Endovascular treatments of peripheral artery disease: revascularization techniques for patients presenting with: claudication, critical and acute limb ischae-rias

BONVINI, Robert

Abstract
The present document will discuss in the first part the etiology, the pathophysiology, the incidence and the natural history of PAD, while in the second part the diagnostic modalities aimed for the detection and the quantification of the PAD will be reviewed. Finally in the third part of the manuscript, the most frequent three clinical scenarios (intermittent claudication, CLI, ALI) will be described, with a special attention to the endovascular approach by treating these pathologies.

Reference

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ENDOVASCULAR TREATMENTS OF PERIPHERAL ARTERY DISEASE

Revascularization Techniques for Patients presenting with:

Claudication, Critical and Acute Limb Ischemias

Thesis submitted to the Medical School of
the University of Geneva
for the degree of Privat-Docent
by

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To my family:

My beloved wife Paola, my son Richard Mark and my daughter Helen Rose
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ABBREVIATIONS

ABI = ankle-brachial index
ACC = American College of Cardiology
ACE = angiotensin-converting enzyme
ACC = American College of Cardiology
ACT = activated clotting time
AHA = American Heart Association
CI = confidence interval
CFA = common femoral artery
CIA = common iliac artery
CLI = critical limb ischemia
CTA = computed tomographic angiography
DNA = deoxyribonucleic acid
DSA = digital subtraction angiography
EIA = external iliac artery
ePTFE = expanded polytetrafluoroethylene
FDA = Food and Drug Administration
FMD = fibromuscular dysplasia
HDL = high-density lipoprotein
IC = Intermittent Claudication
IIA = internal iliac artery
LAO = left anterior oblique
LDM = low-density lipoprotein
MI = myocardial infarction
MRA = magnetic resonance angiography
OR = odds ratio
p = statistical significance
PA = posterior-anterior
PAD = peripheral arterial disease
PGE-1 = prostaglandin E1
PTA = percutaneous transluminal angioplasty
PVR = pulse volume recording
RAO = right anterior oblique
SFA = superficial femoral artery
TASC = TransAtlantic Inter-Society Consensus Working Group
TBI = toe-brachial index
3D = 3-dimensional
UK = Urokinase
US = United States
VA = Veterans Affairs
VEGF = vascular endothelial growth factor
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1.0 INTRODUCTION

Peripheral artery disease (PAD) is associated with a prevalence of 4 to 12 % in the adult population, and it may present up to 20% in the elderly (i.e.>70 years old) (1-3). Peripheral arterial disease is a marker of systemic atherosclerosis and it is associated with an increased cardiovascular morbidity and mortality. Symptomatic PAD may be observed as frequently as cardiac angina, with an estimated annual incidence of 26/10,000 in the male and 12/10,000 in the female population (4).

It is estimated that in the United States at least 10 million people suffer from a PAD of different degree, ranging from the typical intermittent claudication to the most severe critical limb ischemia (CLI). Accordingly, it is also estimated that at least three times more individuals do not present any sign or symptoms of their underlying PAD, thus being considered asymptomatic (5). On the opposite site the most severe PAD form, namely the CLI is reported with an incidence of approximatively 500-1000 new CLI cases every year every million habitants (2).

Finally, as suggested by Figure 1, the incidence of PAD is increasing by age.

![Figure 1: mean prevalence of intermittent claudication in population-based studies](image)

[reproduced from the TASC II Guidelines (2)]

The majority of patients with PAD have atherosclerotic disease of the lower extremity. The infrarenal abdominal aorta, the iliac arteries, the femoral arteries and the below the knee (BTK) arteries are among the most common sites of chronic obliterative atherosclerosis, accounting for up to 90% of all symptomatic PAD cases (2, 3). Atherosclerotic PAD of the upper extremity is much less common, thus it will not be further discussed in the present manuscript (6).
Patients with compromised blood flow to the extremities as a consequence of PAD may present with pain of one or more muscle groups, atypical pain or no symptoms. Intermittent claudication (IC) is the first described symptom and is defined as a reproducible discomfort of a defined group of muscles that is induced by exercise and relieved with rest. This disorder results from an imbalance between supply and demand of blood flow that fails to satisfy ongoing metabolic requirements.

Limb-threatening ischemia or newly defined critical limb ischemia (CLI) occurs when arterial blood flow is insufficient to meet the metabolic demands of resting muscle or tissue, resulting in ischemic rest pain or ischemic trophic lesion, which most of the time, if not rapidly and correctly managed leads to a minor (i.e. toes) or major (limb) amputation. The natural history of CLI usually involves inexorable progression to amputation unless there is an intervention that results in the improvement of arterial perfusion. This is in contrast to the often benign natural history of mild and moderate claudication.

Acute limb ischemia (ALI) is defined as a sudden decrease in limb perfusion that causes a potential threat to limb viability and is manifested by ischemic rest pain, ischemic ulcers, and/or gangrene in patients who present within two weeks of the acute event (2, 3). Patients with similar manifestations who present later than two weeks are considered to have critical limb ischemia, which is by definition chronic.

The first medical approach in patients presenting with PAD, consists in the screening of other associated cardiovascular pathologies, with special attention to the coronary artery and the cerebrovascular circulation. Secondarily an optimal medical management of the cardiovascular risk factors is essential with also an attempt for healthy life-style modifications. Third and this especially for claudicant patients, walking exercises are necessary in order to improve walking capacity, thus quality of life. Finally, in case of severe life-limiting claudication or sign of critical limb ischemia a revascularization procedure should be attempted.

In the past, most of the peripheral vascular obstructions were treated surgically, mainly with different types of bypasses (e.g. aorto-iliac, aorto-femoral, femoro-femoral, femoro-popliteal and femoro-tibial) while the percutaneous approach was used only for the minority of the cases (i.e. focal simple stenosis). Thanks to the technical developments of the endovascular materials as well as the skill of the operators, the percutaneous approach has become the treatment of choice for the majority
of patients presenting with atherosclerotic PAD. The aim of these procedures is to improve claudication symptoms, ischemic rest pain or to allow an ischemic ulcer to heal, finally avoiding major amputation.

The present document will discuss in the first part the etiology, the pathophysiology, the incidence and the natural history of PAD, while in the second part the diagnostic modalities aimed for the detection and the quantification of the PAD will be reviewed. Finally in the third part of the manuscript, the most frequent three clinical scenarios (intermittent claudication, CLI, ALI) will be described, with a special attention to the endovascular approach by treating these pathologies.
1.1 DEFINITIONS

Peripheral arterial disease is a very broad disease including different noncoronary arterial syndromes secondary to an altered structure and function of the arteries supplying the brain, visceral organs, and the limbs. Numerous pathophysiological processes may contribute to the development of arterial narrowing (i.e. stenosis) even if atherosclerosis remains the most common disease leading to PAD.

The term “peripheral arterial disease” includes different disorders that lead to progressive stenosis or occlusion, or aneurysmal dilation, of the vessels. The affected arterial territoires may range from the aorta and its ramification, which includes the carotid, upper extremity, visceral, and lower extremity arterial branches.

Although, historically the term “peripheral vascular disease (PVD)” has been used to describe all noncardiac pathologies affecting the arterial, venous, and lymphatic circulations, due to its increased prevalence, to these days PAD or PVD are generally used by describing syndromes and symptoms affecting the arterial circulation.

Arterial diseases include those disorders that cause either fixed or dynamic obstruction secondary to atherosclerotic narrowing or abnormal vascular reactivity, impairing blood supply to a given tissue, finally resulting in tissue ischemia or necrosis. For the purposes of this review, the term “peripheral arterial disease” will be used to broadly describe the vascular diseases caused primarily by atherosclerosis or thromboembolic processes altering the normal structure and function of the aorta and the arteries of the lower extremities.

The definition of PAD includes the presence of symptoms related to a lower limb hypo-perfusion (e.g. claudication), associated with the non-invasive objectivation of an impaired lower limb perfusion (e.g. ankle-brachial index <0.9). In case of severe and advanced PAD, the definition of critical limb ischemia may be adopted if the patient presents with an ischemic rest pain or an ischemic trophic lesion at the foot’s level and the non-invasive evaluation confirms a severely decreased ABI (i.e. <0.4 or ankle blood pressure <50-60 mmHg) or a toe pressure <30 mmHg, or a transcutaneous oxygen measurement (TcpO2) <30 mmHg (1, 2).

Two different classifications exist in order to define symptoms related to a PAD. The Leriche-Fontaine and the Rutherford-Baker classifications (7, 8). Because the Fontaine classification is mostly used in Europe and the Rutherford classification in the United States, and also because the Fontaine
classification is more intuitive adopting only patients’ symptoms in order to classify the degree of the
disease (the Rutherford classification associates symptoms and lower limb pressures), in the present
manuscript only the Fontaine classification will be used by describing patients’ symptoms:

- Fontaine stage I = asymptomatic
- stage IIa = claudication with a walking perimeter >200 meters
- stage IIb = claudication with a walking perimeter <200 meters
- stage III = ischemic rest pain
- stage IV = ischemic trophic lesions (e.g. ulcers, necrosis or gangrene).
1.2 EPIDEMIOLOGY

1.2.1 Prevalence

The prevalence of PAD increases progressively with age, beginning after age 40 (9-12). As a result, PAD is growing as a clinical problem due to the increasingly aged population in developed countries.

The prevalence of lower extremity PAD has been defined by a series of epidemiological investigations that have used either claudication as a symptomatic marker of lower extremity PAD or an abnormal ankle-to-brachial systolic blood pressure to define the population affected. In general, the prevalence of lower extremity PAD is dependent on the age of the studied cohort, the underlying atherosclerosis risk factor profile, and the presence of other concomitant manifestations of atherosclerosis (e.g., clinical coronary or cerebrovascular disease or past organ transplantation) (13, 14).

The prevalence of PAD, defined as an ankle-brachial index (ABI) <0.90 in either leg, was 0.9% between the ages of 40 and 49, 2.5% between the ages of 50 and 59, 4.7% between the ages of 60 and 69, and 14.5% age 70 and older (12, 15). Accordingly, the age-specific annual incidence of intermittent claudication for ages 30 to 44 years was 6/10'000 men and 3/10'000 women, and this incidence increased to 61/10'000 men and 54/10'000 women within the ages of 65 to 74 years (4).

Peripheral artery disease can be present in subclinical forms that can be detected by use of sensitive vascular imaging techniques. Such techniques may reveal early manifestations of arterial disease before it is detected by either limb pressure measurements or clinical symptoms. When so defined, as, for example, by measurement of the intimal-medial thickness in the carotid or femoral artery, early forms of PAD are easily detected in populations at risk (16).

