD has not been as successful as the medical treatment of coronary artery disease. In particular, vasodilators as a class have not proved to be beneficial. During exercise, peripheral vasodilatation occurs distal to sites of significant arterial stenosis. As a result, perfusion pressure falls, often to levels less than that generated in the interstitial tissue by the exercising muscle. Drugs such as α-adrenergic blocking agents, calcium channel antagonists, papaverine, and other vasodilators have not been shown to be effective in patients with PAD[24].

Two prescription medications are approved by the U.S. Food and Drug Administration for treating intermittent claudication: pentoxifylline (Trental), an oral methylxanthine derivative, and cilostazol (Pletal), a phosphodiesterase III inhibitor. Pentoxifylline, a substituted xanthine derivative, has been reported to decrease blood viscosity and to increase red cell flexibility, thereby increasing blood flow to the microcirculation and enhancing tissue oxygenation. Several placebo-controlled studies hav that pentoxifylline increased the duration of exercise in patien claudication, but its efficacy has not been confirmed in all clinical trials.

Cilostazol, a phosphodiesterase inhibitor with vasodilator and antiplatelet properties, has been reported to increase claudication distance in multiple trials. A recent randomized controlled trial [25] comparing the two drugs found cilostazol to be significantly more effective in improving walking distance than pentoxifylline, which was equivalent to placebo. However, cilostazol is associated with a greater frequency of minor side effects, including headache and diarrhea, and is contraindicated in patients with congestive heart failure [26].

Several drugs with phosphodiesterase III inhibitor activity (such as cilostazol) have shown decreased survival rates compared with placebo in patients with class III or IV failure [27].

Several studies have suggested that long-term parenteral administration of vasodilator prostaglandins decreases pain and facilitates healing of ulcers in patients with severe limb ischemia. Clinical trials with angiogenic growth factors such as vascular endothelial growth factor (VEGF) and basic fibroblast growth factor (bFGF) are proceeding. One placebo-controlled trial reported that intra-arterial administration of recombinant bFGF modestly increased walking time in patients with claudication. Intramuscular gene transfer of DNA encoding VEGF or bFGF may promote collateral blood vessel growth in patients with critical limb ischemia, but e documenting clinical efficacy is not available and awaits the outcome of ongoing trials.

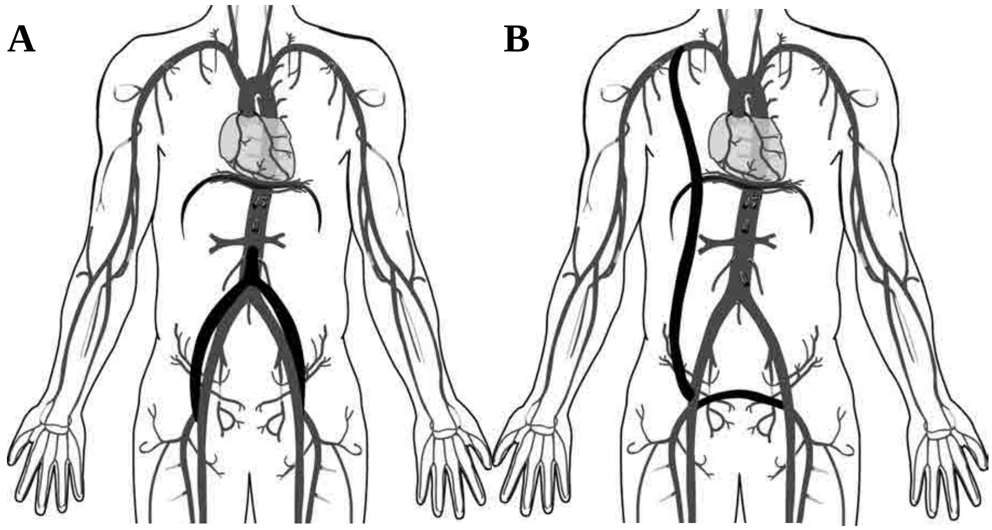
Antiplatelet/antithrombotic therapy also may be considered for use in these patients. Platelet inhibitors, particularly aspirin, reduce the risk of adverse cardiovascular events in patients with peripheral atherosclerosis. Studies have shown that aspirin therapy may modify the natural history of chronic lower extremity PVD [1]. It also has been suggested that use of aspirin may prevent death and disability from stroke and myocardial infarction secondary to underlying disseminated atherosclerosis[1].

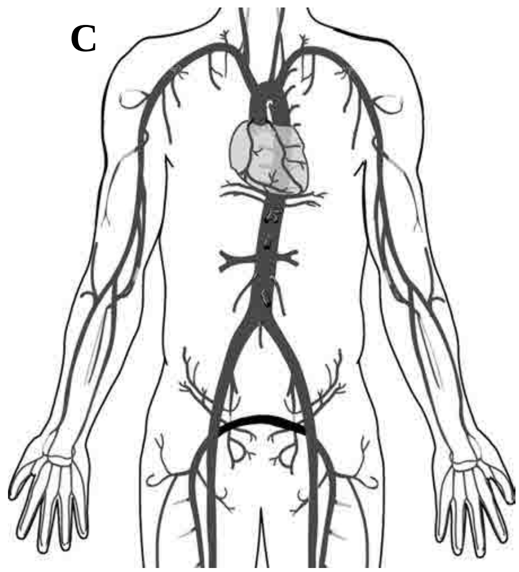
Clopidogrel, a drug that inhibits platelet aggregation via its effect on ADP-dependent platelet-fibrinogen binding, appears to be more effective than aspirin in reducing cardiovascular morbidity and mortality in patients with PAD. The anticoagulants heparin and warfarin have not been shown to be effective in patients with chronic PAD but may be useful in acute arterial obstruction secondary to thrombosis or systemic embolism. Similarly, thrombolytic intervention using drugs such as streptokinase, urokinase, or recombinant tissue plasminogen activator (tPA) (alteplase) may have a role in the treatment of acute thrombotic arterial occlusion but is not effective in patients with chronic arterial occlusion secondary to atherosclerosis.

Revascularization

Revascularization procedures, including *nonoperative* as well as *operative interventions*, are usually reserved for patients with progressive, severe, or disabling symptoms and ischemia at rest, as well as for individuals who must be symptom-free because of their occupation. Angiography should be performed mainly in patients who are being considered for a revascularization procedure. *Nonoperative interventions* include PTA, stent placement, and atherectomy. PTA of the iliac artery is associated with a higher success rate than PTA of the femoral and popliteal arteries. Approximately 90 to 95% of iliac PTAs are initially successful, and the 3-year patency rate is >75% [18]. Patency rates may be higher if a stent is placed in the iliac artery. The initial success rate for femoral-popliteal PTA is approximately 80%, with a 60% 3-year patency rate [18]. Patency rates are influenced by the severity of pretreatment stenosis; the prognosis of total occlusive lesions is worse than that of nonocclusive stenotic lesions.

Several *operative procedures* are available for treating patients with aortoiliac and femoral-popliteal artery disease. The preferred operative procedure depends on the location and extent of the obstruction(s) and general medical condition of the patient. Operative procedures for aortoiliac disease include *aortobifemoral bypass*, *axillofemoral bypass*, *femoral-femoral bypass*, and *aortoiliac endarterectomy*. [Figure 12]





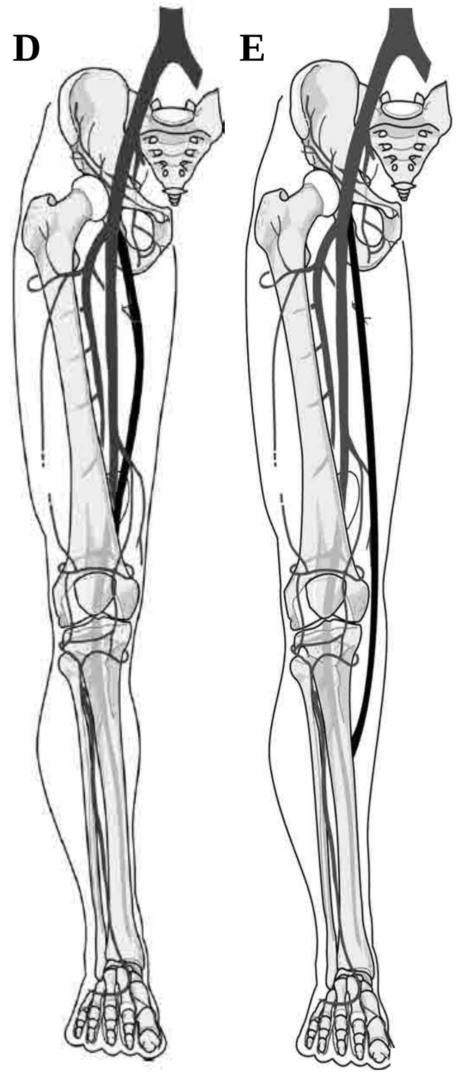


Figure 12. Surgical by-pass type

A Bilateral bypass from infra renal abdominal aorta to both femoral arterie
B Axillo (bi) femoral bypass
C Cross-over femoral bypass
D Above-knee femoral popliteal bypass
E Femoral tibial bypass

Immediate graft patency approaches 99%, and 5- and 10- year graft patency in survivors is >90 and 80%, respectively [18].

Operative complications include myocardial infarction and stroke, infection of the graft, peripheral embolization, and sexual dysfunction from interruption of autonomic nerves in the pelvis. Operative mortality ranges from 1 to 3%, mostly due to ischemic heart disease.

Operative therapy for femoral-popliteal artery disease includes in situ and reverse autogenous saphenous vein bypass grafts, placement of *polytetrafluoroethylene* (PTFE) or other synthetic grafts, and *thromboendarterectomy*. Operative mortality ranges from 1 to 3% [18]

The long-term patency rate depends on the type of graft used, the location of the distal anastomosis, and the patency of runoff vessels beyond the anastomosis. Patency rates of femoral-popliteal saphenous vein bypass grafts at 1 year approach 90% and at 5 years, 70 to 80% [18].

Five-year patency rates of infrapopliteal saphenous vein bypass grafts are 60 to 70%. In contrast, 5-year patency rates of infrapopliteal PTFE grafts are <30% [18]. Lumbar sympathectomy alone or as an adjunct to aortofemoral reconstruction has fallen into disfavor.

Table 3 compares the use of angioplasty with bypass surgery in the treatment of PVD [22].

Table 3. Angioplasty vs. Bypass Surgery for PVD of the Lower Extremities

Angioplasty	
Advantages	***Disadvantages***
Offers faster recovery Requires shorter hospital stay Requires no general anesthesia Maintains all options for extremity revascularization Allows for preservation of the saphenous veins for future use (for extremity or coronary artery bypass) May be repeated if necessary May be combined with surgery to improve inflow or outflow of surgically placed grafts Cost-benefit ratio	Lower primary patency rates Reintervention due to restenosis may be necessary
Bypass surgery	
Advantages	***Disadvantages***
Considered the gold standard Has good long-term patency May be preferable to treat multiple stenosis if venous conduit available	A higher rate of morbidity Potential systemic complications Typically requires general anesthesia Requires harvesting of saphenous veins and upper extremity veins, precluding their use for coronary artery bypass

PVD = peripheral vascular disease.

Preoperative cardiac risk assessment may identify individuals especially likely to experience an adverse cardiac event during the perioperative period. Patients with angina, prior myocardial infarction, ventricular ectopy, heart failure, or diabetes are among those at increased risk. Noninvasive tests, such as treadmill testing (if feasible), dipyridamole or adenosine radic myocardial perfusion imaging, dobutamine echocardiography ambulatory ischemia monitoring permit further stratification of patient risk. Patients with abnormal test results require close supervision and adjunctive management with anti-ischemic medications. β-Adrenergic blockers reduce the risk of postoperative cardiovascular complications. It is not known whether coronary angiography and coronary arterial revascularization reduce overall perioperative mortality in high-risk patients undergoing peripheral vascular surgery, but cardiac catheterization should be considered in patients suspected of having left main or three-vessel coronary artery disease.

3. Objective

- To prove the possibility of native artery recanalization in patients with critical limb ischemia followed bypass graft failure.

- To evaluate the outcomes of endovascular treatment for limb salvage in those critical limb ischemic patients who are otherwise would be candidates for major amputation.

4. Materials and methods

4.1 Study design

This study was a single centre experienced, retrospective clinical analysis of 29 consecutive high surgical risk patients with CLI treated with PTA/Stent following the failure of open surgery bypass grafts reconstruction. Eligibility was based on the presence of nonhealing ulcerations or gangrene. (Rutherford [14] limb ischemia category 5 or 6) [Table 1]. All patients had occlusion of previous bypass graft and were considered poor candidates for a new bypass operation on the basis of:

- absence of an adequate greater saphenous vein for distal bypass
- presence of poor distal bypass target vessel (no angiographically visible tibial vessels, vessels ≤1 mm in diameter, or diffusely diseased vessels)
- presence of severe comorbid conditions such as recent myocardial infarction (< 6 weeks), symptomatic coronary artery disease or severe chronic obstructive pulmonary disease [7].

The occlusive lesion length doesn't have importance in inclusion criteria. The only objective was to achieve ''straight-line'' flow to at least one of the anterior tibial or posterior tibial arteries.

Exclusion criteria included myocardial infarction (MI) in the prior month, previous endarterectomy at the treatment site, pre-existing venous stasis ulcers, renal insufficiency (creatinine >2.5 mg/dL), untreated ipsilateral iliac stenosis >70%, and contraindication to intended medications.

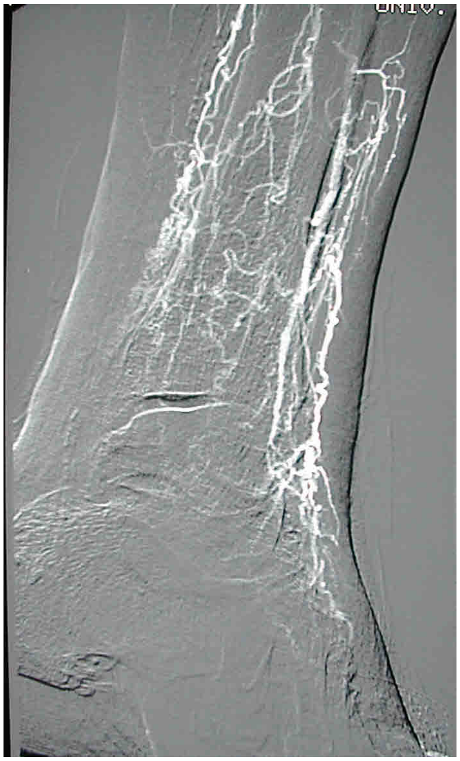


Figure 13. Absence of distal vessels of the foot

The one important criterion for exclusion was absence of distal vessels such as plantar arch and pedal arteries. [Figure 13]

Patients with coronary artery diseases or with hemodynamically significant stenosis of internal carotid arteries (ICA) were treated preliminarily before the procedure.

Preprocedural and postprocedural ankle-brachial index (ABI), TcPO2 and TcPCO2 were used to evaluate hemodynamic and tissue perfusion improvement. The oxymetry level between 10-20 mmHg represents critical ischemia and therefore indicates for limb salvage revascularization. The oxymetry also considered as an "objective measurement" of effectiveness of the recanalization and also pharmacological treatments. In our study the pressure level over 50 mmHg was considered normal, while the value between 10-30 were considered severe ischemia.

The parameters of $TcPO_2$/$TcPCO_2$ were continued to measure at 1, 2, 3, and 4 weeks after the procedure.

In all cases, the patients were studied with a color-Doppler-Ultrasound (color-Doppler-US). An MR angiography with MIP rotational protocol or an MsCT angiography with three-dimensional reconstructions was used as a diagnostic pre-procedure to define the location of lesions and to plan the revascularization strategy.

Ulcers on the lower limb were photographically recorded with a digital camera for core laboratory assessment. Photography was repeated at 3 and 6 months.

Post procedure follow-up performed by Doppler-US, percutaneous oxymetry, ABI and clinical examination was scheduled 1, 3, 6 months and yearly thereafter.

4.2 Patient population

Based on these criteria, since march 2006 to march 2007 revascularization was attempted in 29 patients (21 men; mean age 72.6 ± 9 years, range 46-87) with 30 critically ischemic limbs were enrolled at our study. Of these, all patients presented with a failed bypass graft, 3 (10.3 %) patients had previous minor amputations. Risk factors included 16 (55.1%) patients had type II diabetes, 15 patients (51.7%) had pharmacologically controlled hypertension, 12 (41.4%) coronary artery disease, 8 (27.6%) were ex smokers, 14 (48.3 %) smokers, 12 patients (41.4%) had dyslipidemia, 13 patients (44.8%) had obesity. [Table 5]

Table 5. Demographics

Variable	*Data*
Mean age (y)	72.6 yr
Male	21
Female	8
Diabetes	16
Coronary artery disease	12
Hypertension	15
Obesity	13
Smoker (even in the past)	22
Dyslipidemia	12

Ankle-brachial index (ABI) prior to treatment averaged *0.32 ± 0.18* (excluding 6 patients with calcified vessels and false positive ABI >1.0).

4 (13.3%) limbs presented with acute bypass failure, 26 (86.7%) limbs with chronic bypass failure. 5 (16.7%) suprainguinal bypass occlusions (1 aorto-femoral, 1 aortobifemoral, 3 femoral-femoral cross-over bypasses), 25 (83.3%) infrainguinal (femoral-popliteal) bypass occlusions.

By morphologic classification of arterial lesion all patients were classified using the Texas University Classification III C, n = 22 (75.9%) and III D, n = 7 (24.1%) patients [29]. [Table 4]

Table 4. University of Texas Wound Classification System.

Stage / *Grade*	0	I	II	III
A	Pre or postulcerative lesion completely epithelized	Superficial wound, not involving tendon, capsule, or bone	Wound penetrating to tendon of capsule	Wound penetrating to bone or joint
B	Infection	Infection	Infection	Infection
C	Ischemia	Ischemia	Ischemia	Ischemia
D	Ischemia & Infection	Ischemia & Infection	Ischemia & Infection	Ischemia & Infection

4.3 Endovascular Treatment Techniques

All patients were started on *Clopidogrel bisulphate 75 mg* daily and A*cetylsalicylic acid 100 mg* daily 3 days before the procedure. The double anti-aggregation had been continued for 6 weeks after the procedure and acetylsalicylic acid was prescript "quod vitam".

Our procedural strategies changes if we have an acute or chronic occlusion. In Patient with acute occlusions we performed a pharmacological fibrinolysis of by-pass (24 hours infusion →100 IU/kg/h of Urokinase) and/or thrombectomy with Fogarty catheter. If the bypass graft after several attempts is still not functioning as planed we performed native artery recanalization. Instead, in patient with chronic malfunction of bypass we directly performed native artery recanalization.

The endovascular procedure was performed in dedicated angiographic suites. On patients under local anaesthesia, the baseline arteriography was performed to quantify the extension of the disease. Heparin anticoagulation (Heparin sodium 2500-5000 IU) was administered systematically. All patients were considered, starting before the PTA procedures, for 24 hours hydrotation with physiologic saline to protect from the damage the kidneys by contrast media.

Angioplasty, depending of localization of the lesion, was performed through a combination of followed approaches:

- ipsilateral anterograde common femoral approach
- ipsilateral anterograde common femoral and transpopliteal double approach
- ipsilateral anterograde common femoral and transtibial double approach
- retrograde common femoral approach
- controlateral cross-over femoral approach
- retrograde common femoral and transbrachial double approach

In 18 patients were used anterograde, ipsilateral to the lesion, approach of common femoral artery, in 6 patients double combined approaches and in 5 patients with suprainguinal bypass occlusions were used transbrachial and retrograde approaches.

Multiple stenosis and occlusions in the SFA, popliteal, and tibial arteries were typically treated in the same setting, with the objective being to achieve ‘‘straight-line’’ flow to the foot.

Threatened closure caused by flow-limiting dissection or significant residual stenosis was addressed with deployment of self-expanding stents (SMART, Wallstent, Edwards, Protegé, and eV3).

Iliac artery recanalization

In 5 patients with CLI after suprainguinal bypass failure the endovascular recanalization was performed throuth the combination of retrograde, controlateral cross over and transbrachial approaches. The occluded lesions were crossed by hydrophilic Terumo guide wire and were positioned metallic stents of various dimensions. (6-9 mm) The stents were dilated with the 6-8 mm diameter balloon catheters.

Superficial femoral artery recanalization

⎞ **Endoluminal recanalization**

The revascularization of superficial femoral artery (SFA) was performed by endoluminal recanalization technique in 4 (13.3%) limbs when the total length of SFA occlusion was less than 10 cm.

Through the transfemoral anterograde access the 6 F (Terumo) introducer sheath was positioned and the lesion was localized with baseline angiogram or "Road-map".

Under the fluoroscopic guidance the straight 0.035 inch hydrophilic Terumo guidewire and the catheter, positioned proximally to the lesion to have an additional support for pushability, was advanced toward the occluded part of lesion and was successfully passed through the occlusion. After the occlusion was measured with on-line quantitative angiography the lesion was dilated with 5-6 mm diameter balloon, using the lowest p

that will fully expand the balloon. [Case 1]

In 2 (6.7 %) limbs after the several dilation the residual stenosis was over 30 % therefore self expandable stent (6-8 mm of diameter) was deployed. [Case 2]

Subintimal recanalization

The revascularization treatment of SFA by subintimal technique [Figure 14] was performed in occlusions with extremely high calcifications and occlusions with total length over 10 cm.

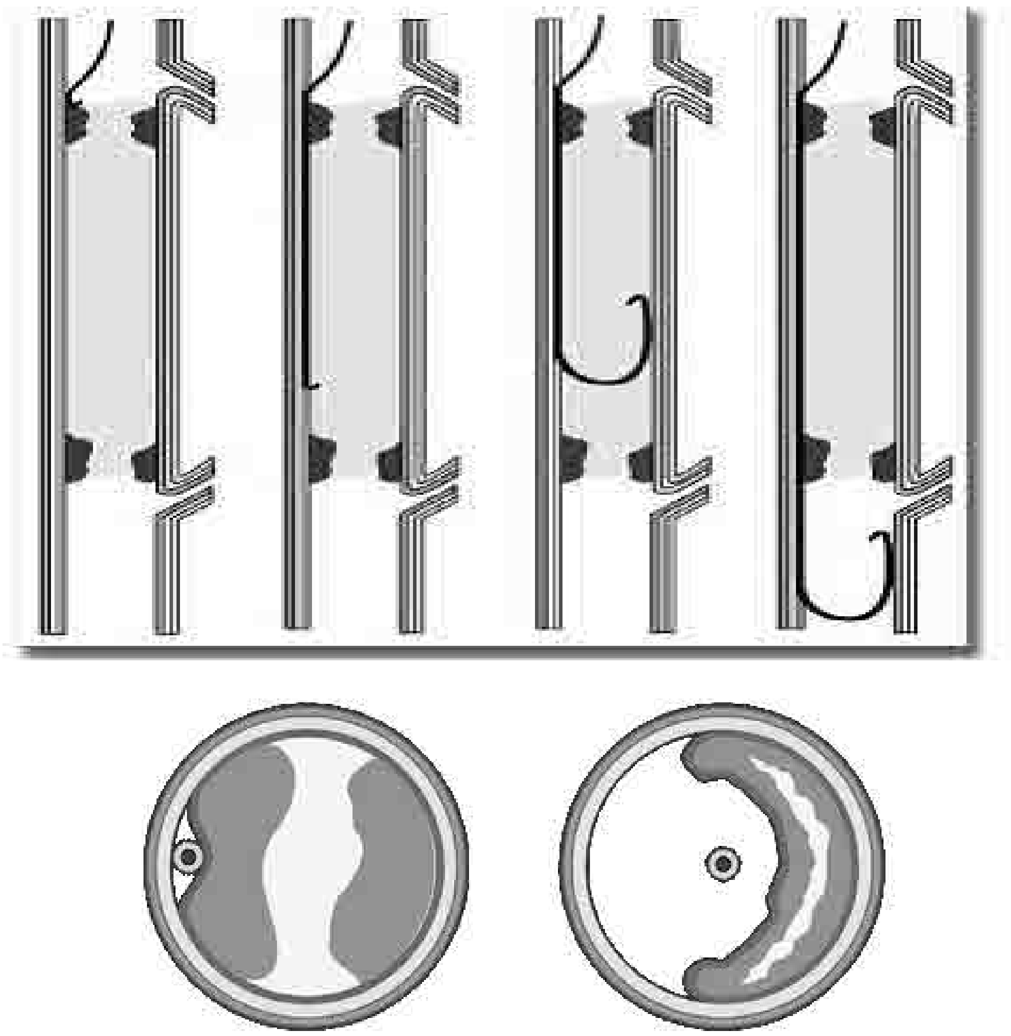


Figure 14. Illustration of subintimal angioplasty technique.

In our study we treated 10 limbs with SFA occlusion by subintimal technique. The procedure starts with 5F rigid catheter with a slightly angulated tip (Bernstein or KMP), which is positioned in the stump of the SFA just cranial of the occlusion. By pushing the catheter slowly forward and with minimal rotation, the tip of the catheter has entered the extraluminal space creating a subintimal dissection. With the catheter in the extraluminal space, a standard 0.035 inch angled guide wire (Terumo) is pushed down until it forms into the large loop configuration. With this loop the extraluminal space is explored distally. The wire-loop can be supported by the catheter, but the loop must always be ahead to make the subintimal dissection. By pushing the loop and the catheter towards the distal patent part of the vessel, a sudden decrease of the resistance can be felt and the wire seems to move down freely. After bringing the catheter down and removing the wire, the intraluminal alignment of the catheter should be checked by the contrast injection. To prevent a damage of the first major collateral artery, the site of the entry should not be too distal. Successful true lumen re-entry was definite as re-entry $\leq$ 2 cm of the optimal angiographically defined target vessel beyond the occlusion without compromise of significant collaterals or branches. After the re-entry into the true patent distal lumen is confirmed with contrast, the new lumen is dilated with a 5-6 mm balloon catheter.

In the case of significant residual stenosis, flow limiting dissention or abrupt occlusion we proceeded with the stenting. In our study we deployed stent after subintimal recanalization in 5 limbs.

Common femoral anterograde approach with subintimal recanalization was performed in all infrainguinal bypass failure patients, but in the cases with failure of re-entry into the true lumen or when it was impossible to visualize the origin of SFA the double approach was used.

In 6 cases there was necessary to perform anterograde and transtibial double approach. These cases were presenting following conditions:

- Occlusion of all three arteries of the tibia at the origin
- Occlusion of the popliteal artery with impossibility to cross by anterograde approach
- Indefinite identification of tibial vessels due to compensated collateral circulations.
- Impossibility to re-entry into the true lumen in cases with subintimal dissection technique. [Figure 15]

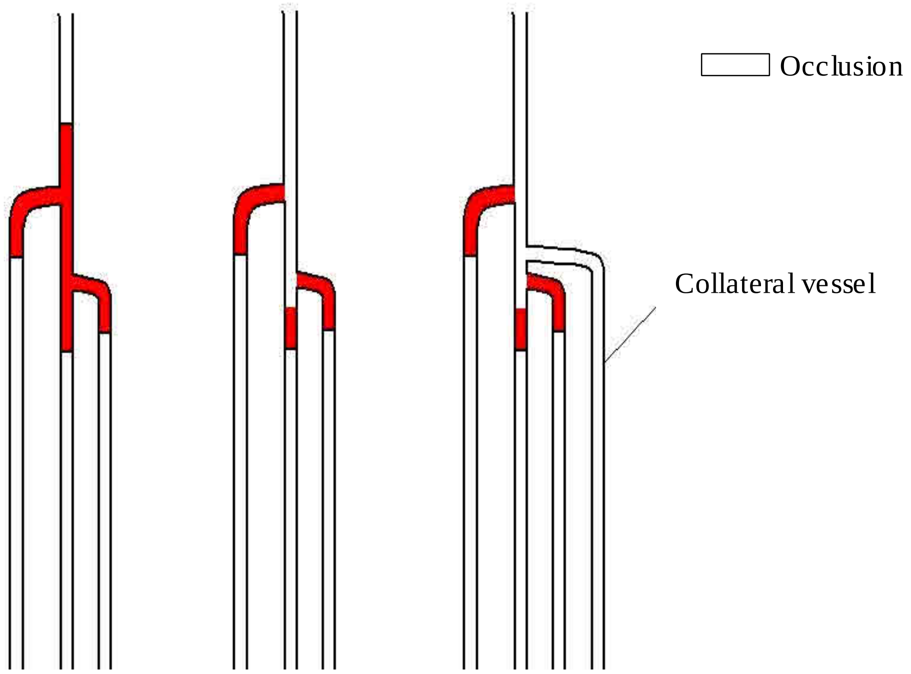


Figure 15. Conditions for "Double approach"

In these cases if we continue to attempt to re-entry into true lumen we can create the damages to arterial wall at the trifurcation level or in the case of dilation of collateral vessel, identified as a posterior or anterior tibial artery, we can create vascular rupture.

This situation represents the indications for distal puncture (pedal artery if we need to recanalize ATA or distal portion of posterior tibial artery). The distal puncture can be performed under fluoroscopy or under ecography guidance: under fluoroscopic guidance if the artery is very calcified; under ecography guidance when the artery is not calcified. [Figure 16]

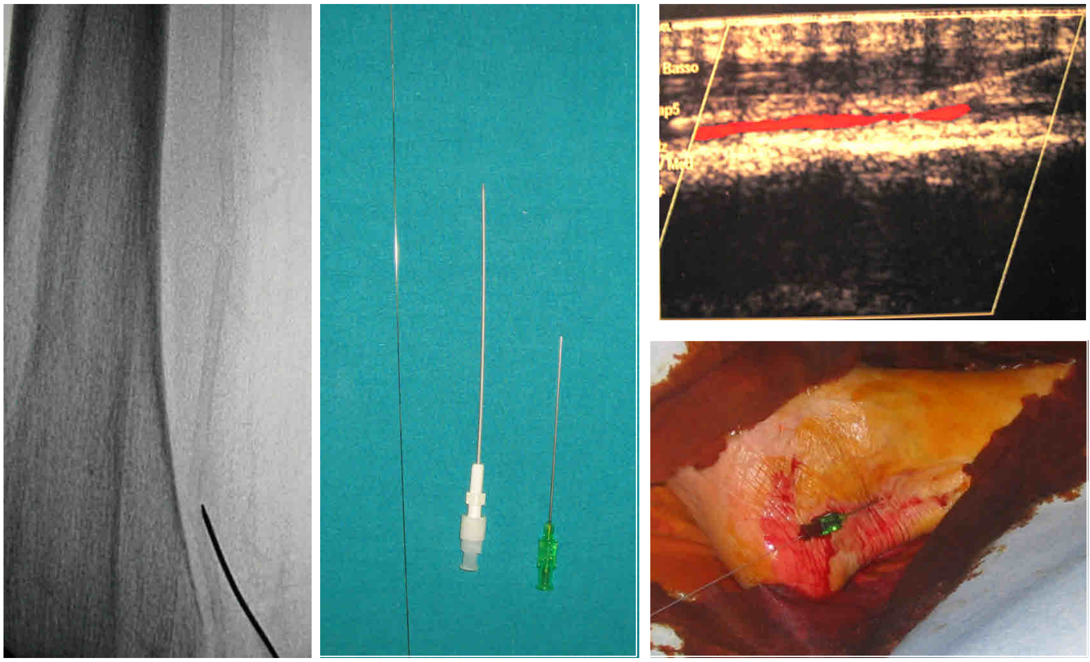


Figure 16. Distal punctures under fluoroscopic and ecography guidance

The 18 G or 20 G puncture needle and 4F introducer are needed to puncture and get distal approach. After that with 0.014 inch guide wire (PT Graphix or Choice, Boston Scientific) was used to cross the lesion retrogradely. Then the tip of the guide wire was inserted into the catheter previously positioned anterogradly "Rendezvous" technique (also called "Michelangelo maneuver" with reference to famous fresco of Michelangelo "Creation of men" at the Sistine Chapel) [Figure 17 and Case 3].

Then the guide wire was inserted into the lumen of the catheter and was pulled out from the introducer placed from the inguinal access. Through this guide wire the angioplasty balloon catheter was advanced and l the occluded arterial segment was performed. Balloon inflation times from 15 to 60 seconds at 8 to 14 atm. The lowest dilation pressure was used to achieve complete balloon expansion.