In 2007 a consensus document on the management of PAD made the following estimates for the prevalence of PAD in western countries (e.g., Europe or North America) (2):

- 27 million affected individuals,
- 413,000 hospital discharges of patients with chronic PAD per year with 88,000 hospitalizations involving lower extremity arteriography and 28,000 discharges for embolectomy or thrombectomy of lower limb arteries.
1.3 PATHOPHYSIOLOGY AND ETIOLOGIES

1.3.1 Pathophysiology

Peripheral arterial disease is often the consequence of a systemic disease that affects multiple arterial circulations. These systemic pathophysiological processes are diverse and include:

- atherosclerosis,
- degenerative diseases,
- dysplastic disorders,
- vascular inflammation (arteritis),
- in situ thrombosis and thromboembolism,
- peripheral vascular malformations.

Clinicians providing care for patients presenting with PAD should know and recognize these different pathophysiological patterns, because this recognition is required to create an inclusive differential diagnosis and a comprehensive long-term treatment plan. The most common cause of PAD worldwide is atherosclerosis, and thus its epidemiology and clinical consequences are closely associated with classic atherosclerosis risk factors (e.g., smoking, diabetes, hypertension, hyperlipidemia, family history) (17, 18).

Peripheral arterial disease may be secondary to degenerative or inflammatory disorders, which may lead to a loss of the normal vessel’s structure resulting in either a dilation of the arterial wall (i.e., aneurysm), or an intimal dissection, finally resulting in arterial rupture or occlusion. In this category one may find:

- Collagen abnormalities:
  - Marfan syndrome (19),
  - Ehlers-Danlos syndrome (20),
- Other vessel architecture defect:
  - Erdheim’s cystic medial necrosis,
  - Neurofibromatosis,
- Large vessels arteritis:
  - Takayasu’s disease (21),
  - Giant cell or temporal arteritis,
  - Behçet’s syndrome, relapsing polychondritis,
- Vasculitis associated with arthropathies (22),
  - Medium-sized vessels arteritis (23):
    o Polyarteritis nodosa,
    o Wegener’s or lymphoid granulomatosis,
    o Churg-Strauss syndrome,
    o Kawasaki disease
    o Thromboangiitis obliterans (Buerger’s disease)
  - Small-vessel arteritis:
    o Rheumatoid arthritis,
    o Systemic lupus erythematosus,
    o Other connective tissue or autoimmune diseases,
    o Thromboangiitis obliterans (Buerger’s disease),
    o Polyarteritis nodosa.

The group of the peripheral vascular malformations may be further differentiated in three different categories (24):
  - Vascular malformations of the newborn (i.e., the hemangiomas):
    o The tuberosis form,
    o The subcutaneous form,
    o The mixte form (i.e., tuberosis and subcutaneous).
  - Superficial vascular malformations, which may be:
    o Hemodynamically inactive:
      ▪ The plan angiomas,
      ▪ The venous malformation,
      ▪ The lymphatique malformation.
    o Hemodynamically active (i.e., arteriovenous malformation):
  - Complex vascular malformations:
    o Systematic or disseminated
Finally, radiation-associated arteritis can affect vessels of any size, while the most common dysplastic disease remains the fibromuscular dysplasia (FMD), which may affect many noncoronary arterial beds, especially the renal, carotid and iliac arteries (25, 26).

In case of pathological arterial vaso-constriction the term “vasospastic diseases” is usually adopted. This constriction which involves preferentially muscular vessel of the body may cause migraine headache, cerebral vasospasm associated with intracranial bleeding, Prinzmetal’s angina, Raynaud’s phenomenon, and ergot toxicity (27). In the extremities (e.g., fingers, nose, toes), vasospasm is tipically described as a Raynaud phenomenon, which may occur as a primary event or secondary to an underlying disease such as scleroderma or systemic lupus erythematosus (6).

Whereas PAD includes a large series of disorders affecting all arterial beds, this review will limit its attention to the diseases affecting the lower limbs, excluding for didacting reasons all the diseases involving arterial aneurysm, all diseases involving the cerebral and the extra-cranial circulation, the thoracic and the upper extremity arteries, as well as the renal and the mesenteric arteries.

1.3.2 Etiologies

Although many diseases can cause intermittent claudication, the vast majority of patients with claudication suffer from PAD. The clinical history can help distinguish among some of the less common causes of this disorder. As examples, a history of limb trauma, radiation exposure, vasculitis, or ergot use for migraines represents some important clues to the etiology of claudication.

Popliteal entrapment syndrome can also present with intermittent claudication, and should be suspected in the young patient who presents with claudication but lacks atherosclerotic risk factors. Popliteal entrapment syndrome is due to anomalous musculoskeletal attachments, which cause compression of the popliteal artery with activity, potentially leading to an acute vessel occlusion.

In endurance athletes, especially cyclists, an even more unusual cause of claudication is due to repeated kinking of the external iliac artery, which can result in endofibrosis of the vessel (28).

Nonarterial pathologic conditions should also be considered in the differential diagnosis of limb discomfort mimiking intermittent claudications. These include:

- Deep venous thrombosis,
- Musculoskeletal disorders,
• Peripheral neuropathy,
• Spinal stenosis (pseudoclaudication).

1.3.3. Diagnosis and Differential Diagnosis

As noted above, there is a high prevalence of lower extremity PAD in patients over age 70 and in patients between the ages of 50 and 69 with atherosclerotic risk factors, particularly smoking and/or diabetes (2, 3).

Based upon these observations, the 2005 ACC/AHA guidelines on PAD and the 2007 TASC II consensus document on the management of PAD recommended that the standard review of symptoms should include questions related to a history of walking impairment, symptoms of claudication, ischemic rest pain, or nonhealing wounds in patients ≥70 years of age, those ≥50 years of age with a history of smoking and/or diabetes, or those with a Framingham risk score of 10 to 20 percent at 10 years (2, 3). Measurement of the resting ankle-brachial systolic pressure index (ABI) should be performed in patients with one or more of the above findings on the review of symptoms (2).

The etiology of leg pain can be divided into categories that include vascular, neurogenic, and musculoskeletal causes. Vascular pain includes classic claudication, "atypical" claudication, and rest pain. Neurological pain is predominantly due to neurospinal (e.g., disc disease, spinal stenosis, tumor) or neuropathic causes (e.g., diabetes, alcohol abuse). Musculoskeletal pain derives from the bones, joints, ligaments, tendons, and fascial elements of the lower extremity.

Classic claudication is characterized by cramping pain that is consistently reproduced with exercise and relieved with rest. However, many patients have atypical symptoms that may be confused with a number of other disorders (2, 15, 29).
1.4 RISK FACTORS

The major cause of lower extremity PAD is atherosclerosis. Risk factors for atherosclerosis such as cigarette smoking, diabetes, dyslipidemia, and hypertension increase the likelihood of developing lower extremity PAD, as they do for other manifestations of atherosclerosis (12, 14, 15, 30-33).

Data from the Framingham Heart Study revealed that the odds ratio for developing intermittent claudication was 1.2 for each 1 mmol/L elevation in the serum cholesterol concentration, 1.4 for each 10 cigarettes smoked per day, 1.5 for mild and 2.2 for moderate hypertension, and 2.6 for diabetes mellitus (14).

**Cigarette smoking** is an exceptionally powerful etiologic risk factor for lower extremity PAD (13). It is 2 to 3 times more likely to cause lower extremity PAD than coronary artery disease (36). Large epidemiological studies have found that smoking increases the risk of lower extremity PAD by 2- to 6-fold and the risk of intermittent claudication by 3- to 10-fold (18, 34, 35). More than 80% of patients with lower extremity PAD are current or former smokers (34, 35).

**Diabetes mellitus** increases the risk of lower extremity PAD by 2- to 4-fold (13, 35-37) and is present in 12% to 20% of persons with lower extremity PAD (35, 37). In the Framingham Heart Study, diabetes increased the risk of intermittent claudication by 3.5- and 8.6-fold in men and women, respectively (38). The risk of developing CLI is also greater in diabetics than non-diabetics (39). Diabetic patients with lower extremity PAD are 7- to 15-fold more likely to undergo a major amputation than non-diabetics with lower extremity PAD (40, 41).

**Lipid abnormalities** that are associated with lower extremity PAD include elevated total and low-density lipoprotein (LDL) cholesterol, decreased high-density lipoprotein (HDL) cholesterol, and hypertriglyceridemia (11, 18, 37). In epidemiological studies, total cholesterol levels are generally higher in patients with intermittent claudication than in those without lower extremity PAD (11, 34). Similarly, levels of LDL are higher and HDL levels are lower in patients with lower extremity PAD than in age-matched controls (14, 42). Elevated levels of triglycerides have been reported to be associated with lower extremity PAD in some studies but not in others (43, 44).

**Hypertension** is associated with lower extremity PAD, although the association is generally weaker than that with cerebrovascular and coronary artery disease (13, 14). In the Framingham Heart Study, hypertension increased the risk of intermittent claudication 2.5- to 4-fold in men and women, respectively, and the risk was proportional to the severity of high blood pressure (38).
In summary, and according to the usual cardiovascular risk factors, the risk of PAD was significantly increased in current smokers (odds ratio [OR] 4.46), in patients presenting with diabetes (OR 2.71), hypercholesterolemia (OR 1.68) or hypertension (OR 1.75).

Not only are these atherosclerotic risk factors associated with an increased prevalence of PAD, they are also associated with earlier PAD onset. Patients who are 50 to 69 years with a history of cigarette smoking (more than 10 pack-years) or diabetes may have an incidence of asymptomatic PAD similar to patients ≥70 years of age without these risk factors (15).

Based in part upon the above observations, the 2005 ACC/AHA guidelines on PAD, identified the following groups at risk for lower extremity PAD (3):

- Age ≥ 70 years.
- Age 50 to 69 years with a history of smoking or diabetes.
- Age 40 to 49 with diabetes and at least one other risk factor for atherosclerosis.
- Leg symptoms suggestive of claudication with exertion or ischemic pain at rest.
- Abnormal lower extremity pulse examination.
- Known atherosclerosis at other sites (eg, coronary, carotid, or renal artery disease).
1.5 NATURAL HISTORY AND CLINICAL PRESENTATION

Claudication — The 2005 ACC/AHA guidelines on PAD estimated the following rates of limb and cardiovascular outcomes at five years in patients presenting with intermittent claudication (3):

- **For limb morbidity** — Stable claudication in 70 to 80%, worsening claudication in 10 to 20%, and critical limb ischemia in 1 to 2%
- **For cardiovascular morbidity and mortality** — Nonfatal myocardial infarction or stroke in 20%, and death in 15 to 30% (three-quarters due to cardiovascular causes) (45-47).

Critical limb ischemia — Among the 1 to 2% of patients with critical limb ischemia, the guidelines estimated the following outcomes at one year (15):

- Alive with two limbs — 50%
- Amputation — 25%
- Cardiovascular mortality — 25%

These general estimates do not apply equally to all patients. The prognosis for both limb loss and survival is significantly worse in diabetic patients and those who continue to smoke (48).

1.5.1 Coprevalence of Coronary Artery Disease and Carotid Artery Disease

The prognosis of patients with lower extremity PAD is characterized by an increased risk for cardiovascular ischemic events due to concomitant coronary artery and cerebro-vascular diseases (13, 49). There is approximately a 2- to 4-fold excess of coronary artery and cerebrovascular diseases in patients presenting a concomitant lower extremity PAD (13, 49). Among those PAD-patients, approximately 30-50% have evidence of coronary artery disease based on clinical history and electrocardiogram and up to 70% based on an abnormal stress test (50, 51). Approximately 12% to 25% of patients with lower extremity PAD have hemodynamically significant carotid artery stenoses detected by duplex ultrasound (52). Conversely, approximately up to 33% of men and up to 25% of women with known coronary or cerebrovascular disease also have lower extremity PAD (13). Thus, physicians caring for patients with lower extremity PAD should be aware of the frequent coexistence of coronary and cerebrovascular disease.
1.5.1.1 Risk of Cardiovascular Events:

As a consequence of coexisting coronary and cerebrovascular disease, there is an increased risk of myocardial infarction (MI), stroke, and cardiovascular death in patients with lower extremity PAD. There is a 20% to 60% increased risk for MI and a 2- to 6-fold increased risk of death due to coronary heart disease events (34, 53). The risk of stroke is increased by approximately 40%.

The annual mortality rate derived from epidemiological studies of patients with lower extremity PAD is 4% to 6% and is highest in those with the most severe disease (47, 54). This 1-year mortality rate may increase up to 25% in patients presenting with CLI and may be as high as 45% in those who have undergone amputation (47, 55).

1.5.2 Prognosis of the Limb

The prognosis of the limb is determined by the extent of arterial disease, the acuity of limb ischemia, and the feasibility and rapidity of restoring arterial circulation to the foot. For the patient with chronic arterial occlusive disease and continued progression of symptoms to CLI (e.g., development of new wounds, rest pain, or gangrene), the prognosis is very poor unless revascularization can be timely established. For patients with acute occlusive events (i.e., sudden embolic occlusion of an extremity with little underlying arterial disease), the long-term prognosis of the limb is related to the rapidity and completeness of revascularization before the onset of irreversible ischemic tissue or nerve damage.

Few studies of the natural history of PAD have been performed to objectively quantify disease progression. Claudication symptoms usually remain stable and do not worsen or improve at rapid rates (56). Indeed, the temporal progression of symptoms across arterial beds in patients with known atherosclerotic disease has also been very rarely reported (57).

1.5.3 Clinical Presentation

The different clinical manifestations of PAD are a major cause of acute and chronic illness, leading to an impaired functional capacity and quality of life, as well as source of limb amputation or increased risk of death. Because atherosclerosis is a systemic process patients presenting with PAD frequently also present concomitant disease of the arteries to the heart and brain. This multi-level impairment of the arterial bed is the leading cause of morbidity and mortality in these patients, who frequently will experience several cardiovascular ischemic events, such as MI, or ischemic cerebral...
stroke. Since many years, PAD has become a major health problem in western countries with huge social and economic burden especially in the United States and Europe, and due to an upcoming increased prevalence of cardiovascular risk factors, mostly diabetes, also in Asia and other developing countries, PAD is increasingly recognized as a health burden worldwide.

**TransAtlantic Inter-Society Consensus (TASC) Working Group**

In 2000 the TASC working group published an international document dealing with the “Management of Peripheral Arterial Disease” (1). This TASC document, which was update in 2007 (2), was aimed to create a consensus that provides an evidence-based, detailed review of the diagnosis and treatment of intermittent claudication (IC), critical limb ischemia (CLI) and acute limb ischemia (ALI).

The purposes of these guidelines were to (1) aid in the recognition, diagnosis, and treatment of PAD of the aorta and lower extremities; (2) aid in the recognition, diagnosis, and treatment of renal and visceral arterial diseases; and (3) improve the detection and treatment of abdominal and branch artery aneurysms. This document was addressed to all vascular and endovascular specialists, including angiologists, interventional radiologists, cardiologists and vascular surgeons who deal daily by treating PAD patients with these different types of atherosclerotic manifestations.

Patients with PAD often present with symptoms of leg ischemia. However, many patients are asymptomatic, particularly those first detected by ABI screening, and, among symptomatic patients, atypical symptoms are more common than classic claudication (15, 29). Accordingly, the TASC II and the 2005 ACC/AHA guidelines on PAD suggested the following distribution of clinical presentation of PAD in patients ≥50 years of age (2, 3):

- Asymptomatic — 20 to 50%
- Atypical leg pain — 40 to 50%
- Classic claudication — 10 to 35%
- Critical limb ischemia — 1 to 2%

**1.5.3.1 Asymptomatic disease:**

The majority of individuals with lower extremity PAD do not experience recognizable limb ischemic symptoms, and by this definition, they are “asymptomatic.”
Many patients with PAD have unrecognized disease as illustrated by the following observations. Detection of asymptomatic PAD has value because it identifies patients at increased risk of atherosclerosis at other sites. As an example: as many as 50 percent of patients with PAD have at least a 50 percent stenosis in one renal artery (58). Thus, patients with asymptomatic PAD, most often detected by ABI, should be aggressively treated with risk factor reduction (e.g. aspirin, lipid lowering, blood pressure control). In addition to protecting against coronary disease and stroke, lipid lowering may also slow progression of the PAD (59).

1.5.3.2 Symptomatic disease:

Intermittent claudication is the most common symptom in patients with lower extremity PAD. Patient interviews, however, can be both an insensitive and poorly reproducible tool to define lower extremity PAD symptoms. In epidemiological surveys, population-based classification of lower extremity PAD symptom status is performed by use of standardized questionnaires (60, 61). Data from such surveys in both the United States and Europe have demonstrated that asymptomatic lower extremity PAD is 2 to 5 times more prevalent than symptomatic lower extremity PAD.

By using the common ABI definition of lower extremity PAD (i.e. ABI<0.9), 11.7% of the population may present large vessel lower extremity PAD on noninvasive testing, with a prevalence of intermittent claudication in this population of 2.2% in men and 1.7% in women (10).

Similarly, abnormal femoral or posterior tibial pulses were present in 20.3% of men and 22.1% of women, suggesting that, the fraction of individuals with intermittent claudication dramatically underestimated the true prevalence of lower extremity PAD. Conversely, the presence of claudication symptoms was also an imperfect marker (i.e., had poor specificity) for lower extremity PAD, because an ABI<0.90 was found in only 69% of those with claudication symptoms. This suggests that the vast majority of lower extremity PAD patients have no classic claudication symptoms.

Among symptomatic patients, the perception of claudication can vary from severe, debilitating discomfort at rest to a bothersome pain of seemingly little consequence. The severity of symptoms of claudication depends upon the degree of stenosis, the collateral circulation, and the vigor of exercise.

Patients with claudication can present with buttock and hip, thigh, calf, or foot pain, either singly or in combination. The usual relationships between pain location and corresponding anatomic site of arterial occlusive disease can be summarized as follows:
- Buttock and hip = aortoiliac disease
- Thigh = aortoiliac or common femoral artery
- Upper two-thirds of the calf = superficial femoral artery
- Lower one-third of the calf = popliteal artery
- Foot claudication = tibial or peroneal artery

Physical examination in the patient with claudication can be normal, but commonly reveals diminished or absent pulses below the level of stenosis with occasional bruits over stenotic lesions and evidence of poor wound healing over the area of diminished perfusion (62). Other physical findings may include a unilaterally cool extremity, a prolonged venous filling time, shiny atrophied skin, and nail changes (63).

**Buttock and hip claudication:**

Patients with aortoiliac occlusive disease (Leriche's syndrome) may complain of buttock, hip, and, in some cases, thigh claudication. Bilateral aortoiliac disease that is severe enough to cause symptoms almost always causes erectile dysfunction in men; another diagnosis should therefore be entertained if impotence is absent. Conditions that resemble Leriche's syndrome are:

- Osteoarthritis of the hip or knee joints,
- Neurogenic claudication

Osteoarthritis can be distinguished clinically from aortoiliac disease because osteoarthritic pain may not disappear promptly after exercise, may be associated with weather changes, and may vary in intensity from day to day (usually worse in the morning or upon wakening).

Neurogenic claudication, also called pseudoclaudication, describes a pain syndrome due to lumbar neurospinal canal compression, which is usually due to osteophytic narrowing of the neurospinal canal. The clinical presentation often helps to distinguish vasculogenic (i.e. true) claudication from pseudoclaudication. Unlike true claudication, which occurs with walking and is relieved by stopping, pseudoclaudication causes pain with erect posture (lumbar lordosis) and is relieved by sitting or lying down. Patients with pseudoclaudication may also find symptomatic relief by leaning forward and straightening the spine.
Thigh claudication:

Atherosclerotic occlusion of the common femoral artery may induce claudication in the thigh, calf, or both. Patients with occlusive disease of the superficial femoral or popliteal arteries have normal groin pulses but decreased pulses distally.

Calf claudication:

Calf claudication is the most common complaint. It is usually described as a cramping pain that is consistently reproduced with exercise and relieved with rest. Cramping in the upper two-thirds of the calf is usually due to superficial femoral artery stenosis, whereas cramping in the lower third of the calf is often due to popliteal disease. This type of cramping pain in the calf can be confused with two other conditions:

- Nocturnal leg cramps — Nocturnal leg cramps occur among older and infirmed patients and are not associated with exercise. This complaint is thought to be neuromuscular rather than vascular in origin.
- Calf pressure and tightness — This symptom is primarily seen in athletes, and is usually associated with chronic exercise. It is thought to be due to increased compartment pressure and may persist even after rest.

Foot claudication

Claudication of the foot is usually accompanied by occlusive disease of the tibial and peroneal vessels. Isolated foot claudication is rarely seen with atherosclerotic occlusive disease, but is commonly seen with thromboangiitis obliterans (Buerger’s disease).