Local arterial dissections were usually treated with prolonged low atmosphere balloon inflations. In the case of impossible “Michelangelo maneuver” the Amplatz “Goose-neck” Snare kit (ev3 Inc.) was used to capture and pulled out the guide wire. [Case 4]

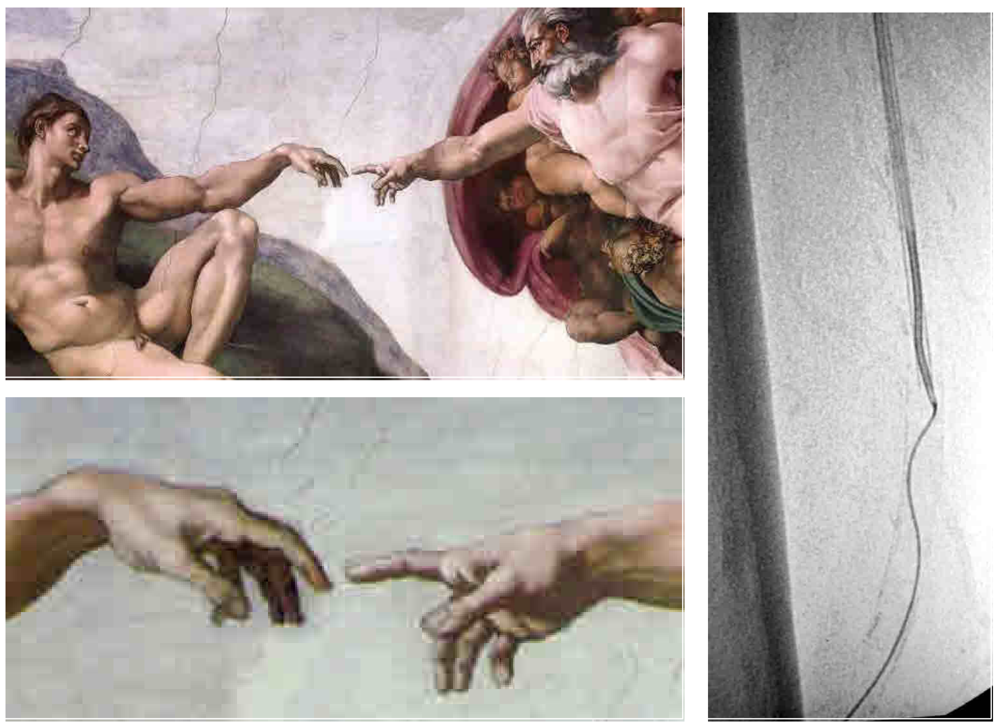


Figure 17. “La Creazione dell’uomo” Michelangelo; fresco at the Sistine Chapel.

In another two cases after 10-20 minutes of manipulation attempts to gain access to the true lumen after subintimal dissection technique in the SFA, the Outback True Lumen Re-entry Device (Cordis Corporation, Johnson & Johnson, Miami) was used. This system consists of double lumen monorail catheter, which tracks over a 0.014 inch guide wire. The second lumen of the catheter contains a curved puncture needle for penetration of the intimal membrane, which allows advancement of a 0.014 inch guide wire into the true vessel lumen. [Figure18]

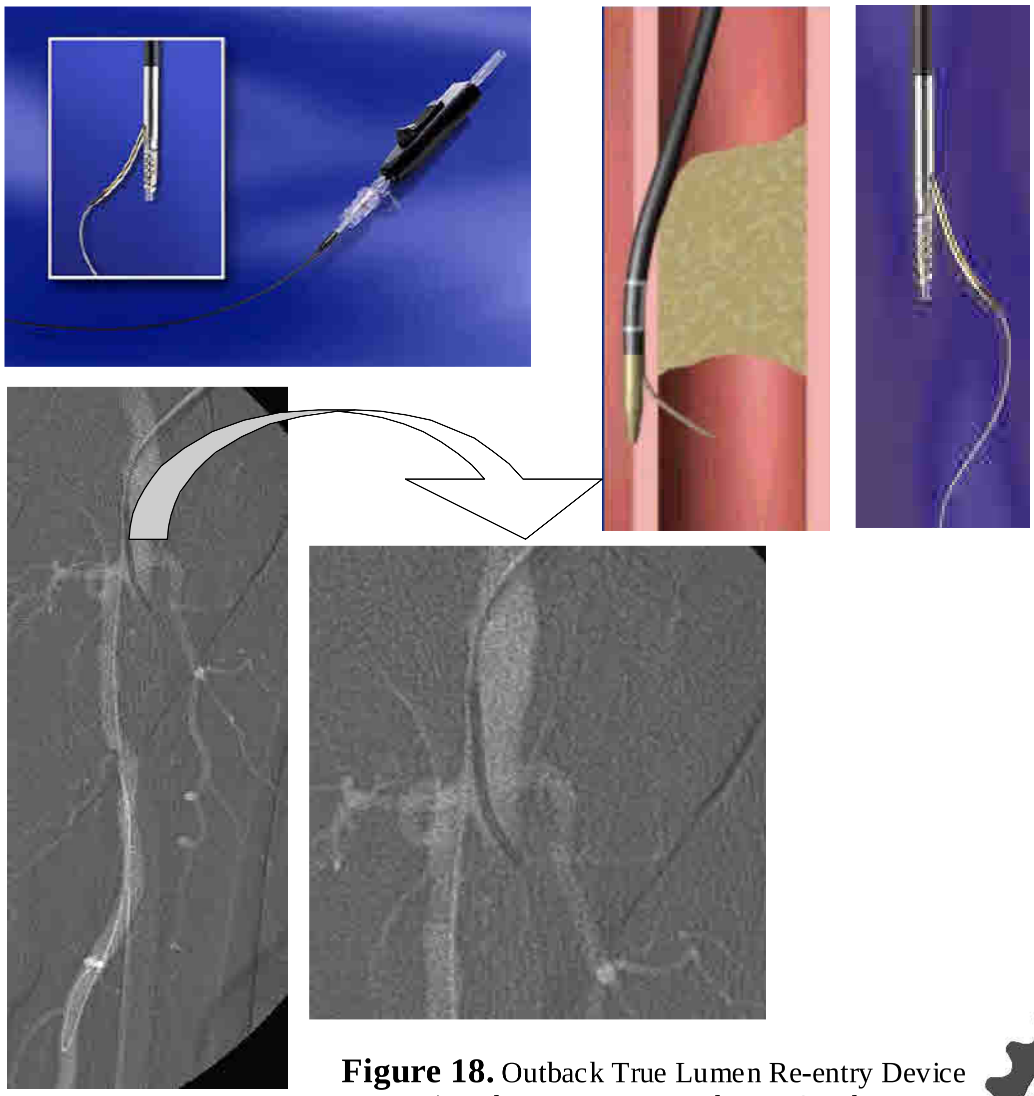


Figure 18. Outback True Lumen Re-entry Device (Cordis Corporation, Johnson & Johnson, Mi

Recanalization of foot arteries

In our study 18 limbs were treated by endovascular recanalization at least one of below the knee arteries. Of these 18 limbs, 7 limbs had combined occlusion of SFA and popliteal arteries.

In all these patients the anterograde access was performed and the long 6F Terumo introducer sheath was positioned with continuous flushing by saline. After the baseline angiography and detection of distal “run-off” with the reabitation segment, the Terumo 0.035 inch angled “J” guide wire was used for catheterization of the origin of occluded tibial artery. Then the “J” guide wire was exchanged with Terumo 0.035 inch straight guide wire to recanalize until plantar arch or pedal artery. After that, 4F diagnostic catheter was advanced to exchange the Terumo guide wire with 0.014 inch (Choice or PT Graphix Super Support, Boston Scientific) guide wire. With 0.014 inch guide wire the distal occlusions of plantar arch or pedal artery were successfully passed. In the plantar arch and in the pedal artery angioplasty was made with low profile 2 mm diameter balloon catheter, instead 2.5-3 mm diameter balloon catheter is used to dilate ATA, posterior tibial and peroneal arteries [Case 5]. In our study we used 12-15 cm long low profile balloon catheters to have a major cover of occluded tract.

Another advantage of using this balloon is reduced number of dilation, reduced risk of dissections and reduced time of procedures [Case 6].

In 3 cases (2 ATA and 1 posterior tibial artery) were presented occlusion with extremely high calcifications with inability to cross the lesion due to high resistance. So, to get the perforation in this high calcify plaque, the back end of the hydrophilic wire was used to cross short, resistant segments of occlusions.

In one case after successfully recanalization and dilation we had a distal thromboembolic occlusion. This was resolved by catheter thrombus aspiration with 6F multipurpose (MACH) guiding catheter and 60 ml syringe. [Figure 19]

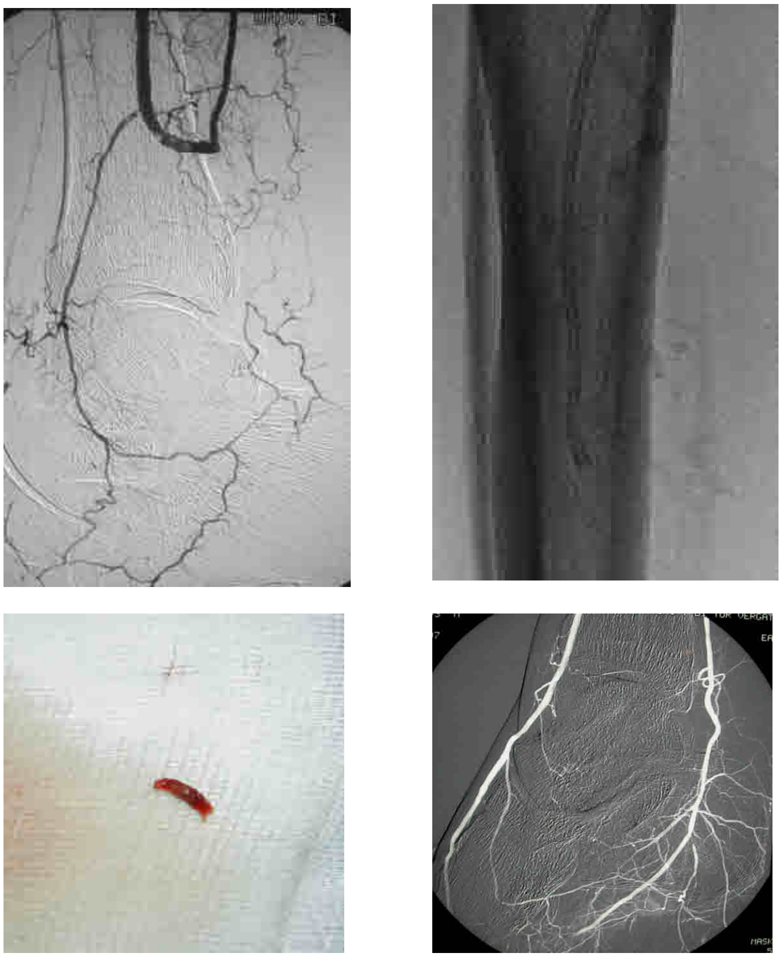


Figure 19. Catheter thrombus aspiration with 6F guiding catheter

4.4 Post-procedural treatment

At the end of the procedures all patients were considered to endovenous infusion of physiologic solution for 24 hours and antibiotic therapy.

All patients were considered for double antiaggregation therapy with Ticlopidine (250 mg x 2) for 6 months and Acetylsalicylic Acid (100 mg) in association with gasteroprotectors "quod vitam".

4.5 Definitions and Statistical Analysis

The results were analyzed as a technical success, clinical success, systemic and local acute complications, death in 30 days after procedure and death in the period of follow-up.

Acute or technical procedural success was defined by recovery of native vessel with vascular lumen estimated > 50% of the original lumen, absence of stasis of contrast media in the treated segments and patient's "sensation of warming" of the temperature in the treated extremity is an arbitrary criterion to indicate an adequate haematic flow.

Clinical success was defined as resolving rest pain and pain at night, healing of the ulcer or toe amputation site, or avoiding below- and above-the knee amputations and an increasing of the percutaneous oxymetry > 50 mmHg was based on our experience.

The evaluations of hemodynamic improvements were estimated on the basis of $TcPO_2$ /$TcPCO_2$ parameters. The improvements of ABI parameters greater than 0.10 was considered significant [7].

In all patients were measured the parameters of $TcPO_2$ /$TcPCO_2$ at 1, 2, 3 and 4 weeks after the procedures. The patients with ulcers were examined and medicated every week until healing and every 2 months.

Limb salvage at 6 months referred to the absence of major (above the metatarsal) amputation. Adverse events were recorded at hospital discharge and at 1, 3, and 6 months.

Continuous variables are presented as mean ± SD (range). Comparisons were analyzed with the Student *t* test; significant difference was assumed for $p<0.05$. [Figure 20]

$$t = \frac{\bar{x}_1 - \bar{x}_2}{\sigma_d} \quad \text{where} \quad \sigma_d^2 = \frac{\sigma_1^2}{n_1} + \frac{\sigma_2^2}{n_2}$$

$\bar{x}_1$ and $\bar{x}_2$ - mean of each sample

σ_d^2 - the variance of the difference between the two means

Figure 20. Calculations of Student ***t*** test

5. Results

Since March 2006 to march 2007 revascularization was attempted in 29 patients with 30 critical ischemic limbs. [Table 5] Distribution of the occluded segments in the study population was: 5 limbs were with Iliac artery occlusions (IA), 7 limbs with SFA occlusions, 7 limbs with SFA and popliteal artery (PA) occlusions, in 5 limbs associated occlusions of PA, ATA, posterior tibial artery (PT) and peroneal artery (P), in 3 limbs associated occlusions of ATA, TP and P, in 3 limbs associated occlusions of pedal artery and plantar arch. [Table 6]

Table 6. Distribution of the lesions in study population

N° Limbs	Occluded segments
5	**IA**
7	**SFA**
7	**SFA and PA**
5	**PA + ATA/PT/P**
3	**ATA + PT + P**
3	**Pedal artery + Plantar arch**
Total Limbs	Total of occluded segments
30	**48**

The mean follow-up period was 48 ± 12 weeks. 2 patients were l

follow-up.

The technical success was achieved in 28 (93.3%) of 30 limbs. In these 28 limbs subintimal technique was incorporated in 92.8 % of cases. Mean lesion length was 12.3 ± 6.3 cm (4.8–29). In 7 (23.3%) limbs were positioned stent. The first technical failure in the femoral-popliteal bypass occlusion patients was due to surgical disconnection of the native artery made by previously bypass surgery. Therefore, underwent another elective bypass grafting. The second failure was due to very high calcified plantar arch, which caused impossibility to cross the lesion, and received no further treatment and eventually underwent amputation. The clinical success was corresponding to all patients who had a technical success; the pain was regressed, the ulcers were healed.

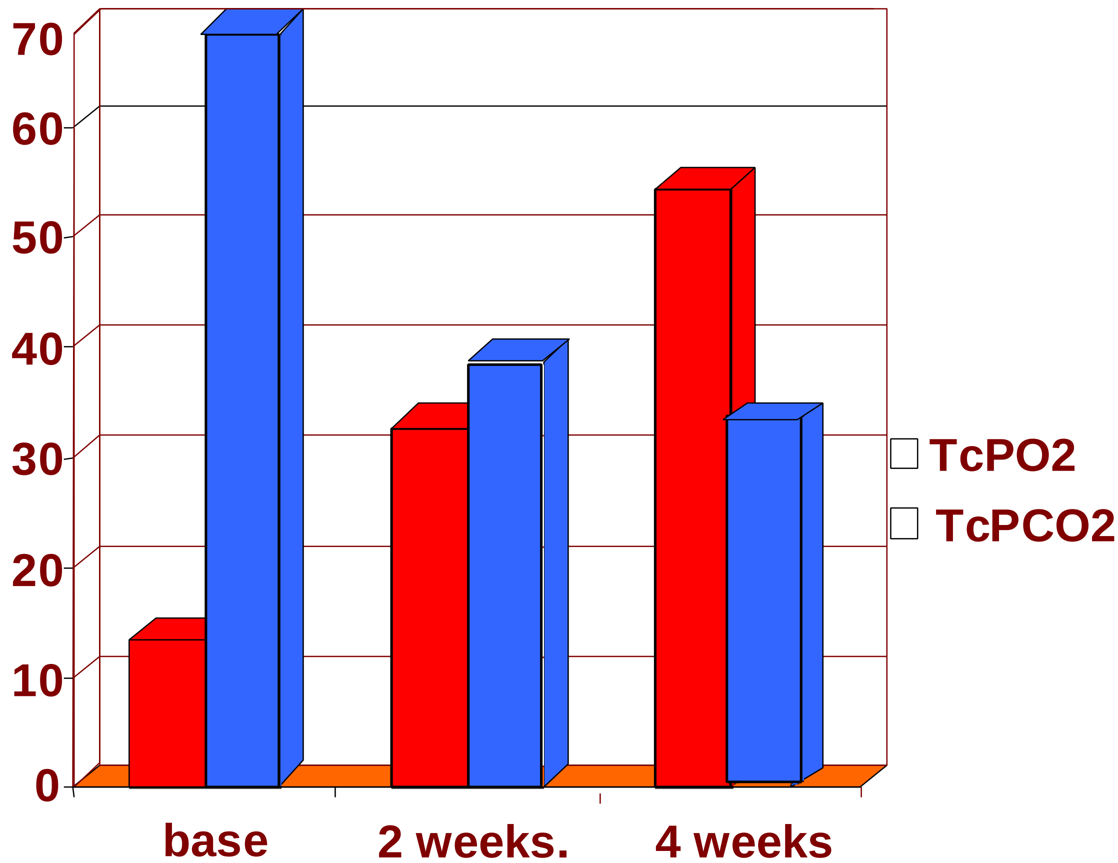
The preprocedural level of $TcPO_2$ was 13.8 ± 6 mmHg; in patients with technical success this parameter was increased after first week up-to 26.83 ± 13 mmHg. ($p<0.05$) The pressure was continuing to increase and at the 4th week was evident the improvement of the clinical condition of the foot.

Proportionally opposite of this, was transcutaneous tension of CO_2 ($TcPCO_2$). Preprocedural mean of $TcPCO_2$ in extremely ischemic foot was 71.2 ± 27 mmHg, but postprocedural mean, after first week, was decresed significantly and was continuing to decrease in subsequently. ($p<0.001$) Table 7 and relative graphic shows the hemodynamic parameters b
and after the PTA procedure.