Ischemic rest pain

A severe decrease in limb perfusion can result in ischemic rest pain. Such discomfort typically occurs at night and involves the digits and forefoot. The pain may be more localized in patients who develop an ischemic ulcer or gangrenous toe. Affected patients frequently find that the pain is relieved by hanging their feet over the edge of the bed or, paradoxically, by walking around the room because of the gravitational effect of dependence on limb blood pressure. Chronic tissue ischemia may also result in ischemic neuropathic pain that is frequently described as throbbing or burning with a superimposed severe shooting pain up the limb.
2.0 VASCULAR EXAMINATION AND DIAGNOSTIC VASCULAR MODALITIES

2.0.1 The Vascular Anamnestic Review of Systems:

Patients do not always report symptoms that may be vital to their health, and they do not always associate specific symptoms with underlying arterial disease (e.g., the walking impairment of claudication, the presence of a poorly healing wound). A detailed history of the symptoms initiation, evolution and its associated phenomena is one of the key to correctly and rapidly unmask an underlying vascular problem. During the clinical examination one should be attentive to the following points:

- Any exertional limitation of the lower extremity muscles or any history of walking impairment.
  - The characteristics of this limitation may be described as fatigue, aching, numbness, or pain.
  - The primary site(s) of discomfort in the buttock, thigh, calf, or foot should be recorded, along with the relation of such discomfort to rest or exertion.

- Any poorly healing or non-healing wounds of the legs or feet.

- Any pain at rest localized to the lower leg or foot and its association with the upright or recumbent positions.

2.0.2 The Vascular Physical Examination:

The pulse examination, although critical to good care, has well-defined limitations. Recognition of the limited sensitivity, specificity, and predictive value of the pulse examination has led to recognition that this examination must be supplemented by objective vascular testing in case PAD is suspected (10).

Key components of the vascular physical examination must include the following:

- Measurement of blood pressure in both arms,
- Palpation of the carotid pulses and notation in the presence of bruits,
- Palpation and auscultation of the abdomen and flank for bruits,
- Palpation of pulses at the brachial, radial, ulnar, femoral, popliteal, dorsalis pedis, and posterior tibial sites,
- Performance of Allen’s test when knowledge of hand perfusion is needed,
- Auscultation of both femoral arteries for the presence of bruits,
- Inspection of the feet's color, temperature, and integrity of the skin.
2.1. DIAGNOSTIC VASCULAR MODALITIES IN LOWER EXTREMITY PAD

In patients with suspected lower extremity PAD based upon the history and physical examination (e.g. intermittent claudication, ischemic ulcer, gangrene) or in patients with risk factors for vascular disease (e.g. older age, smoking, diabetes mellitus), noninvasive tests are performed to confirm the clinical diagnosis and to further define the level and extent of obstruction (64).

The location of pain in patients with claudication varies with the vessels that are involved. The usual relationship between the site of pain and site of arterial disease was already mentioned. Despite these general relationships, the history and physical examination are not reliable for the detection of lower extremity PAD. It has been estimated that relying solely on the classic symptoms of claudication will miss up to 90% of the PAD cases (15).

The physical examination is also unreliable. As an example, an abnormal femoral pulse has a high specificity and positive predictive value but low sensitivity for large vessel disease (65). The best single discriminator is an abnormal posterior tibial pulse.

Patients with vascular disorders can usually be assured that an accurate anatomic diagnosis will be made with modern noninvasive vascular diagnostic techniques (e.g., ankle- and toe-brachial indices, duplex ultrasound imaging, doppler waveform analysis, and exercise testing).

Figure 2 proposes a diagnostic algorithm for detecting PAD in asymptomatic patients or patients presenting with atypical symptoms.
Figure 2: steps towards the diagnosis of PAD [reproduced from the ACC/AHA guidelines and Hiatt WR (3, 66)]
2.2 NON-INVASIVE TESTS

A variety of noninvasive examinations are available to assess the presence and degree of PAD. They include the ankle-brachial index (ABI), exercise treadmill test, segmental limb pressures, segmental volume plethysmography, and ultrasonography. Furthermore, recent data suggest that computed tomography angiography (CTA) and magnetic resonance angiography (MRA) have become important noninvasive methods for the PAD assessment (67); however, the cost and the time necessary for these studies will limit their use as evaluation modalities only for patients with a high clinical suspicion of significant PAD, and not as a routine screening investigational tool in asymptomatic patients.

2.2.1 Ankle-brachial index (ABI)

A relatively simple and inexpensive method to confirm the clinical suspicion of arterial occlusive disease is to measure the resting and/or post-exercise systolic blood pressures in the ankle and arm (Figure 3). This measurement is referred to as the ankle-brachial (or ankle-arm) index or ratio, and provides a measure of the severity of PAD (68).

The ABI is a measurement that provides objective data for the diagnosis of lower extremity PAD. The normal ABI is >0.9 to as high as 1.3, since the pressure is physiologically higher in the ankle than in the arm. Values above 1.30 suggest a noncompressible calcified vessel. An ABI ≤0.9 has 95 percent sensitivity (and 100 percent specificity) for detecting angiogram-positive PAD and is associated with ≥50% stenosis in one or more major vessels. An ABI of 0.4 to 0.9 suggests a degree of arterial obstruction often associated with claudication, while an ABI below 0.4 represents advanced ischemia and may be associated with ischemic rest pain or pedal gangrene (69-71).

Patients with either severely stenotic or totally occluded iliofemoral arteries may also have a normal ABI value at rest if sufficient collaterals are present. Thus, for patients in whom symptoms strongly suggest lower extremity PAD, the presence of a normal or high ABI should not be resumed to rule out this diagnosis, and an alternative diagnostic test (e.g., toe-brachial pressure, Doppler waveform analysis, pulse volume recording, exercise ABI test, or duplex ultrasound) should be performed (72).

The ABI may not be accurate in individuals in whom systolic blood pressure cannot be abolished by inflation of an air-filled blood pressure cuff, as often occurs in diabetics and elderly
patients. Despite the artifactually high systolic pressure, these individuals may have severe arterial
disease, mandating further arterial examinations (73).

2.2.1.1 Correlation of ABI with symptoms and site of PAD:

The ABI correlates with clinical measures of lower extremity function, such as: walking distance,
velocity, balance, and overall physical activity (74, 75). In addition, a low ABI has been associated with
a higher risk of coronary heart disease, stroke, transient ischemic attack, progressive renal
insufficiency, and all-cause mortality (73, 76, 77).

There is a general, but not absolute, correlation between symptoms and the site and severity of
PAD, with severity being estimated from the ankle-brachial index (ABI, abnormal <0.90). Not
surprisingly, since PAD is a manifestation of systemic atherosclerosis, a low ABI is also predictive of
an increased risk of all-cause and cardiovascular mortality (45, 46) and of the development of
coronary artery calcification (78).

The relationship between ABI and morbidity and mortality in patients with lower extremity PAD
has also been quantitated with a 5-year cumulative survival rate of 63% for subjects with a resting ABI
less than 0.50, 71% for subjects with an ABI between 0.50 and 0.69, and 91% for subjects with an ABI
between 0.70 and 0.89 (79).

Figure 3: Ankle-brachial index measurement and interpretation [reproduced from Hiatt WR (66)]
2.2.1.2 High Ankle-Brachial-Index:

The ABI may not be accurate in individuals in whom systolic blood pressure cannot be abolished by inflation of the blood pressure cuff. A potential source of error with the ABI is that calcified vessels may not compress normally, possibly resulting in falsely elevated Doppler signals.

The incidence of non-compressible arteries is highest in diabetics and elderly patients; in these individuals, it may be impossible to abolish the systolic pressure signal despite cuff inflation to pressures > 200 mmHg. Despite the artifactually high systolic pressure, these individuals may have severe arterial disease, as well as a higher incidence of cardiovascular event rates (adjusted hazard ratios 2.5 and 2.1) (73).

2.2.2 Toe-Brachial Index and Toe pressure Measurements

As mentioned, in patients presenting with long-standing diabetes, elderly patients, and individuals who require dialysis for end-stage renal disease the ABI may falsely normal or elevated. For this reason the TBI and the TP are usually preferred as a diagnostic tool for diagnosis of the presence of a significant PAD, or in case of a suspected CLI. The toe pressure measurement remains a sensitive diagnostic test in such patients because digital arteries are usually spared from calcinosis that alters compressibility of more proximal arteries. Accordingly, in this setting, one must recognize that a pressure gradient of 20 to 30 mmHg normally exists between the ankle and the toe, thus toe-brachial index values less than 0.7 are usually considered diagnostic for lower extremity PAD (80, 81).

The Trans-Atlantic Inter-Society Consensus working group has published in 2000 and updated in 2007 several comprehensive guidelines of the management of different pathologies dealing with different type of peripheral artery diseases (1, 2). While the cut-off values by defining the presence of a CLI have well been established, no clear consensus was obtained by defining the presence of a mild-to-moderate PAD.
Table 1 summerizes the most used criteria by defining the presence of a mild to moderate PAD, as well as the presence of a severe PAD (i.e. CLI).

<table>
<thead>
<tr>
<th></th>
<th>Normal</th>
<th>Mild-Moderate PAD</th>
<th>CLI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ankle Pressure</td>
<td>NA*</td>
<td>NA*</td>
<td>&lt; 50 mmHg</td>
</tr>
<tr>
<td>Ankle Brachial Index</td>
<td>≥ 0.9 / ≤ 1.3</td>
<td>0.4-0.9</td>
<td>&lt; 0.4</td>
</tr>
<tr>
<td>Toe pressure</td>
<td>NA*</td>
<td>NA*</td>
<td>&lt; 30 mmHg</td>
</tr>
<tr>
<td>Toe Brachial Index</td>
<td>≥ 0.7</td>
<td>0.4-0.7</td>
<td>&lt; 0.4</td>
</tr>
<tr>
<td>tcPO2</td>
<td>≥ 50 mmHg</td>
<td>20-50 mmHg</td>
<td>&lt; 20 mmHg</td>
</tr>
</tbody>
</table>

*Normal values of the ankle and toe pressures depend on the systemic brachial pressure

Table 1: Criteria of PAD and CLI [modified according the TASC II and ACC/AHA guidelines (2, 3)]

2.2.3 Exercise treadmill testing

The dynamics of blood flow across a stenotic lesion depend, in part, upon whether the individual is at rest or exercising and upon the severity of the obstruction. Exercise normally decreases vascular resistance and enhances blood flow to the exercising extremities. An arterial stenosis of <70% may not be of sufficient severity to perturb blood flow at rest or produce a systolic pressure gradient. Exercise, in such patients, can induce a systolic pressure gradient across the stenosis, especially in case there is a summation phenomenon of more intermediate to severe stenoses.