Table 7 - Pre and Postprocedural (follow up) mean of $TcPO_2$ and $TcPCO_2$.

mmHg	Before the procedure (mmHg)	1st week (mmHg)	2nd week e (mmHg)	3rd week (mmHg)	4th week (mmHg)
$TCPO_2$	13.8 ± 6	26.83 ± 13	34.12 ± 22	41.6 ± 22	52.4 ± 22
$TCPCO_2$	71.2 ± 27	43.75 ± 10	39.73 ± 22	34.18 ± 8	32.28 ± 7

Graphic – The follow-up value of TcPO2 and TcPCO2.



The ABI improved to 0.86 ± 0.18 ($p<0.001$ versus pretreatment) and TCO2 improvement was obtained to 52.4 ± 0.22 ($p<0.001$).

Over the 6-month follow-up period, in one limb after 2 months we had occlusion of a popliteal stent. The reintervention was performed and was released a second “intrastent” stent. Successful redilation was performed in 4 limbs.

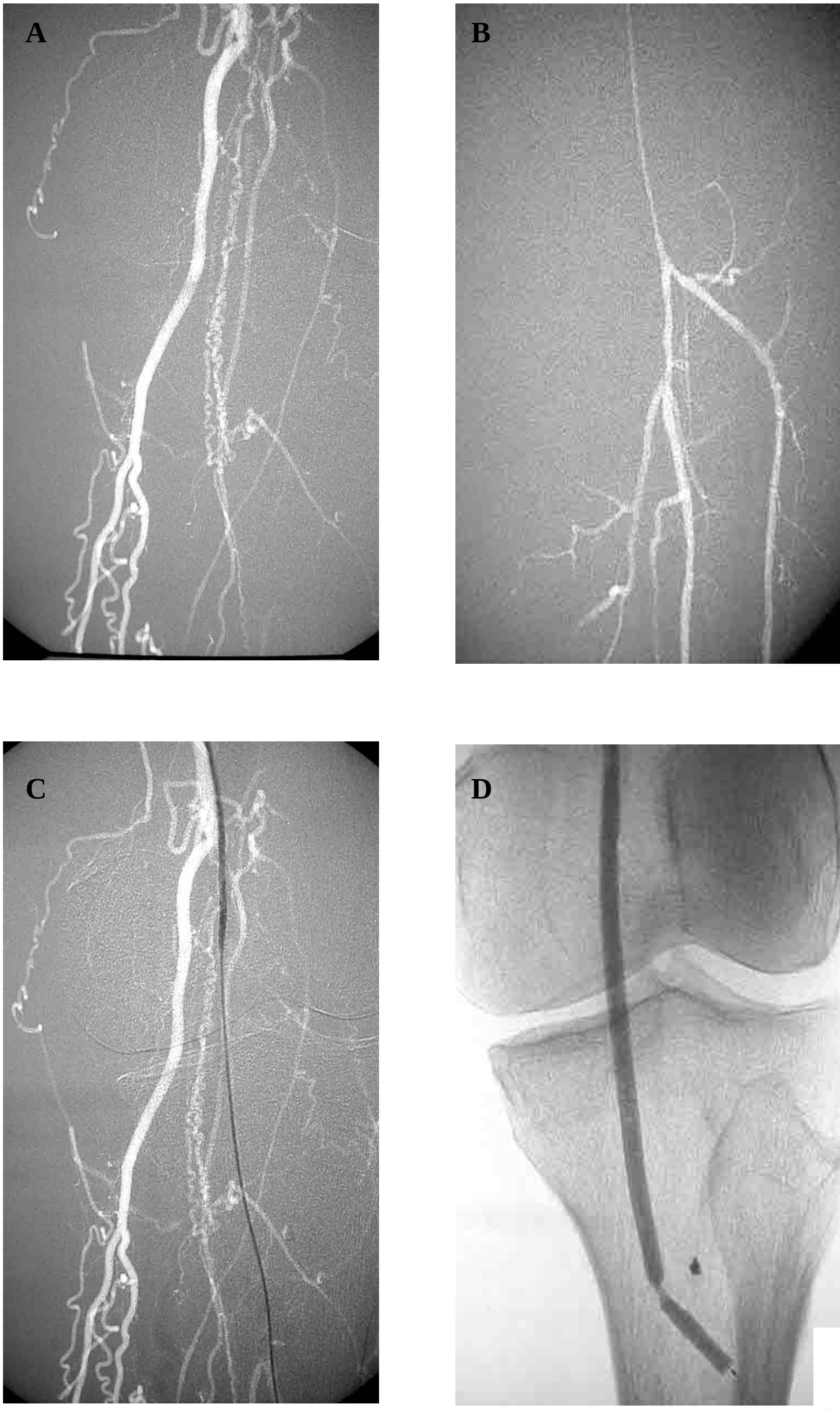
The mean area reduction of ulcers or minor amputation sites was 72% for 23 wounds observed at 3 months, increasing to 93% at 6 months. In the 28 successfully treated patients, the limb salvage rate at 6 months was at least 92.8 %.

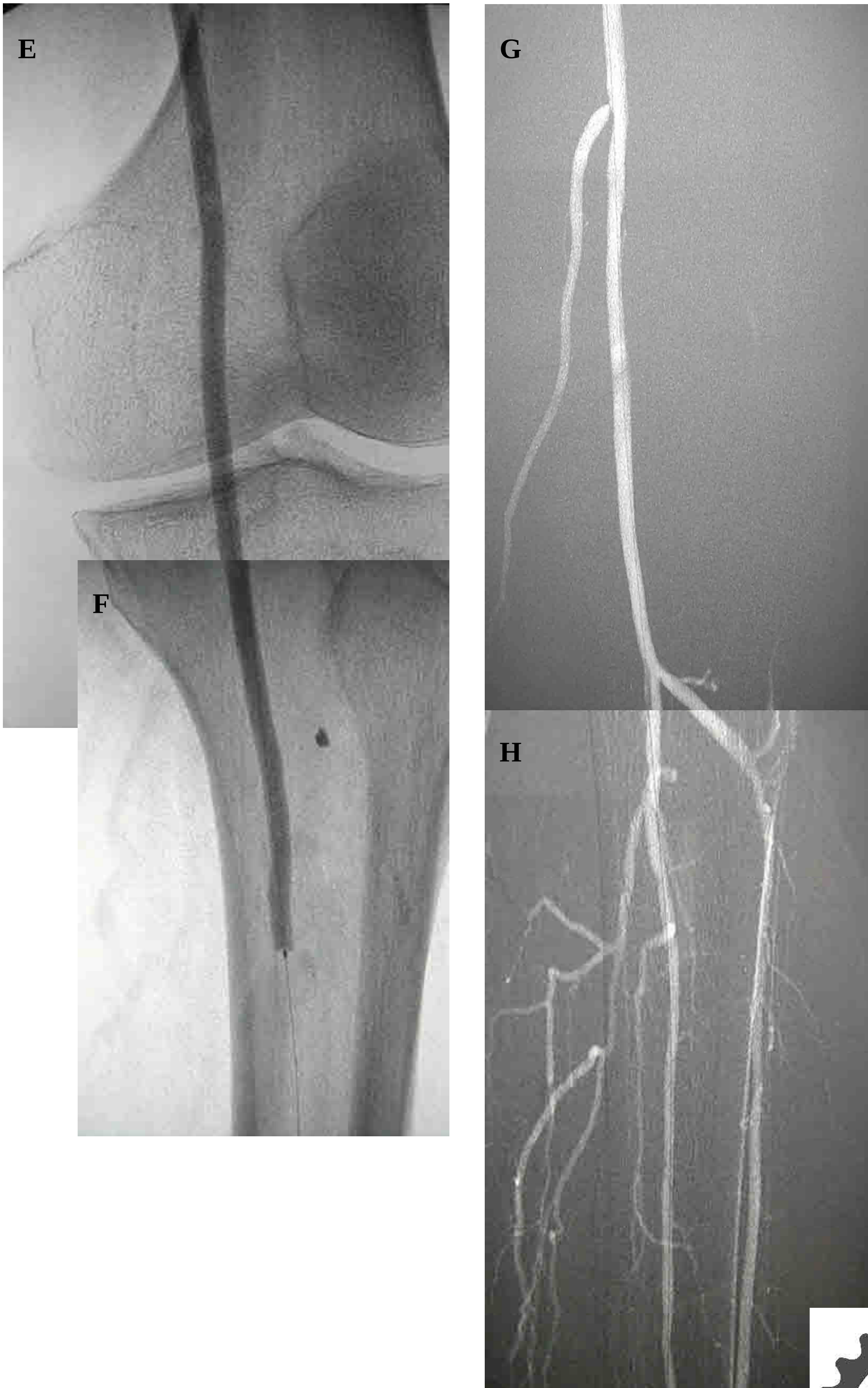
In one case after successfully recanalization and dilation we had a distal thromboembolic occlusion. This was resolved by catheter thrombus aspiration with 6F guiding catheter.

One patient, who had technical and also clinical success, about 3 months after procedure was dead by heart failure.

We didn’t register any intra procedural complication and post procedural complications at 30 days.

Case 1

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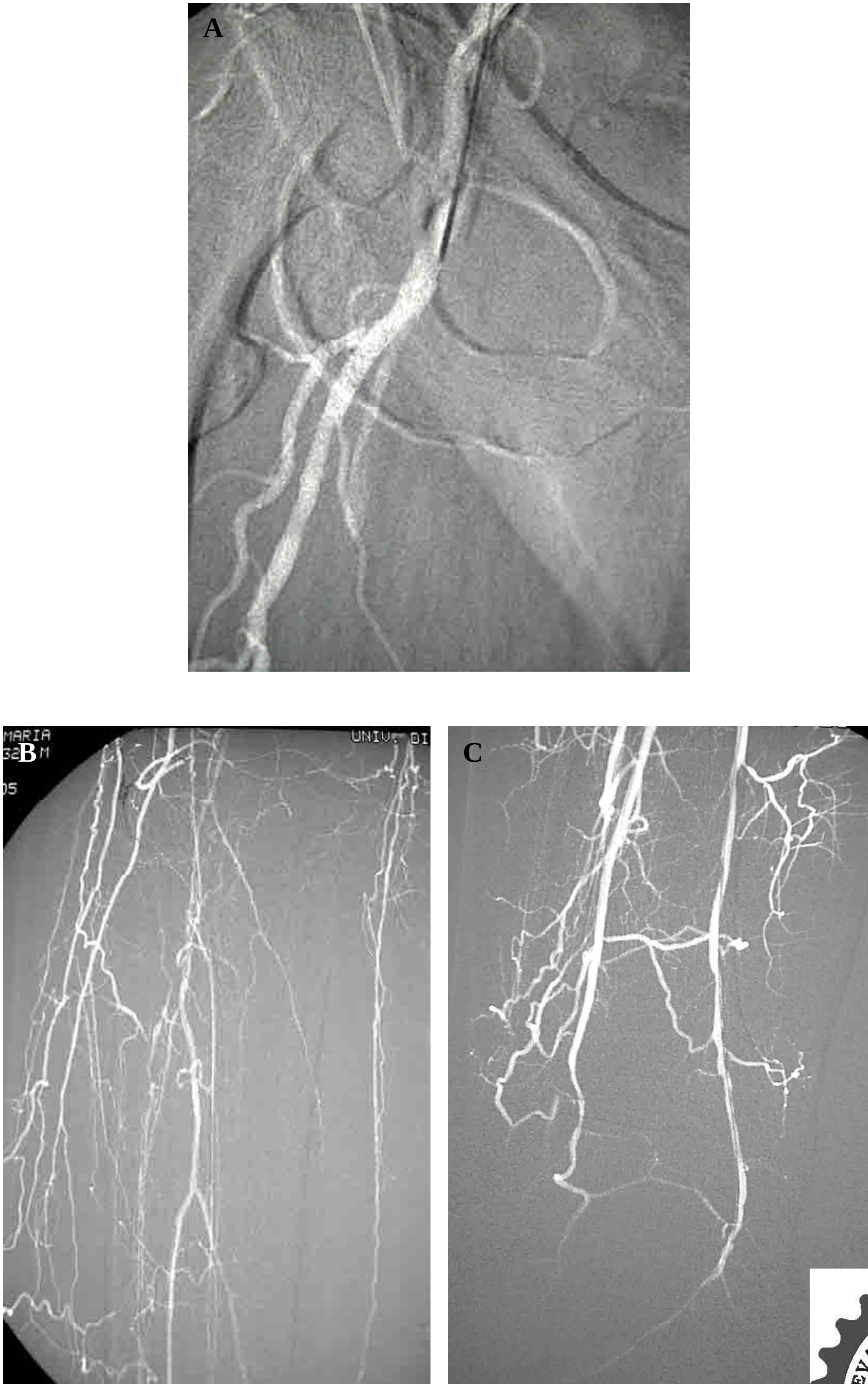
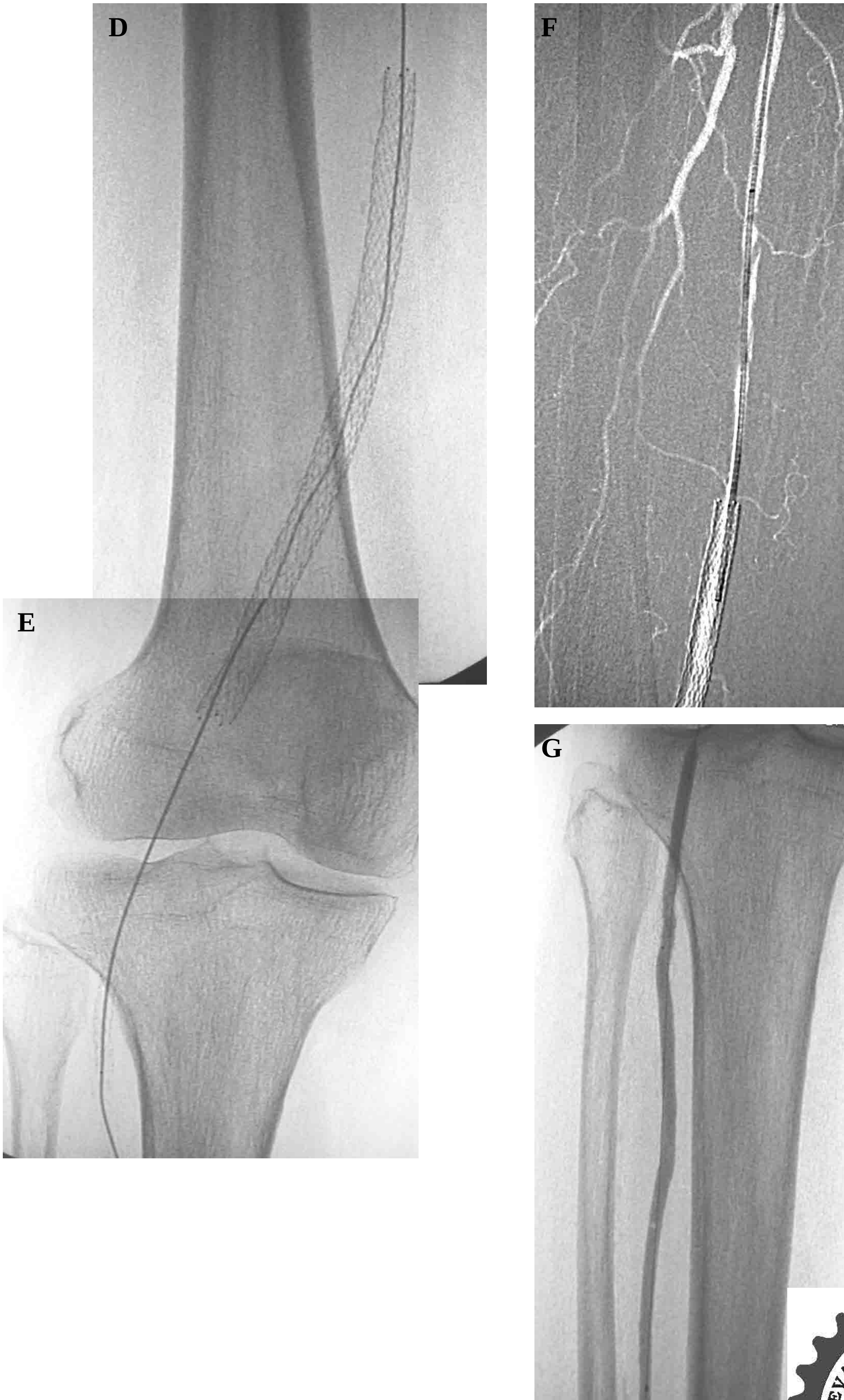
Case 1

The preliminary angiography shows the occlusion of distal part of SFA in origin of Hunter with the reabitation in the proximal third of anterior tibial artery (A and B). The SFA, popliteal artery and tibio-peroneal trunk were successfully recanalized with hydrophilic guide wire and PTA, up to the origin of anterior tibial artery, was performed using 4 mm balloon catheter (C - D - E - F). The control at the end of the procedure shows a satisfactory angiographic result (residual diameter stenosis ≤ 30 %) and no flow-limiting dissection (G and H).

Case 2

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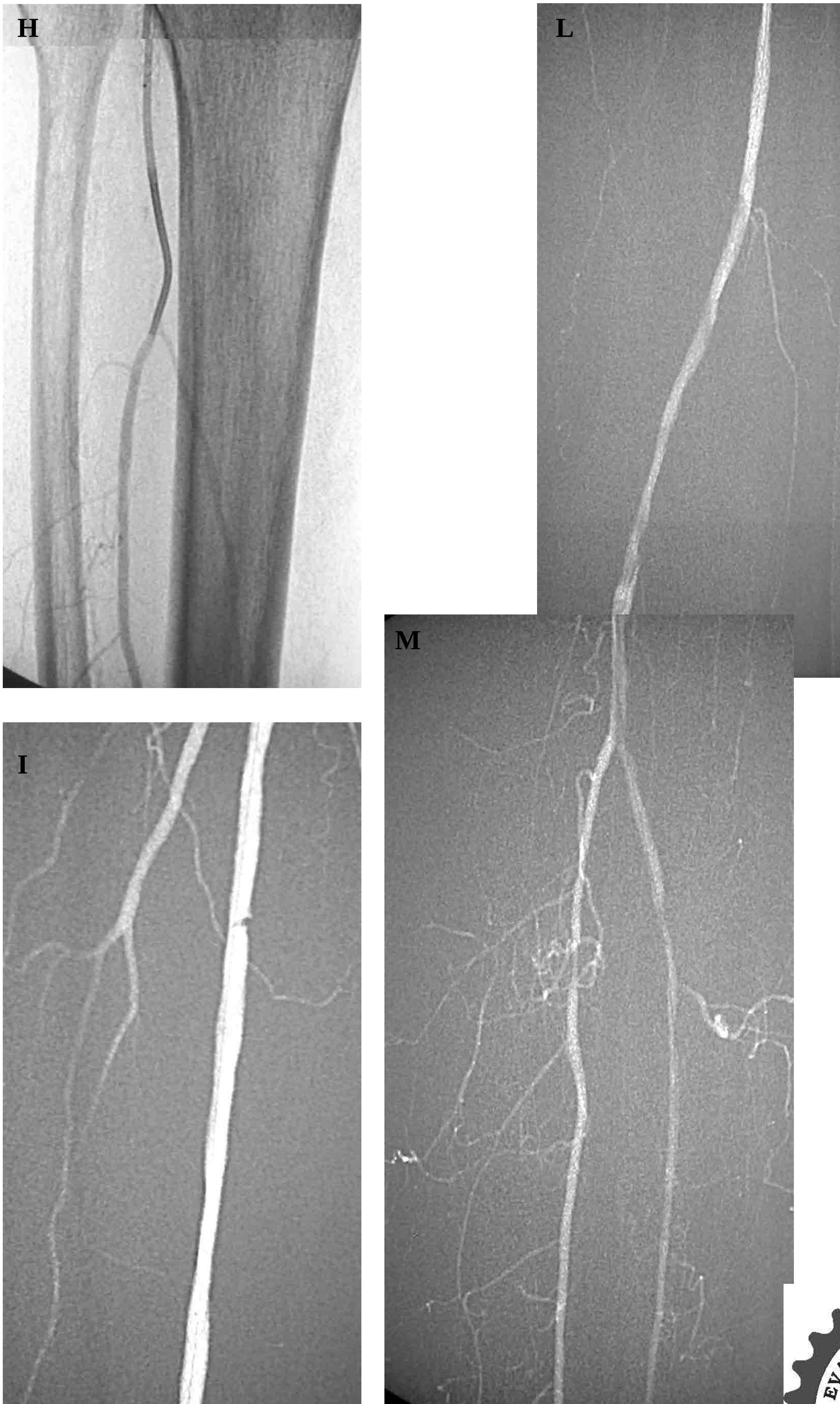
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Case 2

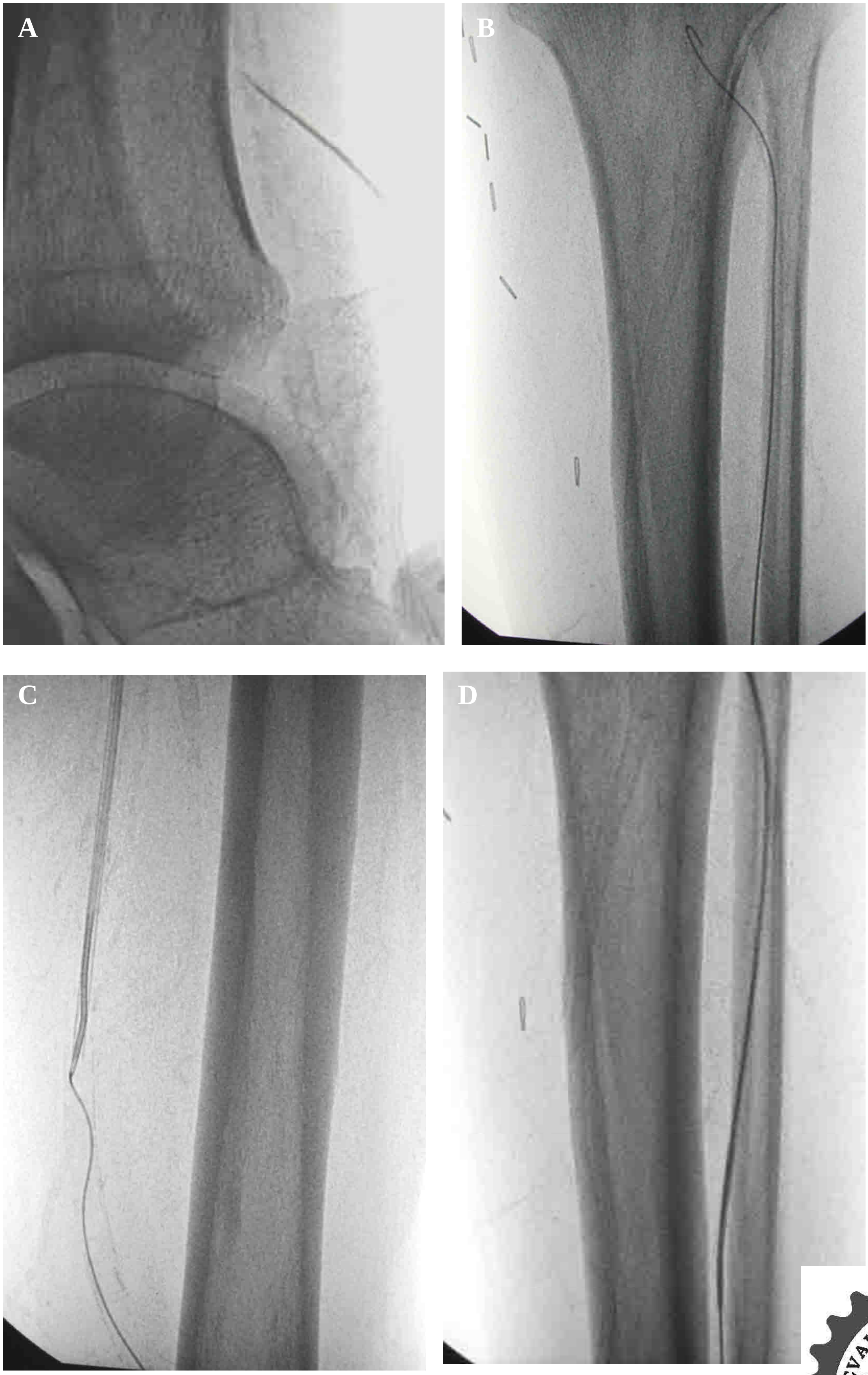
The preliminary angiography performed through anterograde puncture of common femoral artery shows occlusion of omolateral SFA in the origin with reabitation in the level of ATA (A - B - C).

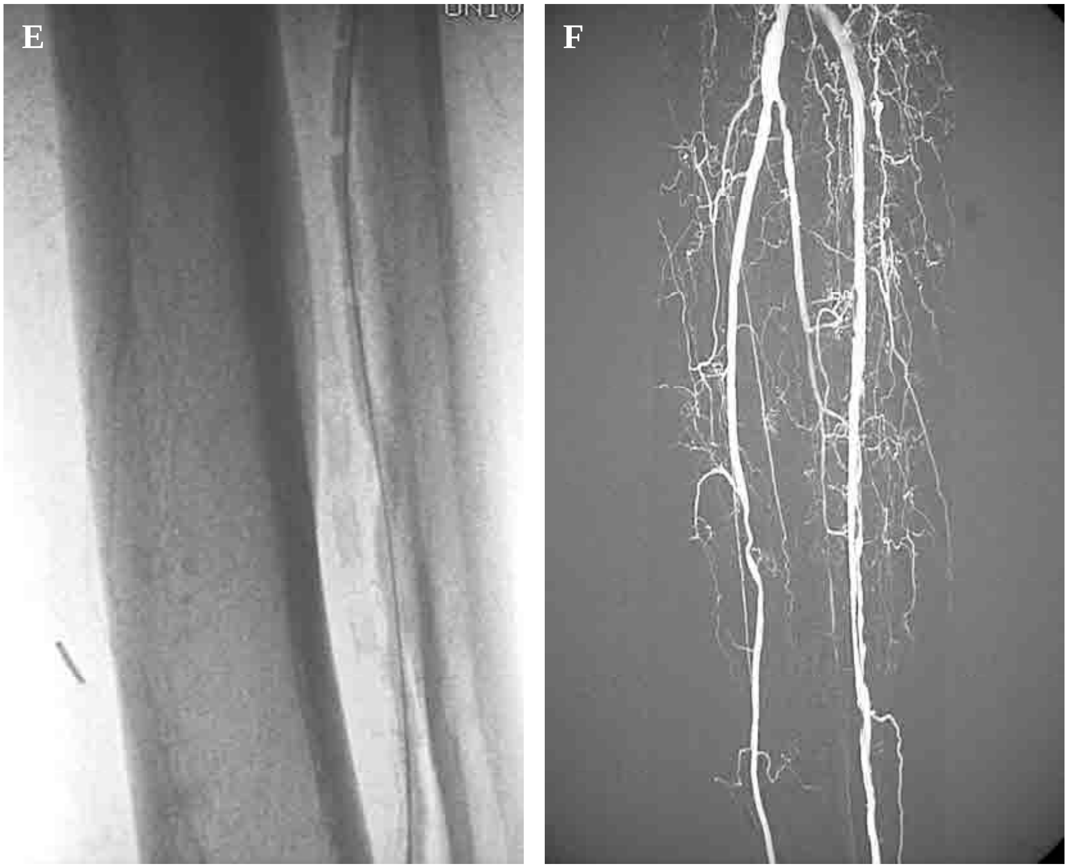
Endoluminal recanalization and PTA/S of SFA with two self expandable was successfully performed (D - E - F).

After that was recanalized tibio-peroneal trunk and initial part of ATA with hydrophilic guide wire and PTA with 2.5-3 mm diameter, 12 cm long balloon catheter has successfully been done (G and H).

The control at the end of the procedure shows a satisfactory angiographic result and no flow-limiting dissection (I - L - M).

CASE 3



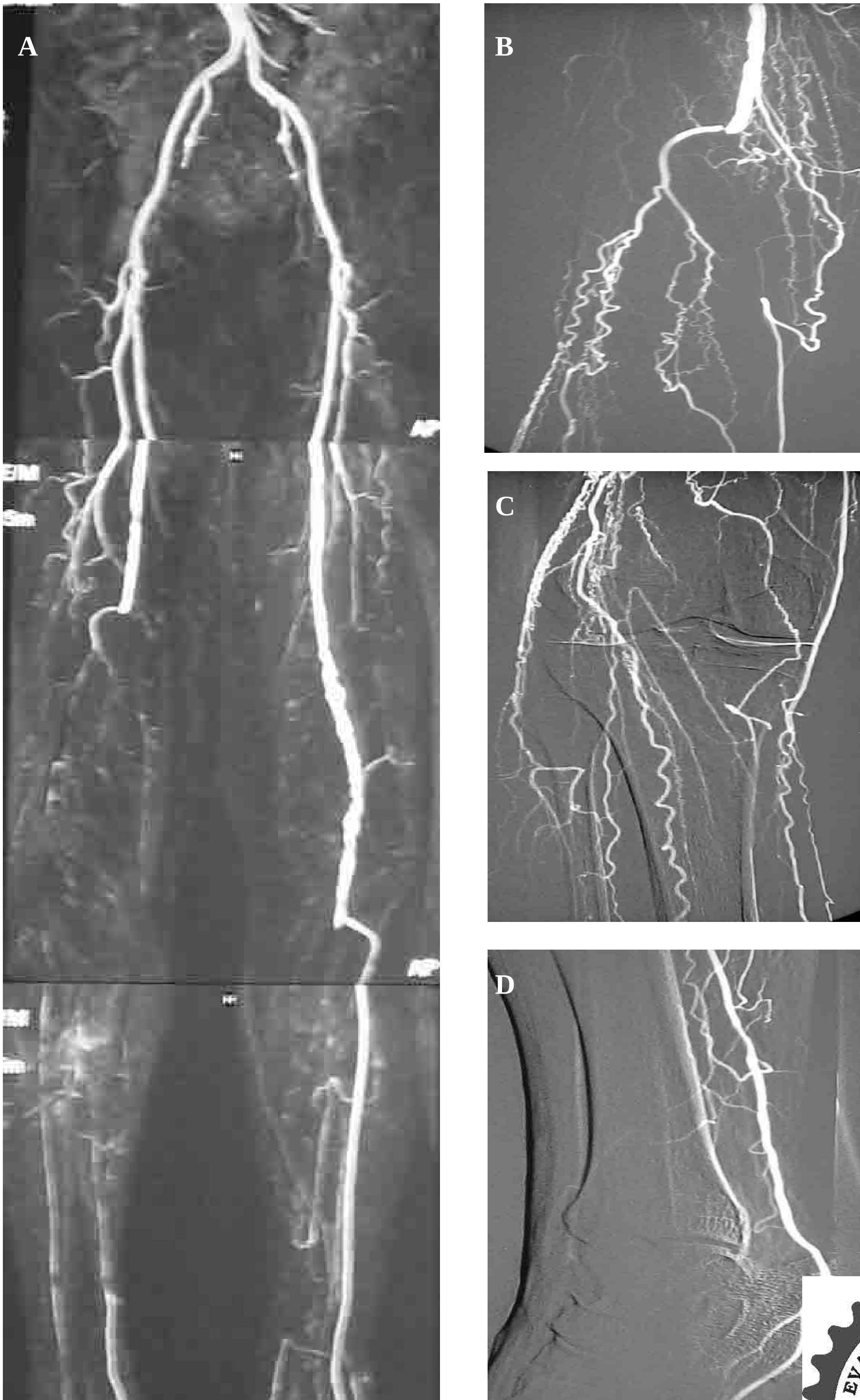


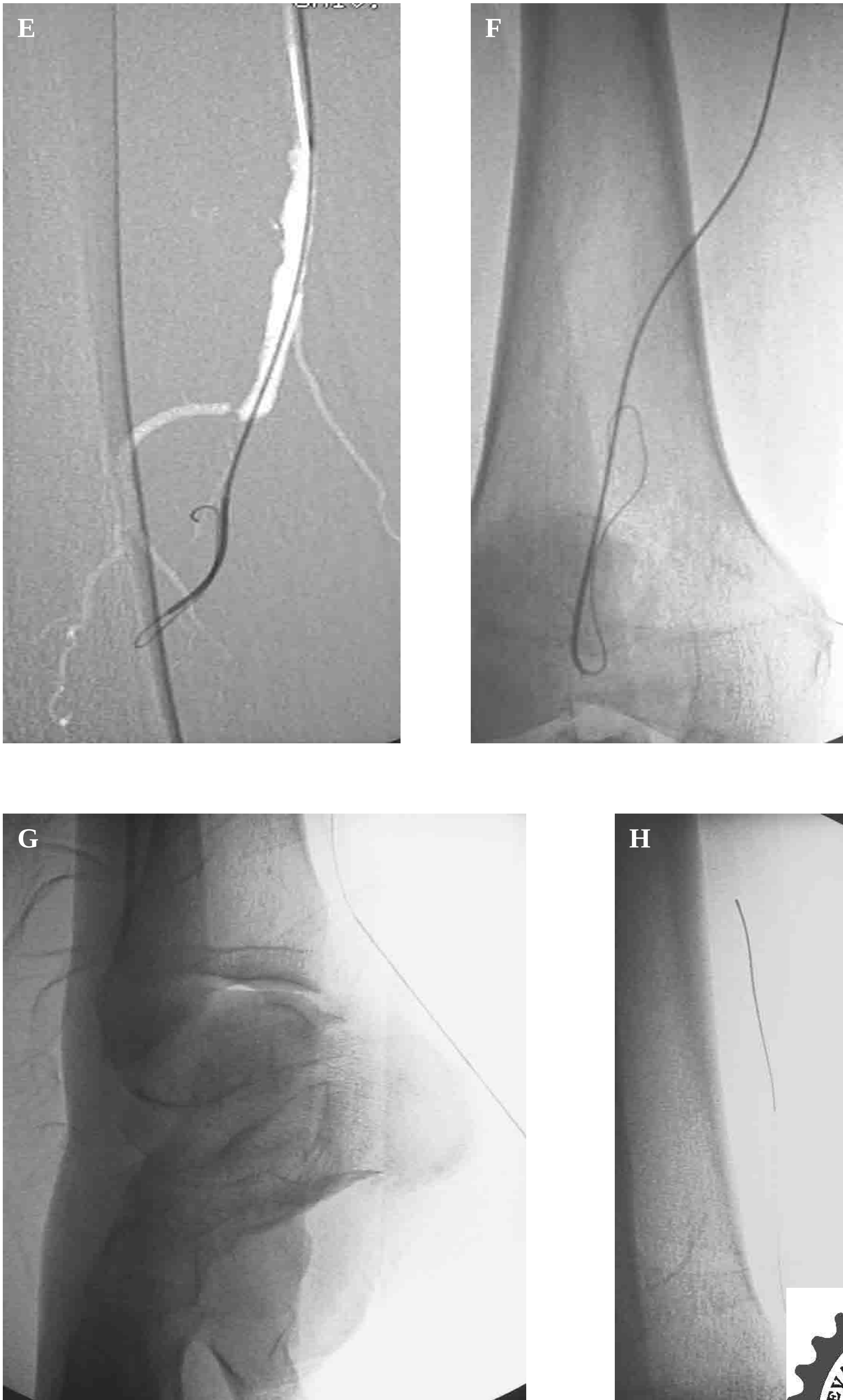
Case 3

Through the distal puncture at the level of pedal artery (A) the recanalization of ATA with 0.014 inch guide wire and 2 mm diameter 12 cm long balloon catheter, using “Michelangelo” of “Rendezvous” technique, was successfully performed (B - C - D - E).