These changes may be detected clinically by a fall in the ABI followed by recovery. This pattern is detected by measurement of the ABI at one minute intervals for five minutes after exercise. As a result, exercise testing is a sensitive method for evaluating patients with typical symptoms of claudication in whom the resting ABI is normal.

Several protocols exist for treadmill testing and are generally divided into those using a fixed versus a graded routine (82). The standard exercise test is a treadmill test for five minutes at 3-5 Km/h.
on a 12% incline. Severe claudication can be defined as an inability to complete the treadmill exercise due to leg symptoms and post-exercise ankle systolic pressures below 50 mmHg.

2.2.4 Continuous-Wave Doppler Ultrasound

Continuous-wave Doppler ultrasound is used to obtain velocity waveforms and to measure systolic blood pressure at sequential segments of the upper or lower extremities and is a traditional component of a non-invasive peripheral arterial evaluation. Use of this technique permits initial estimation of disease location and severity, follow-up of disease progression, and quantification of the effects of revascularization therapies (83).

Analysis of the morphology of the Doppler waveform can add useful localizing information to that obtained by segmental blood pressure recording alone. For example, a unilaterally depressed proximal thigh measurement could be due to occlusive disease in either the ipsilateral common or external iliac arteries or the proximal portion of the superficial femoral artery.

Doppler waveform analysis also can provide useful localizing information in patients with poorly compressible arteries and in patients with a normal resting ABI.

2.2.5 Duplex ultrasonography

Duplex ultrasound of the extremities can be used to diagnose the anatomic location and degree of stenosis of lower extremity PAD. Duplex ultrasound also has broad clinical utility for evaluation of aneurysms, arterial dissection, popliteal artery entrapment syndrome, evaluation of lymphoceles, and assessment of soft tissue masses in individuals with vascular disease.

Although ultrasonography is accurate in detecting PAD, resting segmental pulse volumes and systolic pressures are the initial screening tests in many laboratories. Ultrasonography is currently used to depict anatomy, hemodynamics, and lesion morphology; ultrasonographic equipment used for these tasks includes B-mode imaging, pulse wave Doppler, continuous wave Doppler, and color Doppler (68). Duplex imaging most commonly refers to the combination of B-mode or color imaging and pulsed wave Doppler interrogation.

The normal peripheral arterial velocity waveform is triphasic and consists of (84, 85):

- A forward flow systolic peak
- Reversal of flow in early diastole
- Forward flow in late diastole
With progressive PAD, there is elimination of the reverse flow waveform component, a decrease in systolic peak and an increase in flow in diastole.

Although duplex ultrasound includes images, either in black and white or color format, the primary clinically relevant information derived from duplex studies has been validated from analysis of the velocity of blood flow (86-89). Quantitative criteria used to diagnose stenoses are based on peak systolic velocity and peak systolic velocity ratios within or beyond the stenosis compared with the adjacent upstream segment, the presence or absence of turbulence, and preservation of pulsatility.

In general, peak systolic velocity ratios have been found to be the most accurate diagnostic criterion. A ratio greater than 2.4 is commonly used to diagnose a stenosis greater than 50% diameter (86-89). The sensitivity and specificity of this technique for ≥50% stenosis or occlusion is 86 and 97% for aortoiliac disease and 80 and 98% for femoropopliteal disease (90). Further parameters as the spectral waveform, the diastolic velocity, the b-mode imaging and the presence of turbulence on color-doppler are also routinely evaluated during the duplex examination adding important information in establishing the hemodynamic relevance of a stenosis.

Finally, duplex ultrasound can be used for preintervention decision making. This technique can predict whether a patient has anatomy suitable for angioplasty with an accuracy of 84% to 94% (91).

2.2.6 Magnetic resonance Angiography (MRA)

In a manner similar to duplex ultrasound, MRA of the extremities can be used to diagnose the anatomic location and degree of stenosis of PAD. MRA evaluation is based on imaging the arteries, similar to standard arteriography. The advent of rapid 3-D imaging sequences combined with existing extracellular gadolinium contrast agents, MRA has shown promise to become a time-efficient, sensitive and cost-effective tool for the complete assessment of PAD (92).

A meta-analysis of MRA compared with catheter angiography demonstrated that the sensitivity and specificity of MRA for detection of stenoses greater than 50% were both in the range of 90% to 100%, with greatest accuracy when gadolinium-enhanced MRA was used (93, 94). However, MRA has unique limitations. It tends to overestimate the degree of stenosis because of turbulence. Patients with pacemakers and defibrillators and some cerebral aneurysm clips cannot be scanned safely (95) and finally some caution should be paid in patients with chronic kidney disease.
because several reports suggest the possibility of a gadolinium-induced systemic or skin fibrosis (96, 97)

2.2.7 Computed Tomography Angiography (CTA)

The development of multidetector computed tomographic (MDCT) scanners now allows rapid acquisition of high resolution, intravenous contrast-enhanced images from patients with suspected PAD. Computed tomographic angiography requires intravenous injection of iodinated contrast, which opacifies the arteries. The angiographic image is then constructed from multiple cross-sectional images and then presented as a volumetric as well as a bidimensional reconstruction, which finally allow for the final maximum-intensity projection reconstruction, which results very similar to the appearance of standard arteriography (98-100).

A number of reports of small series of patients have noted excellent correlation between MDCT and digital subtraction angiography (DSA) in the detection of aortic and lower extremity arterial disease (101). The sensitivity and specificity for detecting a stenosis of at least 50% were 95 and 96%, respectively, compared with DSA. Specificity was lower in the tibial arteries compared with the aortoiliac and femoropopliteal segment. Arterial occlusions were correctly identified in 94% of segments and the absence of a significant stenosis was correctly identified in 96% of segments (102).

2.2.7.1 CTA vs. MRA:

CTA has potential advantages over MRA. Patients with pacemakers or defibrillators, who are excluded from imaging within magnetic resonance machines, may be imaged safely with CTA. Metal clips, stents, and prostheses usually do not cause significant CTA artifacts that limit diagnostic utility. CTA has higher resolution and can provide images of calcification in the vessel wall. Scan times are significantly faster with CTA than with MRA. Claustrophobia is far less of a problem. However, CTA also has potential disadvantages compared with MRA. It requires iodinated contrast, which may be nephrotoxic in azotemic patients. It also requires ionizing radiation, although the radiation dose is less than with catheter angiography (103).

2.2.7.2 CTA vs. DSA:

The CTA method has potential diagnostic advantages compared with invasive catheter angiography. The 3-dimensional (3D) images can be freely rotated in space, which permits evaluation of eccentric stenoses. Computed tomographic angiography images tissues surrounding the opacified
lumen of the artery and has demonstrated that some popliteal stenoses and occlusions are due to aneurysms, popliteal entrapment, and cystic adventitial disease, which are not detected with catheter angiography (104).

However, CTA also has potential disadvantages compared with catheter angiography. Spatial resolution is lower than with digital subtraction angiography. Venous opacification can obscure arterial filling. Asymmetrical opacification of the legs may cause CTA to miss the arterial phase in some vessels (103).
2.3 INVASIVE TESTS

2.3.1 Arteriography

Arteriography or angiography is still considered the "gold standard" for diagnostic evaluation of PAD. Nowadays, to establish the diagnosis of PAD and to plan the most adapted intervention, most vascular specialists use three-dimensional reconstructed angiography (CTA or MRA) or bidimensional images obtained with Duplex-ultrasound modalities. However, diagnostic standard angiography may still remain necessary, in selected cases, in whom anatomic details are not correctly visualized by the non-invasive imaging modalities and a specific intervention is being considered. This may be the case in patients presenting with critical limb ischemia secondary to an isolated below the knee or below the ankle disease, in whom a very detailed vascular anatomy mapping (e.g., collaterals) may be necessary in order to correctly plan the revascularization procedure.

With contrast angiography images are easily displayed and interpreted by the vast majority of physicians caring for patients with vascular disease. Technical improvements in X-ray imaging equipment enhance image quality and allow for detection of abnormalities. Progressive improvements in image resolution have enabled better definition of affected vascular territories with contrast and have resulted in a better safety profile of the entire procedure.

Despite the fact that the standard cine-angiography acquisition images are usually of sufficient quality to allow the visualization of the vascular anatomy as well as the presence or absence of any significant disease, the subtraction acquisition modality (i.e., DSA) should be preferred, because it gives better images’ resolution while using less contrast medium. Accordingly, the DSA technique provides superior definition of the vascular tree compared with unsubtracted imaging, because it eliminates much of the artifact due to bony structures and dense body tissues. Finally, selection of the appropriate amount of contrast and application of proper image-acquisition techniques, including masking and digital enhancement, are required to optimize the accuracy of the images obtained, finally resulting in reducing the contrast medium delivery as well as the time of the procedure.

The simultaneous miniaturization of catheters available for angiography and the development of more selective shapes have further enhanced the safety profile of this standard technique. In addition, non-invasive imaging with duplex, MRA, and/or CTA methods may allow for better preparation before initiation of an invasive procedure. Identification of a culprit lesion, preparation of the appropriate
equipment, and selection of the best access sites are all facilitated by information obtained by these non-invasive imaging modalities. Thus, there is now a wide variety of practice patterns with respect to the use of non-invasive imaging modalities for therapeutic planning.

Knowledge of inflow and outflow patterns, as well as characterization of the lesion, may affect decisions regarding therapy. From a technical standpoint, the closer the catheter is to the target vessel to be imaged, the better the image definition is and the less is the volume of contrast that is required. Accordingly, selective and superselective catheter placement is useful in optimizing image quality. This is particularly recommended in the setting of renal insufficiency or when occlusive distal vessels may not be visualized by a more proximal bolus injection of contrast. However, one should also take into consideration that, most of the time with selective or superselective angiography acquisitions, collaterals are not correctly visualized. Accordingly, and especially in case of vascular total occlusions, the distal reperfusion zone may be visualized only by much more proximal injection (e.g., in the distal abdominal aorta or the common femoral artery), which allows an adequate collaterals opacification (e.g., through lumbar or the profunda femoral arteries), thereby a sufficient filling of the reperfusion zone.