The final angiography shows optimal results of the procedure without any complications (F).

Case 4

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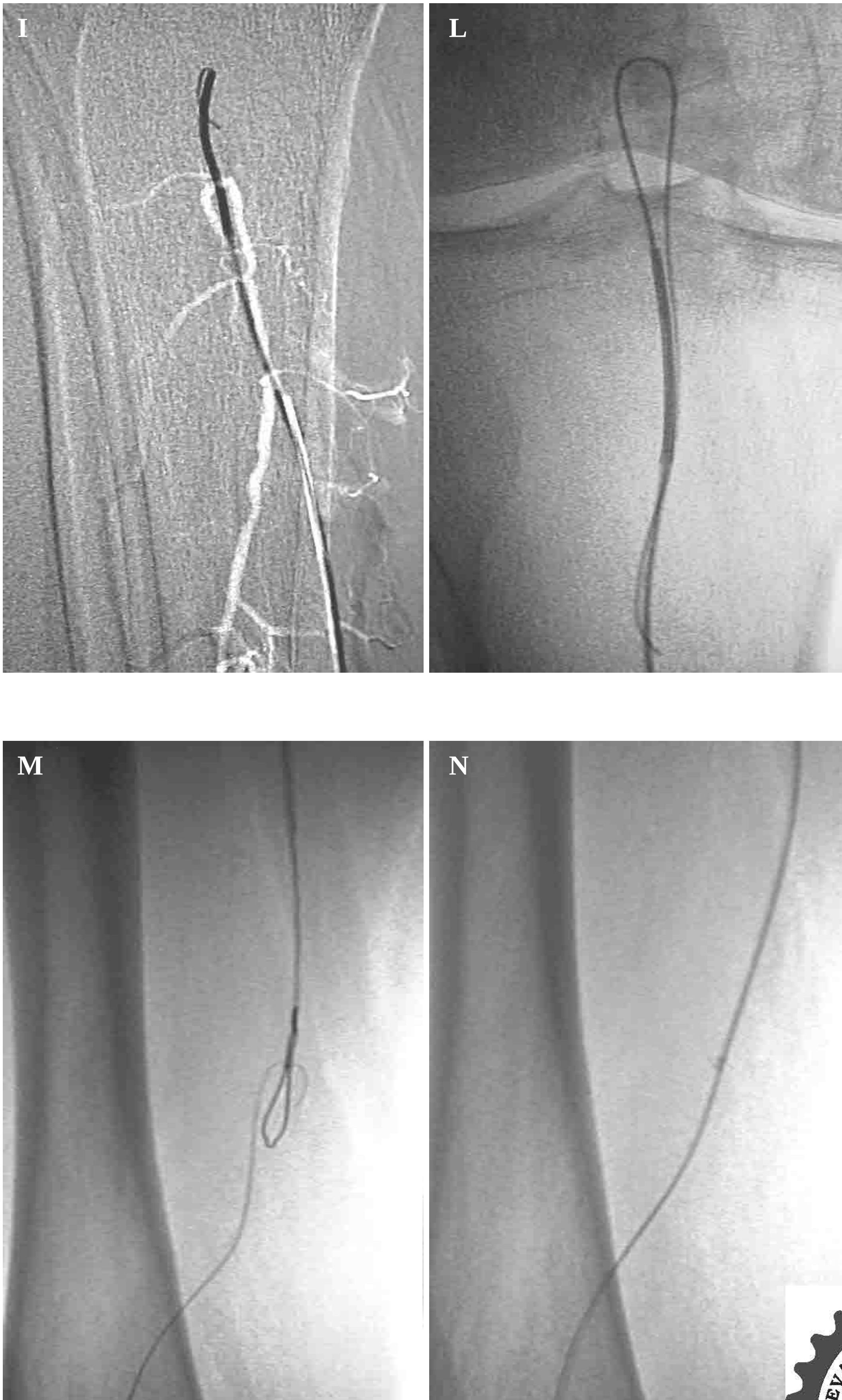
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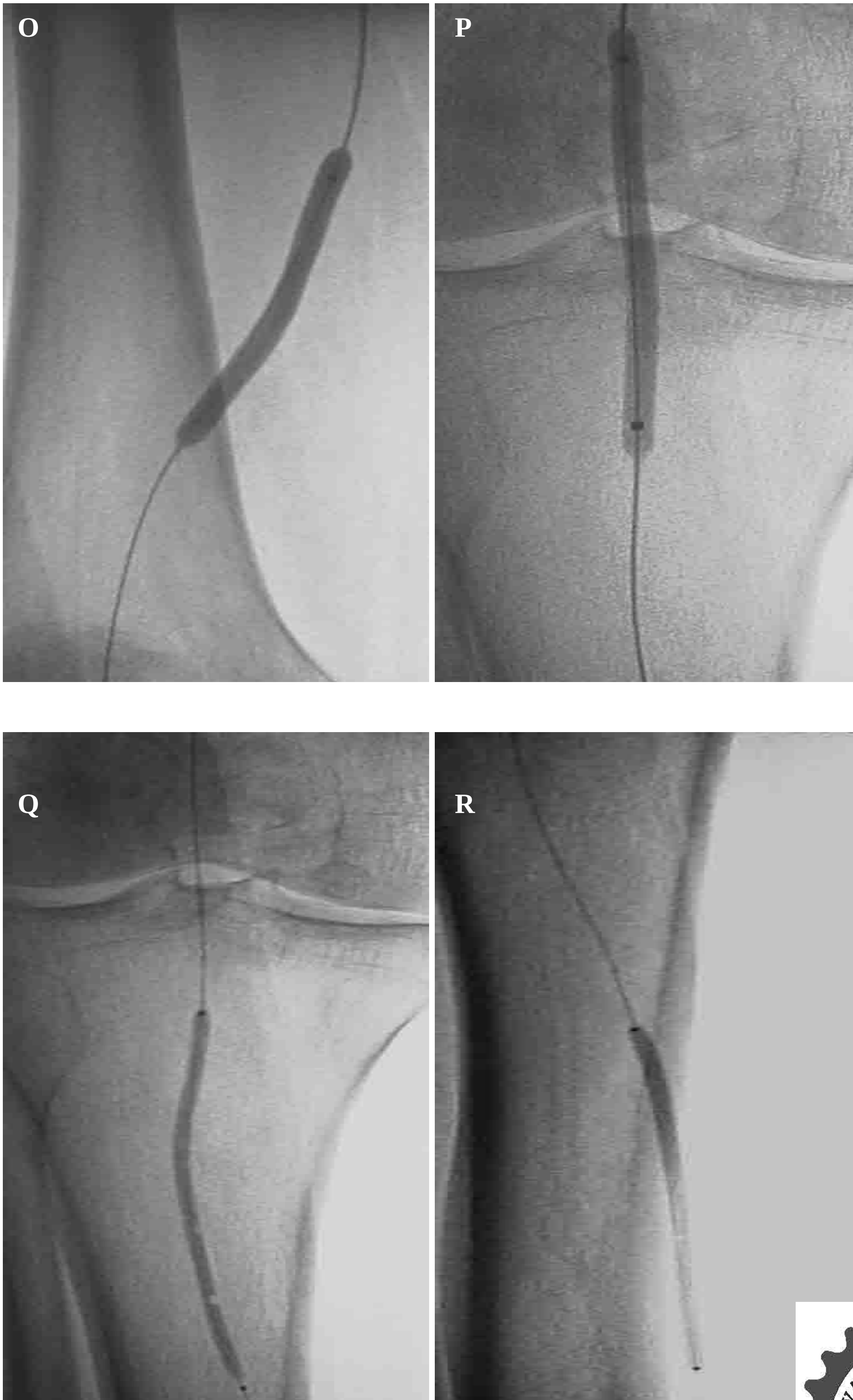
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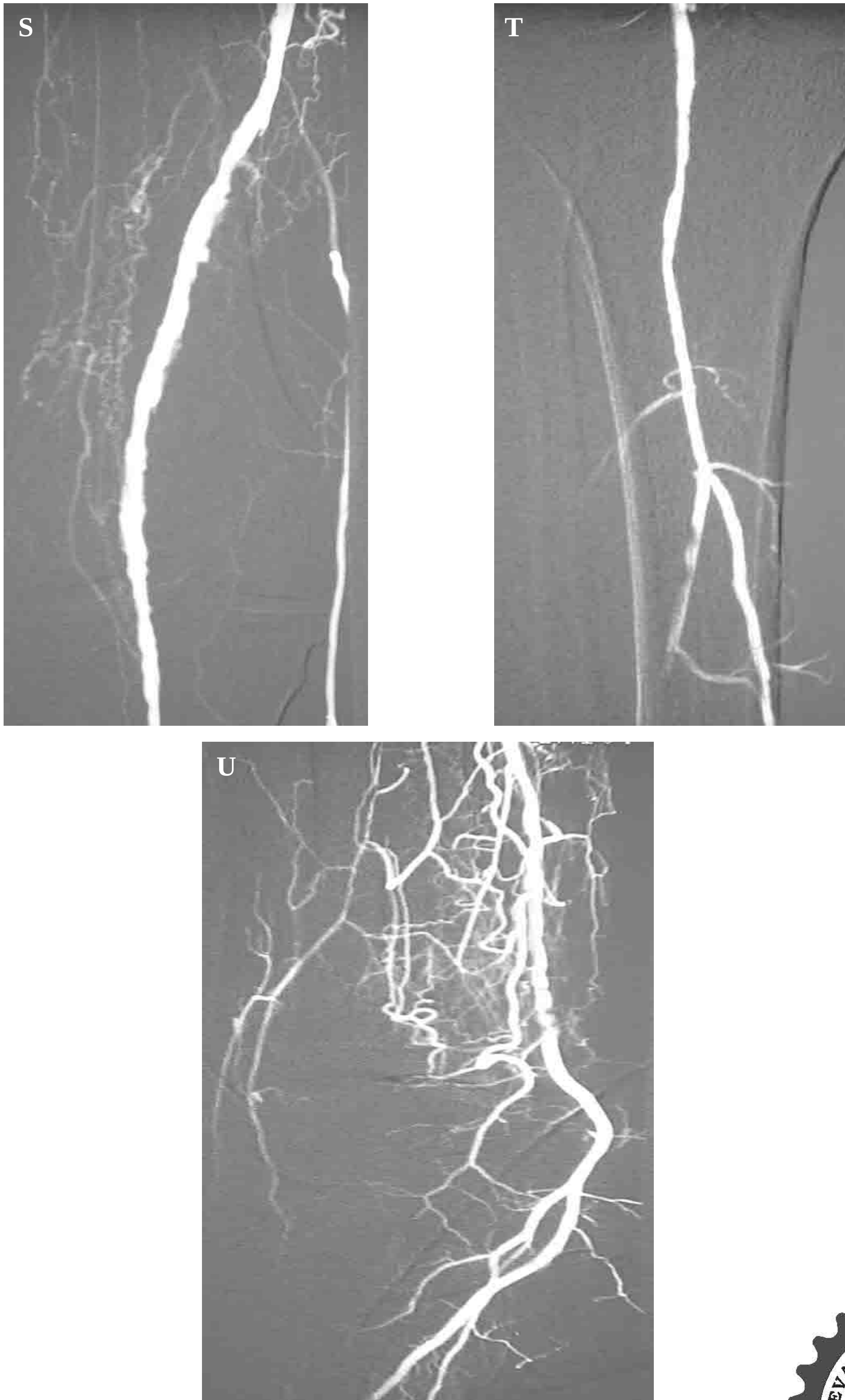
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Case 4

The angio-RM and baseline angiography shows the occlusion of right SFA in the middle third segment with reabitation at distal third of posterior tibial artery (A - B - C - D) .

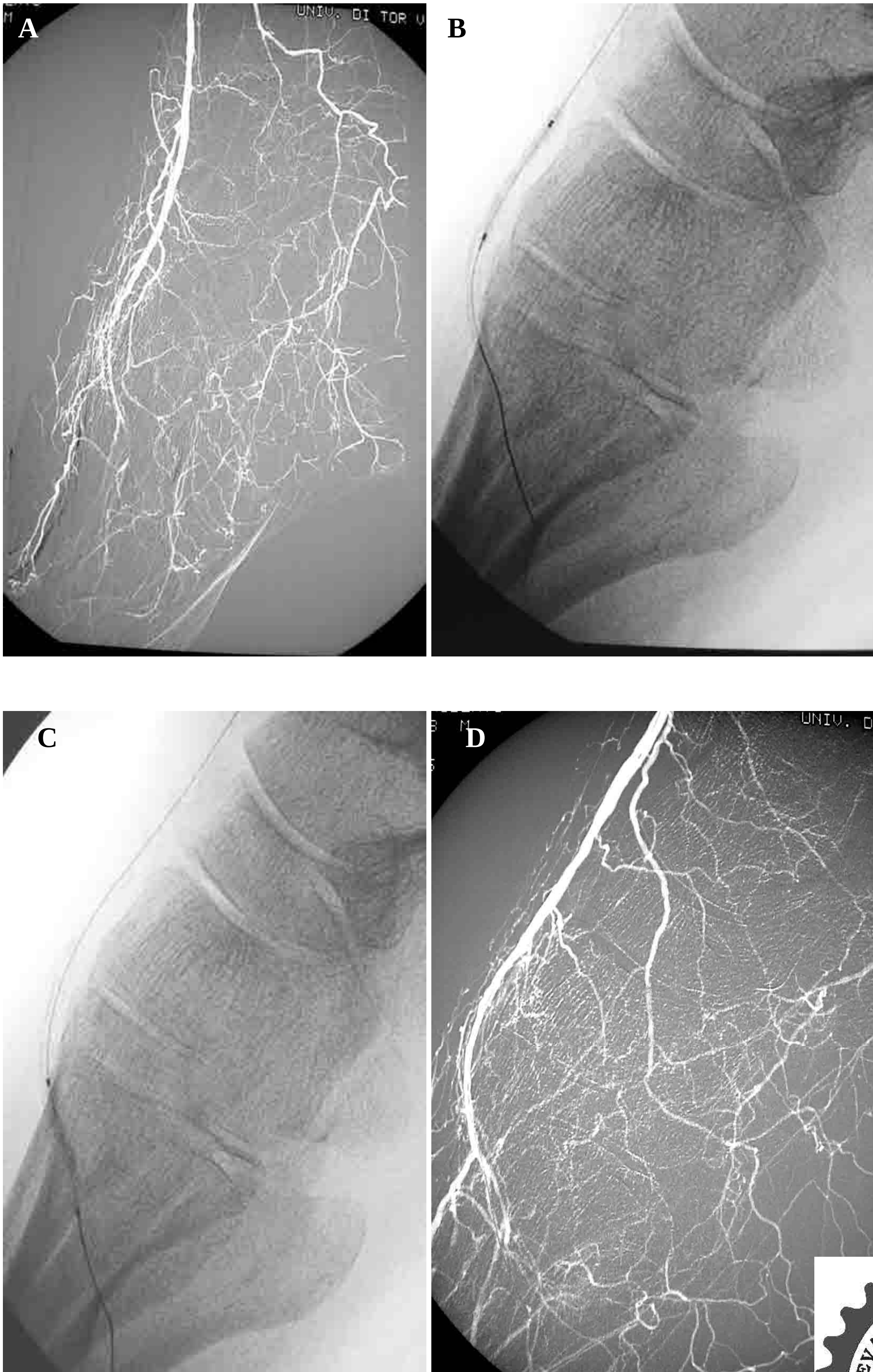
Through a right anterograde common femoral approach was attempted to recanalize subintimally the occlusion (E and F).