The acquisition of views from orthogonal angles, which has been the rule in coronary angiography, is less prevalent in peripheral imaging, largely because of the extensive territory to be covered in a complete diagnostic peripheral runoff angiogram (as opposed to a coronary angiogram). Nonetheless, for areas where there is doubt or uncertainty regarding the presence or absence of a significant lesion, angulated views can be useful to better delineate and define the severity of the lesion and clarify its potential contribution to the clinical syndrome. This does, however, require injection of additional contrast material and prolongs the angiographic procedure.

Adjunctive hemodynamic parameters, such as pressure gradient and duplex velocity measurements, as well as use of supportive imaging modalities, such as intravascular ultrasound, angioscopy, and optical coherence tomography, can be useful and occasionally have been used in lieu of digital subtraction angiography to guide procedures.

Angiography has several liabilities. First, it carries with it the risks associated with any invasive procedure. Such risks include those related to vascular access (e.g., bleeding, infection, and vessel disruption). In addition, there is a small but important risk of contrast reaction; the risk of a severe reaction is approximately 0.1% (105).
Contrast agents are also associated with a small but important incidence of nephrotoxicity. Patients who are at increased risk of contrast nephropathy include those with severe baseline renal dysfunction, diabetes, low cardiac output state, or dehydration. Any combination of these is more problematic than an individual risk factor. Recent studies have suggested that use of low-osmolar contrast agents (e.g., iodixanol) or pretreatment with *n*-acetylcysteine may reduce the incidence of renal compromise (106, 107).

In patients who are high risk for nephrotoxicity, data suggest that vigorous hydration before administration of contrast may serve as the most important strategy to prevent postprocedural deterioration in renal function. Because the occurrence of nephrotoxicity appears to be dose-dependent, it is also important to minimize contrast usage. This dose minimization can be accomplished by using digital subtraction techniques and placing catheters close to the site to be imaged (selective angiography).

Finally, complications typically associated with invasive techniques and catheter manipulation, such as atheroembolization, dissection, and inadvertent vessel-wall disruption or perforation, are all adverse events that can occur with invasive angiography. Vigilant observation and careful manipulation of guidewire and catheter location are imperative.
2.4 DIAGNOSTIC ANGIOGRAPHY

2.4.1 Access

As a general rule, angiography of the lower extremities is performed accessing in a retrograde manner the CFA contralateral to the limb which is more symptomatic and/or shows worse ABI/PVR. If imaging studies — duplex ultrasound, CTA, or MRA — have defined the location of the obstruction, access will be chosen based on the planned intervention. The location of the lesion to be treated is the most important factor determining access. As a general rule, EIA lesions — especially if located in the distal segment — are treated using a crossover approach (Figure 4), while CIA lesions are approached using an ipsilateral retrograde access (Figure 5). On occasion, access may differ if the lesion to treat is a stenosis or an occlusion. In the presence of chronic total occlusions of both CIA and EIA, a crossover approach might be preferred as it may reduce the risk of subintimal recanalization and allow the management of distal embolization.

![Crossover approach for the treatment of a contralateral EIA stenosis](image)

*Figure 4: crossover approach for the treatment of a contralateral EIA stenosis*

[reproduced from Bonvini RF et al. (108)]
Figure 5: retrograde approach for the treatment of an ipsi-lateral CIA stenosis
[reproduced from Bonvini RF et al. (108)]

In case the femoral artery is the main target of the procedure the retrograde approach using the
cross-over maneuver is usually preferred in case of very proximal lesions (i.e. close to the CFA
bifurcation). In case of mid-distal or popliteal lesion the crossover approach is usually attempt,
because associated with less puncture site complication than the antegrade approach. However, in
case an important back-up support is required (e.g. very calcified lesions) the antegrade approach
should be adopted because of a better pushability and torquability of catheters during the intervention
using this approach (Figure 6).

In case of below the knee interventions the antegrade approach should be preferred because
with this approach also very distal lesion (i.e. foot lesions) may be treated.
2.4.2 Views

Excessive tortuous anatomy of the iliac arteries and eccentricity of atherosclerotic involvement is frequent. Therefore, angulated views (right anterior oblique [RAO] or left anterior oblique [LAO]) should be obtained in addition to the standard posterior-anterior (PA) projection if a stenosis is suspected. Additional imaging of the CIA and the proximal EIA segment is best obtained with a contralateral angulated (30-45°) view. Conversely, the same degree of ipsilateral angulation is preferred to delineate pathologies of the distal EIA, the proximal CFA, and the CFA bifurcation. The CFA bifurcation is sometimes difficult to visualize with a clear separation of the superficial and profunda femoral arteries. In these cases, an extreme ipsilateral angulation (> 45°) may be preferred.

For femoro-popliteal interventions ipsilateral oblique views are generally adopted, especially close to the CFA bifurcation, while in case of mid-distal SFA or the popliteal artery lesions, standard AP views may sufficient to correctly visualize the anatomic structures.
For below the knee intervention, oblique views (ipsilateral or contralateral) should be adopted, in order to better separate the infragenicular vessels, especially the peroneal and the anterior tibial arteries which in AP projections tend to overlap.

2.4.3 Catheters

In most cases, pelvic diagnostic angiography can be performed on an outpatient basis using 4Fr or 5Fr pigtail catheter. Imaging of the infrarenal aorta, aortic bifurcation, and pelvic arteries can be obtained with mechanical injection of 20 ml of contrast media at a flow of approximately 15 ml per second using digital subtraction angiography (DSA). However, recent developments in technology (e.g., flat panels) allow good visualization of the pelvic and the femoral vessels also without DSA. Usually, no angulation is needed for the visualization of the aortic bifurcation. However, sometimes an additional angiogram with a 30-45° contralateral angulation is useful for a correct visualization of CIA ostial lesions.

Same-session endovascular intervention should be considered in the majority of the cases, especially in the absence of renal insufficiency or heart failure. Following manual compression and a pressure dressing for few hours, patients who are not anticoagulated may be rapidly mobilized and discharged. In case of used large bored introducer sheath or full anticoagulated patients (especially those already under dual antiplatelet therapy), vascular closure devices have proven their efficacy and safety, in term or similar or even less puncture site bleeding complication, with a better hemostasis and ambulation time (109).
3.0 CLAUDICATION, CRITICAL LIMB AND ACUTE LIMB ISCHEMIAS

As previously mentioned symptoms may be classified in three major categories:

- Patients presenting with intermittent claudication,
- Patients presenting with CLI,
- Patients presenting with ALI.

This kind of classification is based solely on the severity of the symptoms and not on the degree of the disease extension. Accordingly, even if there is frequently a strict correlation between symptoms and disease extension, the opposite may also be frequently observed.

As example one should remember that, in case of an acute embolic occlusion of the common femoral artery bifurcation, in a previously disease free femoral arteries, the clinical picture may be extremely severe with a patient presenting with severe pain and an increased risk of limb necrosis.

Conversely patients presenting with chronic extensive arterial occlusion (e.g., Leriche syndrome, long SFA occlusion) may have developed an extensive collateral circulation (via the lumbar arteries and inferior mesenteric artery in the Leriche syndrome; via the profunda femoral artery in case of SFA occlusion) and therefore present only with mild symptoms.

For these reasons, and especially because the degree of aggressiveness by proposing an arterial revascularization, will depend principally by the clinical status, more then by the disease extension, we have separated the next issues concerning the endovascular options of revascularization according to principal disabiliing symptom: intermittent claudication, CLI and ALI.
3.1 CLAUDICATION

Claudication is defined as fatigue, discomfort, or pain that occurs in specific limb muscle groups during effort due to exercise-induced ischemia. Individuals with claudication have sufficient blood flow so that limb ischemic symptoms are absent at rest. With increased local muscular demand for metabolic support during exercise, blood flow in individuals with lower extremity PAD and claudication is inadequate to meet this demand, and limb muscular fatigue and/or pain results.

Lower extremity ischemia is usually due to atherosclerotic lower extremity PAD and occasionally other causes, including emboli, radiation arteritis, Buerger’s disease (thromboangiitis obliterans), other arteritides, coarctation, popliteal entrapment, cystic adventitial disease, FMD, and trauma may the cause of the disabling symptoms.

Table 2 summarizes the different pathology’s groups mimicking intermittent claudication:

<table>
<thead>
<tr>
<th>Pathology’s Group</th>
<th>Pain Localization</th>
<th>Pain Characterist</th>
<th>Pain at exercise, rest, body position</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Arterial Claudication</strong></td>
<td>Buttock, thigh, calf, (foot)</td>
<td>Cramping, aching, fatigue</td>
<td>After some degree of exercise, quickly relieved at rest</td>
</tr>
<tr>
<td><strong>Venous Claudication</strong></td>
<td>The entire leg: groin &gt; thigh &gt; calf</td>
<td>Thigh bursting pain</td>
<td>Increased at exercise, relieved by elevation of the leg</td>
</tr>
<tr>
<td><strong>Neurological diseases:</strong> (e.g., herniated disc, spinal stenosis)</td>
<td>Radiation down to the leg, follows dermatome</td>
<td>Sharp lancinating pain, motor weakness</td>
<td>Immediate pain onset, remaining longer at rest. Pain may increase by standing and be relieved according to the body position</td>
</tr>
<tr>
<td><strong>Orthopedic disease:</strong> (e.g., hip or knee arthritis)</td>
<td>Usually localized to the disease articulation, usually accentuate by movements</td>
<td>Aching pain</td>
<td>After some degree of exercise but may be present also at rest. Relief by sitting or changing position</td>
</tr>
</tbody>
</table>

Table 2: Differential diagnosis of intermittent claudication [modified according to the TASC Guidelines (1, 2)]
Vascular claudication due to lower extremity PAD is produced by exercise and is relieved with rest and is therefore traditionally referred to as “intermittent claudication,” or simply “claudication.” The pathophysiology of claudication is considerably more complex than can be accounted for by the supply–demand mismatch that results from stenotic disease itself (110). However, diagnosis and treatment can be guided by an understanding of the lower extremity PAD arterial anatomy.

The anatomic site of the arterial stenosis is often associated with specific leg symptoms. Occlusive disease in the iliac arteries may produce hip, buttock, and thigh pain, as well as calf pain. Occlusive disease in the femoral and popliteal arteries is usually associated with calf pain. Occlusive disease in the tibial arteries may produce calf pain or, more rarely, foot pain and numbness.

The pathophysiology of claudication is complex; it is not merely a response to limitations in blood flow but also includes a wide range of skeletal muscle (e.g., metabolic), neurological, and inflammatory effects (110).

The severity of the ischemia can be classified according to either the Fontaine or Rutherford categories. These categories are most commonly used in research settings but may also have value in improving the clarity of communication of lower extremity PAD severity within office practices and in referral from primary practitioner to vascular specialist (2).