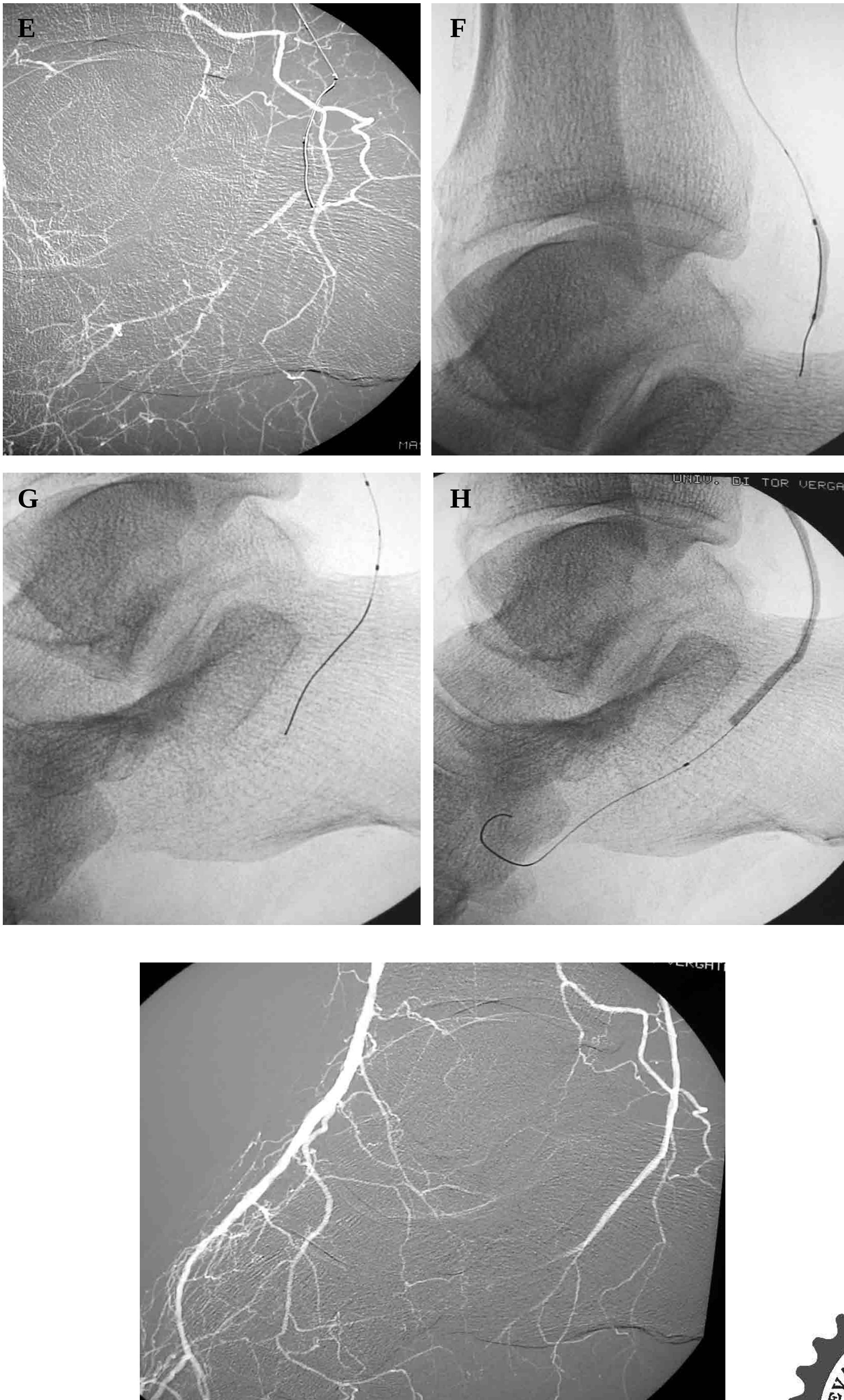
Because of difficulties to re-entry into the true lumen a retrograde puncture of posterior tibial artery was performed (G - H - I - L) and with Amplatz “Goose-neck” snare kit the guide wire was captured and pilled out (M e N). Through this guide wire the balloon catheter was advanced and PTA was performed.

The occlusion of SFA and popliteal arteries were dilated with 5-6 mm (O and P), posterior tibial artery with 2.5 mm diameter 12 cm long low profile balloon catheter (Invatec) [Q and R].

The final angiography demonstrates the successfully performed recanalization (S - T - U).

CASE 5

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Case 5

The preliminary angiography shows the occlusion of pedal artery with reduced visualization of plantar arch (A).

Recanalization with 0.014 inch guide wire followed with angioplasty by 1.5 mm coronary balloon catheter was done (B and C).

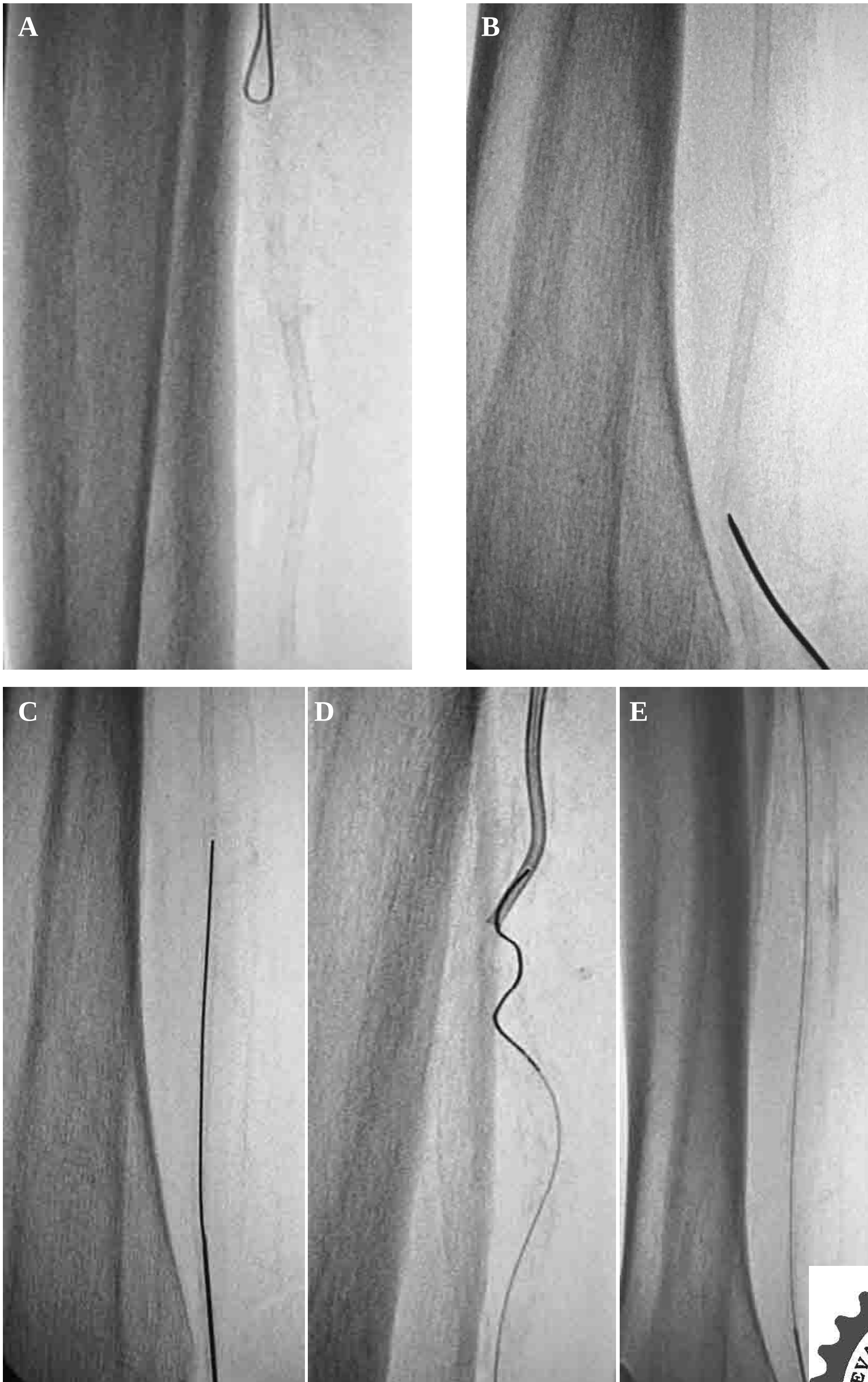
The control angiography shows good expanded pedal artery (D).

Then the recanalization of posterior tibial artery and plantar arch was performed and was dilated with 2 mm diameter balloon catheter (E-F-G-H).

The final angiography demonstrates the successfully revascularization of foot arteries (I).

Figure 21. (A) The ischemic forefoot of the patient before the procedure.
(B) Three months after angioplasty, the forefoot is completely healed.

CASE 6




F
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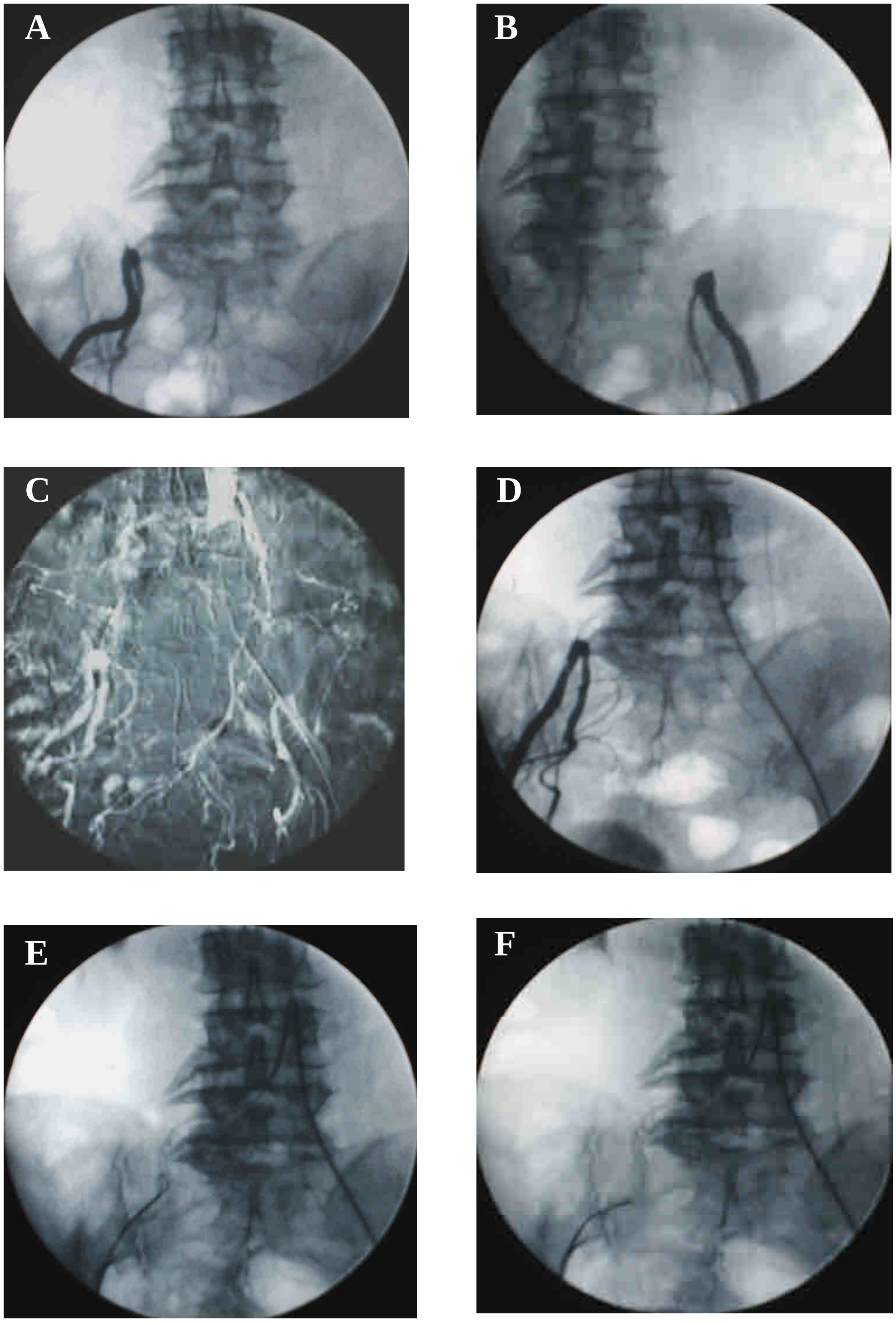
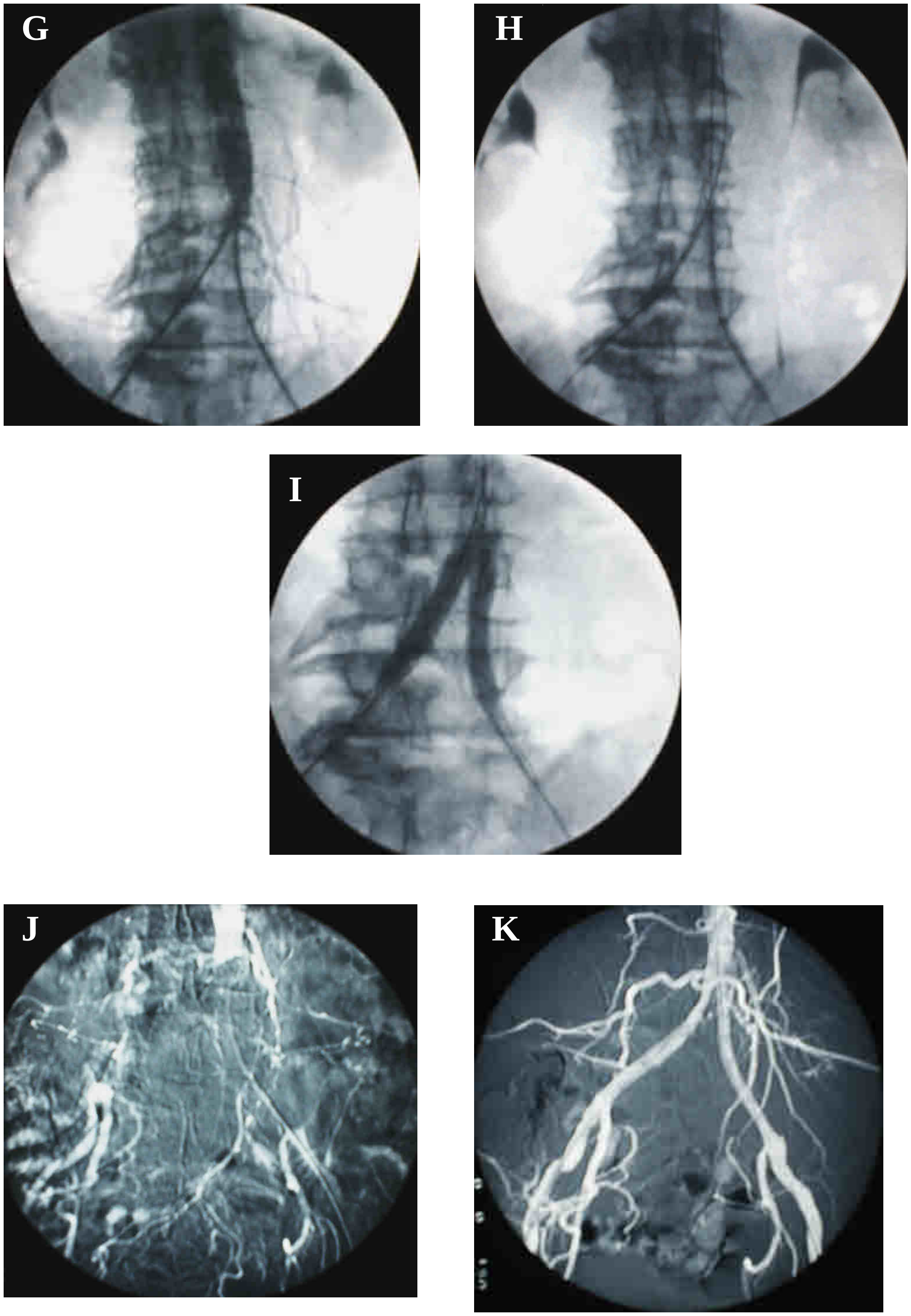
Case 6

Through the puncture of posterior tibial artery at the distal third segment (B) the recanalization of the same artery was performed by using "Michelangelo maneuver" or "Rendezvous" technique (C – D – E), with 0.014 inch Extra support guide wire and 2 mm diameter, 12 cm long balloon catheter (F – G – H).

The control at the end of the procedure shows a satisfactory angiographic result without any complications (I and L).

CASE 7

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CASE 7

In patient with CLI followed bbilateral bypass (from infra renal abdominal aorta to both femoral arteries) failure baseline injection of contrast media through bilateral retrograde accesses shows complete occlusion of distal aortic and bilateral common iliac arteries. (A – B – C)

Intraluminal recanalization of left common iliac artery was successfully performed and through the catheter positioned in the aorta angiography was performed. (C)

Through the left contralateral cross over approach the guide wire was advanced in subintimal space of right common iliac artery. (D)

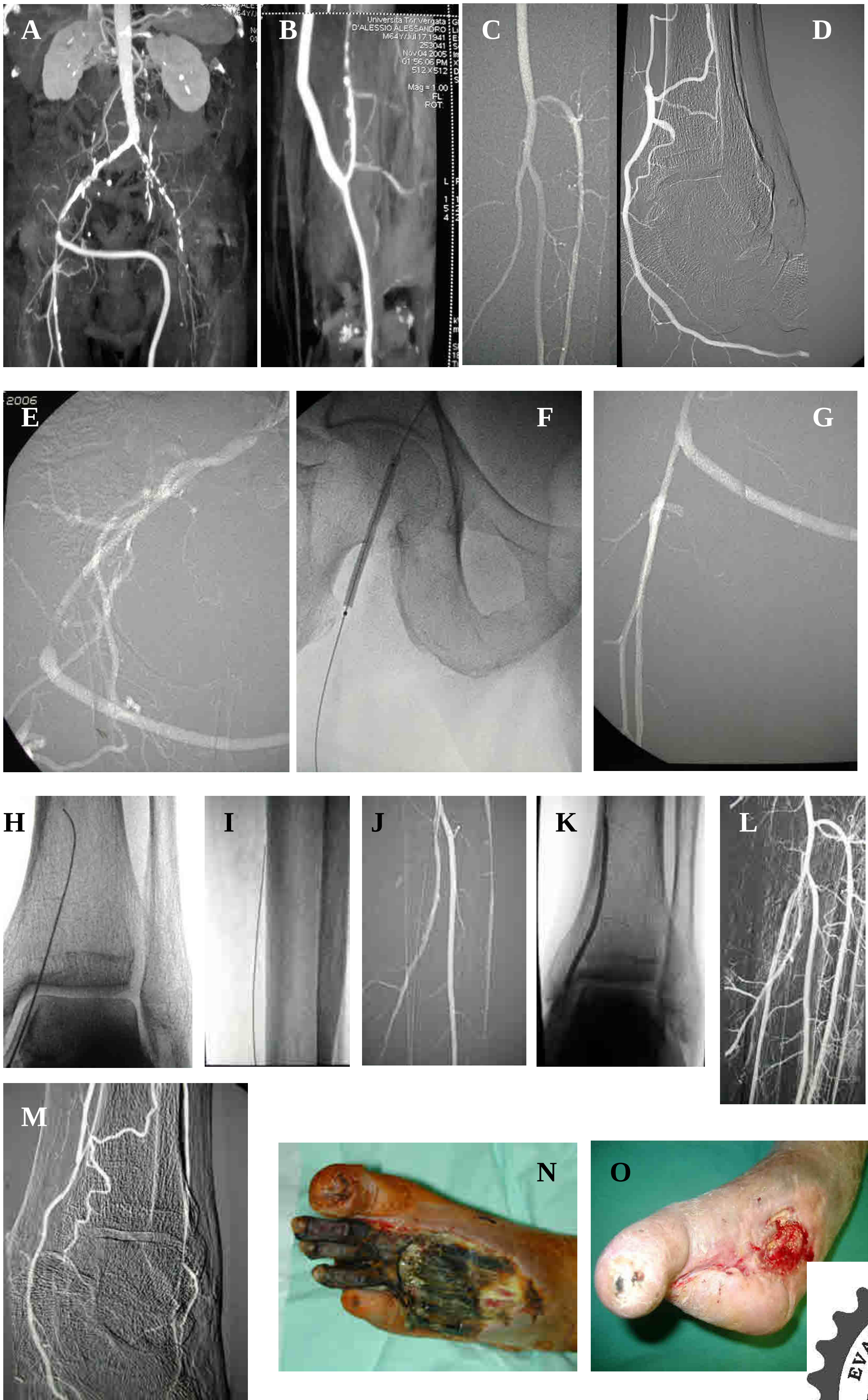
Due to difficulties to re-enter into the true lumen, Amplatz "Goose-neck" snare kit was advanced retrogradely from the right side and the guide wire was captured and pilled out. (E-F)

Then through this guide wire another catheter was advanced until aorta and right common iliac artery was recanalized. (G)

After that, two balloon expandable stents were positioned using "Kissing stent" technique. (H-I)

The final angiography demonstrates the successfully performed recanalization of occluded native arteries after bypass failure. (K)

CASE 8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Case 8

Preliminary angio-MRA of patient with left side CLI, previously treated by femoral-femoral cross over bypass, demonstrates tight preocclusive stenosis of right common femoral artery at the level of proximal anastomosis of bypass. (A) The distal anastomosis was open patent. (B) Baseline angiography performed through transbrachial access shows occlusion of posterior tibial artery with reabitation at the distal third. (C-D) Through the transbrachial approach was successfully performed dilatation of common femoral artery. (E-F-G) Then, was performed right side retrograde puncture of common femoral artery to have controlateral cross over access to the left side through patent bypass graft. Because, from transbrachial access it was too distant to achieve infrapopliteal region. But after several unsuccessfull attemps to recanalize posterior tibial artery from origin the distal tibial access was performed. (H) From this approach, using "Randezvous" technique, the posterior tibial artery was recanalized and successive dilation was performed by balloon catheter. (J-K) The control at the end of the procedure shows a satisfactory angiographic result without any complications (L-M). The clinical condition of the lesion after 6 months follow up is demonstrated at the figure [O].

6. Discussion

Lower extremity bypass surgery has been considered as a gold standard and a primary indication for treatment of chronic CLI[7]. But, it should be noted that the traditional open surgery bypass is not without significant morbidity and mortality. Hynes N. *et al*. demonstrated that surgery has been shown to be associated with increased mortality (30-day survival of 96% *versus* 100% for angioplasty) and morbidity[8].

Vein harvest site and graft infections, when they occur, can be devastating. Bart E. *et al*. showed that in 276 patients who underwent lower extremity revascularization via open surgical bypass the operative morbidity rate was 21%, largely due to wound complications and infections; with only 45% of patients reported being back to normal within 6 months[9].

Also, many patients with peripheral vascular disease usually have several other co-morbidities, such as heart disease, diabetes and renal failure, which would put them at higher surgical and anaesthetic risk. Gray BH *et al*. and Keagy BA *et al*. are reported that in poor surgical revascularization candidates morbidity and mortality associated with major amputation remain high[30, 31]. In addition, some patients may not have an adequate amount of vein to harvest to allow for autologous bypass grafting or not good proximal and distal pathway for the implantation of the new bypass.

Therefore, these patients became poor candidates for surgical vascular reconstruction and the amputation is often the only option of management.

At the same time, it is heavy the destiny of the patients who underwent the amputation; the 63 % of patients with below-knee amputation have the healing from first intention, in 22 % is necessary above-knee amputation, 15% of patients had healing from second intention. After two years only 1/3 of patients achieve discreet autonomy, 1/3 dies and 1/3 have autonomy on wheelchair [32, 33]. This "outcome" is much graver in diabetic patients, due to neuropathy, infection of diabetic foot, with the necessity of repeated hospitalizations for the treatment of the gangrene.

Therefore, investigation of revascularization strategies for Chronic Lower Limb Ischemia is essential[13] and alternative treatment should be considered whenever arterial bypass is not possible or is hazardous[7].

In recent years, because of improved competency and experience of vascular specialists, as well as the advances made in catheter and guidewire technology, catheter-based treatment of lower extremity arterial occlusive disease has shown significantly improved limb-salvage outcomes[7]. Some authors recommend that infrainguinal PTA be offered as the first line of treatment in most patients with CLI[34, 35]. Contemporary reports on PTA suggest that high technical and clinical success rates are possible[36-38].

In our study limb-salvage angioplasty has been introduced as an alternative-last chance method with the primary goal of achieving limb salvage in these selected poor surgical candidates with end-stage arterial occlusive disease following bypass failure. We hypothesized that PTA of the native artery in these patients may lead to a significantly improved limb-salvage rate with low morbidity and mortality compared with primary amputation.

Our technical and clinical success rate was 93.3%. The two technical failures were due to an inability to cross the lesions with guide wire. A deeper investigation of first technical failure (femoral-popliteal bypass occlusion patient) based on an analysis of the surgical report recalled from other nosocomial archives showed that failure of recanalization was due to surgical disconnection by termino-terminal anastomosis of the bypass graft. This is not a conventional technique used in vascular surgery practice but anyway this evidence can be found. So, the patient underwent another elective bypass grafting. This fact confirms that failed PTA does not negatively affect future surgical bypass[37, 39]. The second failure was due to very high calcified plantar arch, which caused inability to cross the lesion, and the patient received no further treatment and eventually underwent amputation.

Our short-term limb salvage rate (92.8%) was high and same with works of Kudo T. et al.[40] but wasn't same with reports of other investigators: 88 % at 12 months[41] and 80 at 18 months[38].

The reason for better primary clinical improvement and limb salvage rates might be explained as follows:

- The use of different endovascular techniques chosen on every single case and the use of peripheral approaches (transtibial, transpopliteal).
- Extra perfusion is necessary to heal the tissue loss, but once it heals, the skin viability can be maintained even though the treated artery re-occluded [42].
- Slow re-stenosis of the treated artery allows time to form new collateral circulation.

Some shortcomings of our study, such as those lost to follow-up, might have partially contributed to the high limb salvage rate. Thus, we re-evaluated the limb salvage rate by excluding these lost to follow-up and one bypass case but still found a similar limb salvage rate (86.7 %) at 48 ± 12 weeks.

The mean follow-up (48 ± 12 weeks) was short, because 40 % of limbs (12/30) were treated in the last 6 months during the study period.

The noninvasive methods, such as ABI, TcPO2 /TcPCO2 had the fundamental role in the indication of distal hemodynamic condition of the limb, demonstrating the dynamic improvement of postpro hemodynamic.

Patients with CLI typically present with systemic arteriosclerosis and other comorbid conditions that lead to expected mortality of 14%, 21%, and 32% at 6, 12, and 24 months, respectively[5].

Peripheral revascularization cannot be expected to prolong life, but can relieve pain, heal ulcers, and prevent major amputation, with the primary goal being the preservation of ambulatory status and quality of life. Long-term patency is not as relevant in this patient group because less blood flow is generally required to maintain tissue integrity than to achieve wound healing. Therefore, temporary (1–6 months) restoration of ‘‘straight-line’’ flow to the foot may be sufficient to relieve CLI, while collateral flow may be all that is necessary to preserve tissue integrity. Because of this, the long-time patency in the treated segments wasn't the primary objective of our study.

In 4 acute occlusions of bypass graft, after several attempts of pharmacological fibrinolysis and thrombectomy with Fogarty catheter, maximum graft patency period was less than 3 weeks. This fact shows that in those patients the bypass graft is not functioning as planed, as we are guess maybe due to the irregularity of internal membrane of PTFA graft which provokes activation of the coagulation inside the graft.

In TOPAS I and II study had been defined that patients with occlusions (<14 days) amputation-free survival rates is in the urok group were 71.8% at 6 months and 65% at 1 year as compared with respective rates of 74.8% and 69.9% in the surgery group[45, 46].

The STYLE trial randomized 393 patients with non embolic native artery or bypass graft occlusion in the lower limb within the past 6 months lysis was unsuccessful in 28% of the patients assigned to trombolysis[47, 48].

All those studies demonstrate that bypass surgery and fibrinolysis therapy is not completely sufficient in treatment of CLI, and its still needs an alternative method for those patients.

The clinical advantages of PTA are well established for the high risk, elderly, and vascularly compromised patient: there is no need for general or spinal anesthesia, there are no or fewer surgical wounds, the hospital stay is shorter, and complication and mortality rates are low[36, 43]. The angiographic evaluation in the operating room on the same day of endovascular procedures reduces both patient stress and the amount of contrast administered: these are particularly relevant in patients with cardiovascular disease or nephropathy[44].

As a multicentre, randomized controlled trial, BASIL[49] compares the outcome of a bypass-surgery-first strategy with a balloon-angioplasty-first strategy in patients presenting with severe limb ischemia. In the short term, a surgery-first strategy was associated with a significantly higher rate of morbidity, significantly greater length of hospital stay, and greater u high-dependency unit and intensive-therapy unit than that c angioplasty-first strategy. Therefore, hospital costs of surgery for the first 12 months after randomization were about a third higher than those of angioplasty. They recorded a high occurrence of cardiovascular, infective, and wound complications after surgery, and a small reintervention rate of graft revision, thrombectomy, and evacuation of haematoma.

On the other hand, patients who have had their saphenous veins harvested for coronary artery bypass may be better candidates for percutaneous transluminal angioplasty than for synthetic bypass grafting, depending on the lesion and location [22].

The outcomes of our study seems like this new kind of approach in patients with occluded bypass graft and critical ischemia have more effective technical success, low cost and good short term outcome. It is necessary to perform a tight, long term follow-up because we expect that the results will be comparable with long term follow up of angioplasty/stent of limb artery occlusions without bypass. In this situation the primary native artery recanalization should become the first and most effective method of choice in treatment of CLI.

In conclusion, our results demonstrate that in patients with failed by-pass, the endovascular treatment performing native artery recanalization is a good alternative to primary amputation and is effective in short term results. The results of this study with small number of patients relatively short-term follow-up may not apply to all low-surgica patients with CLI. Therefore, our study suggests a need for a multicentre clinical trial with more numerous patients and regular follow-up to get a significant data's to be compared with other studies.

Future aspects of treatment of Critical Limb Ischemia

The most striking feature of CLI is the dismal prognosis for both life and limb outcomes no matter what treatment are employed. This is because most patients have generalized atherosclerosis. One may, therefore, consider what magnitude of treatment options is realistic for the single patient. A successful revascularization may reduce pain and improve quality of life for a limited period of time, but frequently this goal is not achieved. Amputation may be a good alternative to reduce pain, though amputees may have an even more reduced life expectancy. Medical treatment that favorably modifies cardiovascular risk is recommended for all patients, while symptomatic treatment of the limb has to be individualized.

Preliminary trials of intramuscular gene transfer utilizing naked plasmid DNA encoding phVEGF165 have given promising results on symptoms of CLI[50] while others have been negative. Several trials are using viral vectors to increase gene transfer efficiency. Besides vascular endothelial growth factor (VEGF), fibroblast growth factor, angiop
and other growth factors are under investigation [51]. Preliminary tri

intramuscular injection of autologous bone-marrow mononuclear cells to stimulate vascular growth [52] have been promising. Most trials are in Phase I or II and the appropriate use of gene therapy in vascular practice remains to be proven.

In conclusion, there is low-level evidence for spinal cord stimulation to improve outcome of patients with CLI, should revascularization not be possible. Prostanoid treatment may also be of value; however, only a limited proportion of patients will respond to this treatment, as mentioned. Results of other pharmacotherapies are far from good [53, 54]. Gene therapy has shown promising early efficacy but further trials are warranted.

7. Conclusion

From the results of our study we can draw out following conclusions:

- Native artery limb-salvage angioplasty can be successfully achieved in amputation candidate, high surgical risk patients with critical limb ischemia followed bypass failure.
- The outcomes of our study shows that the endovascular recanalization (PTA) technique in these high risk group patients is optimal alternative method of treatment with optimal technical success, with low morbidity and mortality, feasible even in multiple, long and high calcify steno-occlusions of limb arteries, which allows immediate clinical results and good limb salvage rate in short term follow-up.
- The advantage of achieving high rate of limb salvage in our study was due to good preliminary diagnosis with advanced diagnostic techniques, good operator skill, aggressive endovascular revascularization technique with complex approaches and materials adapted for every single case.
- Age, diabetes and other co-morbidities did not independently affect clinical outcomes.
- Failure of angioplasty did not preclude the possibility of performing subsequent bypass grafting.

- Vascular surgeons should consider limb-salvage angioplasty before performing primary major amputation in patients who are unfit for bypass surgery and destined for major amputation.

For all this reasons we are considering PTA as a first choice of method in the treatment of amputation candidate, high surgical risk patients with critical limb ischemia followed bypass failure.

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