Vascular claudication must be distinguished from other illnesses that cause exertional leg pain, which have been called “pseudoclaudication.” These other causes include severe venous obstructive disease, chronic compartment syndrome, lumbar disease and spinal stenosis, osteoarthritis, and inflammatory muscle diseases (2).

The clinical history in case of a suspected PAD should also include risk factors for atherosclerotic disease, such as smoking, diabetes, hypertension, hyperlipidemia, and a family history of atherosclerotic disease. In addition to the historical factors that distinguish intermittent claudication from other causes of leg pain, the physical examination should document the presence of diminished pulses in the femoral, popliteal, posterior tibial, and dorsalis pedis arteries. Signs of systemic atherosclerosis, as a clue to a vascular cause of claudication, include femoral bruits, which may be present owing to turbulence from focal stenosis (15). Bruits may also be present in the carotid arteries and renal arteries as a sign of systemic atherosclerosis.

Claudication is usually also associated with reduced ankle blood pressures in the affected leg, which causes a diminished ABI. Some patients may have normal ankle pressures at rest with
abnormal low ankle systolic pressures (and thus low ABI values) detectable only after exercise. Individuals with long-standing diabetes, patients with chronic renal failure, and the very elderly have densely calcified vessels that are poorly compressible and may have spuriously high ankle pressures and ABI values.

The ABI should be measured in all patients with claudication. For individuals who present with classic claudication and in whom the ABI is borderline or normal (0.91 to 1.30) or supranormal (greater than 1.30), alternative diagnostic strategies should be used, including the toe pressure, toe-brachial index, segmental pressure examination, or duplex ultrasound, to confirm the lower extremity PAD diagnosis. This strategy is necessary to distinguish claudication from pseudoclaudication, provides an estimate of the overall severity of occlusive disease in the extremity, and serves as a baseline to assess temporal changes due to disease progression or intervention.

The ABI correlates only weakly with treadmill-based walking ability for any individual patient. For example, some patients with a low ABI report minimal walking impairment, whereas some with a higher ABI report marked walking impairment (111). This is due at least in part to the wide range of comorbidities that can coexist with intermittent claudication in patients who have PAD (29). Systemic atherosclerotic disease, medical comorbidities, and back, hip, and knee symptoms may have a greater impact on an individual’s quality of life than claudication, such that lower extremity revascularization may not significantly improve quality of life (112).

Because the natural history of claudication is relatively benign (from the limb perspective), with few patients progressing to CLI or amputation (57), decisions regarding revascularization of individuals with claudication should be based on improving quality of life. Patients with a low ABI, a significant walking impairment, and no or mild comorbidities would be expected to benefit the most from any claudication intervention, including exercise, pharmacotherapy, or revascularization (111).

### 3.1.1 Exercise and Lower Extremity PAD Rehabilitation

A program of supervised exercise may be considered a primary efficacious treatment modality to alleviate claudication symptoms for all patients with intermittent claudication. Regular walking in a supervised claudication exercise program can be expected to result in an increase in the speed, distance, and duration walked, with decreased claudication symptoms at each workload or distance (113-116). These functional benefits accrue gradually and become evident over 4 to 8 weeks and increase progressively over 12 or more weeks.
Such sustained increases in physical activity, if associated with improvements in cardiovascular risk factors, have the potential to reduce the risk of cardiovascular ischemic events, thereby potentially improving the poor prognosis for survival in this population (117, 118).

Because patients with claudication often have concomitant clinical or occult coronary artery disease, hypertension, and diabetes, adverse cardiovascular and physiological responses during exercise training are possible, and this risk should be evaluated clinically before initiation of the therapeutic program. However, there is no evidence that patients with claudication need to undergo stress imaging or invasive angiographic studies before initiating an exercise program.

A typical supervised exercise program requires the performance of treadmill or track-based exercise for 45 to 60 minutes performed 3 or more times a week for a minimum of 12 weeks. Such exercise is monitored by a physical therapist, nurse, or exercise physiologist. Treadmill exercise appears to be more effective than other exercise modalities, presumably because treadmill walking most closely reproduces walking in the community setting.

Patients are asked to continue to walk at this workload until they achieve claudication of moderate severity. This is followed by a brief period of rest to permit symptoms to resolve. The exercise-rest-exercise cycles repeated several times during the hour of supervision (113, 115, 116).

There are inadequate data to compare such distinct claudication interventions effectively. It is likely that supervised exercise training can serve as a beneficial adjunct to further augment the improvements in walking that can be gained by both endovascular procedures and surgical bypass (119).
3.2 SURGICAL OPTIONS FOR LOWER LIMB REvascularization

There are different types and approaches of performing a lower limb surgical revascularization. The key point of the proposed treatment is the localization of the arterial disease, while the degree of the vascular obstructions (i.e. stenosis vs. occlusions) does not play a major role in the decision making of the surgical intervention. Accordingly, lower limb surgical revascularization may be divided in two major groups: - supra-inguinal (i.e. for aortoiliac diseases) and infra-inguinal (i.e. for femoropopliteal diseases). Further differentiation by performing surgical intervention (usually bypasses) is the type of the adopted conduit: vein bypass (e.g. in-situ devalvulated or reversed saphenous vein grafts) or prosthetic bypass (e.g. Dacron, ePTFE).

3.2.1 Aortoiliac Disease

The infrarenal abdominal aorta and iliac arteries are among the most common sites of chronic obliterative atherosclerosis, accounting for about one third of all PAD cases. The standard surgical treatment for aortoiliac disease is aorto-bifemoral bypass, where a Y-shaped graft is attached the distal abdominal aorta proximally, and each limb of the Y-graft attached to the common femoral artery (CFA) distally (Figure 7).

Occasionally, the distal limb(s) may be anastomosed to the profunda femoral artery (PFA) when the CFA is diseased and the superficial femoral artery (SFA) is occluded. Less common surgical procedures for aorto-iliac disease include: aorto-iliac endarterectomy for the treatment of focal iliac disease, and axillo-femoral bypass for patients with occlusive disease of the distal abdominal aorta and severe comorbidities. In patients with unilateral iliac disease, additional surgical options include femoro-femoral cross-over bypass or ilio-femoral bypass.

With respect to aorto-bifemoral bypass, a meta-analysis of 23 series including over 8000 patients operated between 1975 and 1995 reported an aggregated operative mortality of 4.6% in early studies (performed in the 1970s) and 3.3% in later studies (in the 1990s) (120). The aggregated major morbidity was 13% and 8% for each time period, respectively. Limb-based patency rates for patients with claudication were 91% and 87% at 5 and 10 years, respectively; the corresponding patency rates in patients with critical limb ischemia were 87% and 82%, respectively. No difference in patency was detected between older and more recent studies.
Aorto-iliac endarterectomy has been associated with patency rates in modern series ranging from 88% to 94% at 1 year and from 60% to 80% at 5 years (121, 122). However, since best endarterectomy results were obtained in patients with focal iliac disease, this technique has been largely replaced by endovascular intervention. Axillo-femoral bypass has been performed with patency rates ranging from 78% to 93% at 1 year and from 50% to 80% at 5 years (123).

3.2.1.1 Aortoiliac or aortofemoral bypass graft — Aortoiliac or femoral bypass grafting has become the preferred method of treatment of symptomatic aortoiliac occlusive disease in low-risk patients. The perioperative mortality rates are well under 5%. The choice of either an aortoiliac or an aortofemoral bypass depends on the disease extension (i.e. occluded CIAs alone or CIAs and EIAs). When an aortofemoral bypass is adopted, most of the time a CFA endarterectomy is concomitantly performed.

3.2.1.2 Extra-anatomic reconstruction — There are circumstances in which standard aortobifemoral bypass grafting is not ideal, usually because of a high operative risk or the presence of infection in the operative field precluding the use of prosthetic material in that location.

3.2.1.3 Axillofemoral bypass graft — Axillo-uni or bifemoral bypass grafting offers a reasonable alternative in high-risk patients. Since neither the thoracic nor the abdominal cavity is violated when performing an axillofemoral graft, the procedure usually does not interfere with the patient's ability to breathe, cough, or take oral feedings. In addition, it is possible to perform this procedure under local anesthesia, which is particularly important in patients who are poor candidates for major surgery. Additionally, this option is useful in the setting of an infected field such as following the removal of an infected aortobifemoral bypass graft.

3.2.1.4 Femorofemoral bypass — Femoral bypass is a useful option in patients with unilateral iliac occlusive disease whose aorta and contralateral iliac artery are free of disease. Femorofemoral bypass can be performed under regional anesthesia, an important advantage in high-risk patients. Cumulative five-year patency rates of 70 to 80 percent have been reported (124).

3.2.1.5 In situ autogenous reconstruction — The use of an autogenous superficial femoral vein that usually can be fashioned to be of appropriate length and diameter is an option when there is infection of a previously placed graft and the patient is unable to undergo extra-anatomic revascularization for technical reasons. Sequelae from venous harvest have been surprisingly minimal and the reconstructions durable (125).
Figure 7: Supra-inguinal surgical options [modified according to the TASC II Guidelines (2)]:
- axillo-femoral by-pass (red bypass); Aorto-biiliac (dark blue bypass) or Aorto-bifemoral by-pass (black bypass); Femoro-femoral or cross-over by-pass (light blue by-pass)

3.2.2 Infrainguinal Disease

The guidelines made the following recommendations when surgery is performed for infrainguinal occlusive disease with a clear preference for the use of autogenous vein for the bypass graft (Figure 8) (3):

- Bypass to the above knee or below knee popliteal artery should use autogenous vein if possible.
- A distal bypass should originate at the most distal artery with continuous flow from above and without a greater than 20% stenosis. The tibial or pedal artery that can provide continuous and uncompromised flow to the foot should be the site of distal anastomosis.
Femorotibial bypasses should use autogenous vein, such as the ipsilateral greater saphenous vein or, if this is not available, other autogenous sources from the leg or arm.

When no other form of bypass with an autogenous vein is possible, both a composite sequential femoropopliteal-tibial bypass and bypass to an isolated popliteal artery segment with collateral outflow to the foot can be considered.

When no autogenous vein is truly unavailable and amputation is imminent, a prosthetic femorotibial bypass and possibly an adjunctive procedure, such as arteriovenous fistula or vein interposition or cuff, should be used.

When no autogenous vein is available, it is reasonable (a weaker recommendation) to use prosthetic material for bypasses to the below knee popliteal artery.

### 3.2.2.1 Femoropopliteal bypass —
Femoropopliteal bypass is indicated when arteriography reveals that the superficial femoral artery or proximal popliteal artery is occluded and that the patent popliteal artery has luminal continuity with any of its three terminal branches. Femoropopliteal bypass grafts are categorized as either above knee or below knee as determined by the location of the distal graft to artery anastomosis.

The use of ePTFE is less risky in the above knee position, and some consider it to be the technique of choice in this setting, citing studies demonstrating early patency rates similar to autologous vein grafting (126). The use of ePTFE has the additional theoretical advantage of preserving the saphenous veins for future coronary bypass or more distal peripheral revision.

These findings have led to the recommendation that a saphenous vein graft is preferred for above knee grafts. If a prosthetic bypass graft is used, the human umbilical vein should be considered before ePTFE. The argument to preserve saphenous veins for possible coronary artery grafting does not appear justified, and many vascular surgeons prefer the use of autologous vein graft in any position.

Despite the good outcome from autologous vein grafts, late occlusion due to progressive disease of arteries on either side of the bypass or deterioration of the graft itself is still a concern. Aspirin, with or without dipyridamole or anticoagulation has not been shown to improve limb salvage rates and have an increased the risk for hemorrhage (ie, intracerebral, gastrointestinal) (127-129).
Figure 8: Infra-inguinal surgical options [modified according to the TASC II Guidelines (2)]:
- Femoropopliteal by-pass (above or below the knee; black bypass);
- Femoro-tibial by-pass (tibial or peroneal; green bypass);
- Popliteo-popliteal by-pass (dotted black bypass)
The TASC II Guidelines recommend including all operated patients, independently if they have received a venous or a prosthetic bypass, in a surveillance program. This surveillance program should be aimed to detect as early as possible a bypass degeneration (e.g., stenosis), which may finally lead to an early reintervention, especially in those patients presenting with an impending bypass occlusion.

This program should include: - an interval history (i.e., new symptoms), a vascular examination (i.e., pulses palpation), an ABI measurement at rest, as well as a complete duplex scanning of the entire bypass, with special attention the the proximal and the distal anastomosis sites -. This follow up examinations should be performed immediately after the intervention and at regular intervals (e.g., every six months) for at least two years (2, 3)

3.2.2.2 Infrapopliteal bypass — An infrapopliteal bypass should be performed only in situations of lower extremity ischemia in which femoropopliteal bypass is not feasible or does not allow graft flow into patent runoff vessels.

The most important factor in choosing an outflow vessel for the distal anastomosis of an infrapopliteal bypass is the overall quality of the vessel. If two vessels of excellent quality are available, the preference probably should go to the vessel with the greatest degree of direct continuity with the foot. If no other factors are involved, the generally accepted order of preference for the infrapopliteal anastomosis is the posterior tibial artery, the anterior tibial artery, and the peroneal artery. The peroneal artery may be less desirable because it is deeper and more difficult to expose and because it is not directly continuous with the pedal arteries, and therefore thought by some to produce an inferior result in the setting of foot gangrene (130).
Table 3 summarizes the different bypass procedures with their associated operative mortality and 5 years patency rates.

<table>
<thead>
<tr>
<th>TYPE AND LOCALIZATION OF THE BYPASS</th>
<th>Peri-operative Mortality Rates</th>
<th>Expected Patency Rates</th>
</tr>
</thead>
<tbody>
<tr>
<td>Femoro-popliteal (AK) vein BP</td>
<td>Up to 6%</td>
<td>66% at 5 years</td>
</tr>
<tr>
<td>Femoro-popliteal (AK) prosthetic BP</td>
<td>Up to 6%</td>
<td>50% at 5 years</td>
</tr>
<tr>
<td>Femoro-popliteal (BK) vein BP</td>
<td>Up to 6%</td>
<td>66% at 5 years</td>
</tr>
<tr>
<td>Femoro-popliteal (BK) prosthetic BP</td>
<td>Up to 6%</td>
<td>33% at 5 years</td>
</tr>
<tr>
<td>Femoro-tibial vein BP</td>
<td>Up to 6%</td>
<td>75% at 5 years</td>
</tr>
<tr>
<td>Femoro-tibial prosthetic BP</td>
<td>Up to 6%</td>
<td>25% at 5 years</td>
</tr>
</tbody>
</table>

Table 3: Vascular surgical procedures and their respective outcomes: AK = above the knee; BK = below the knee [modified according to the TASC II and ACC/AHA Guidelines (2, 3)]
3.3 THE ENDOVASCULAR OPTIONS FOR PAD INTERVENTIONS

It is since more than thirty years that vascular specialists have tried to decrease the aggressiveness of surgical revascularization procedures, finally resulting in what is nowadays called the endovascular domain (131-133). Since several years, and especially thanks to the considerable technical improvement of material and techniques, the endovascular approach is nowadays proposed as the first revascularization procedure to attempt in many different clinical scenarios. Due to the variety and complexity of these different techniques, often a multidisciplinary approach involving all the different vascular specialists is required, in order to tailor the revascularization procedure to each single case.

In general the degree of aggressiveness should be less for claudicant patients, then for those presenting with acute or critical limb ischamias, where more complex, thus more risky, procedures may be attempted.

To facilitate the physician’s decision, especially concerning the endovascular vs. surgical procedures, in the year 2000 followed by an update in 2007, specific vascular guidelines were proposed by an international group of specialists: the TASC and the TASC II guidelines (TASC = Trans-Atlantic Inter-Society Consensus) (1, 2).

According to the 2007 TASC II guidelines, TASC II A-B-C lesions, either at iliac or femoral level, should be firstly attempted by an endovascular approach, while TASC II D lesions are probably better approached by a surgical intervention. However, it is only recently, that, thanks to technical improvements of material and operators’ skill, also TASC II lesions may be treated using an endovascular approach, obtaining a high degree of immediate technical success associated with a high patency rate at 2 years (134-136).
Figure 9 proposes a decisional algorithm for the treatment for claudicant patients: conservative vs. endovascular vs. surgery

3.3.1 Endovascular Techniques and Material

The endovascular approach has dramatically improved in the last several years. Thanks to important technical improvements in material, techniques and operators' skill, the endovascular approach may be consider in 2011, as the first revascularization approach to attempt in the vast majority of lesions' and patients' subsets.

The main advantages of an endovascular approach are the high rate of technical success (up to 90% also for more complex lesions (2, 134)) and a very low peri-procedural complication rate.
Accordingly, the estimated complication rate of an endovascular intervention may range from 0.5-4%, which is far below the up to 15% complication rate observed for surgery, especially considering the surgical peri-operative mortality incidence up to 2-3% (2).

The main drawback of the endovascular approaches still remains in 2011, the restenosis (2). Usually, the neo-intimal proliferation responsible for the restenosis formation is the result of a very complex inflammatory response to the balloon induced vascular trauma. The restenosis typically occurs in the first six months after the endovascular intervention and it is strictly related to the type of the treated vessel (muscular vs. elastic artery) as well as the size of the treated vessel, the presence of calcification, diabetes, etc.

Once assumed that at the iliac level, restenosis is no more a major concern, because of an acceptable restenosis rate of 5-15 % at 5 years (137, 138); at the infra-unguinal level the observed restenosis rates are much more prohibitive (139-141).

The superficial femoral artery is the longest artery of the body, it is fixed at two major flexion points (i.e. the hip and the knee). During movements (e.g. walking, stairs climbing, etc.), the SFA is confronted to several mechanical forces, as the flexion, the extension, the torsion and the longitudinal and lateral extrinsic compression (Figure 10). This very specific setting is probably the reason of the observed high incidence of restenosis at 1 year (up to 60%) (139, 141).
Several endovascular techniques with their specific dedicated material are now briefly listed:

3.3.1.1 Balloon Angioplasty:

Percutaneous Transluminal Angioplasty (PTA) using different kind of balloon catheters is the main stem of all endovascular interventions.

Even if stenting is more and more frequently used in case of femoral or especially iliac lesions, simple balloon angioplasty remains the most used approach when dealing with infra-poplitel lesions. Accordingly, stent compression or crushing in the calf, and the lack of robust evidence that stenting is superior to PTA remain and the lack of dedicated BTK stents (i.e. low profile, long stents with good radial force) are some concern for a widespread below the knee stenting approach (142, 143).
3.3.1.2 Stents:

Stent implantation during lower limb endovascular arterial interventions was initially only reserved as bailout indication in case of complication as a flow limiting dissection or an insufficient initial angiographic result (i.e. residual stenosis >50%) due to an important elastic recoil or an insufficient plaque expansion.

Concerning the iliac arteries, and more specifically in the common iliac arteries, since many years, primary intention stenting has become the first adopted strategy, because stent implantation at that level is associated with a very high technical success rate as well as a very high longterm patency rate (> 80% at 5 year) (137, 138). Conversely, of what observed in iliacs, the one year restenosis rate at femoral level has remained for many years exceedingly high and this despite an aggressive stenting approach (139, 141).

Balloon expandable, stainless steel stents are no longer used for femoropopliteal disease, because they have significant reocclusion and restenosis rates and do not appear to improve outcomes after intervention (144-148). Because, the composition of the stent may influence the rate of stent patency after femoropopliteal intervention, a lot of efforts were made from the industry to find the best stent composition to best adapt in this very specific femoropopliteal region.

It is only since 2002, that some improvements were made concerning the SFA stenting outcomes. Accordingly, the SIROCCO I-II studies (149, 150) were aimed to compare the efficacy and safety of new drug eluting stent (DES) dedicated for SFA lesions. The studies have randomized this new DES to a new nitinol bare metal stent (BMS). The restenosis rate at two years, was for the first time acceptable (i.e. up to 25%), but with surprise comparable between the two studied stents (DES = BMS in term of restenosis). The dissapointement concerning this DES “failure” was considerable, however, this new design nitinol BMS was embrassed with enthusiasm. This new combination of Nickel and Titanium = Nitinol has then become the reference for the conception of new stent design, leading to the performance of several randomized trials aimed to demonstrate the supriority of these new Nitinol BMS compared to standard balloon angioplasty. It is finally in 2006, that in the ABSOLUTE trial the stenting approach proved its superiority to PTA also in SFA lesions, and this especially in case of long and complex lesions (139, 151).

Several hypotheses were made concerning this first generation DES “failure”. The excessive distance between stent’s struts, especially if compared to that one present in coronary DES, has
probably led to a too weak and inhomogenous antiproliferative medication delivery. Furthermore, the too rapid drug delivery secondary to an inappropriate polymer-drug association was possibly also one reason of an insufficient antiproliferative effect.

Recently, two studies have again tried to reduce SFA restenosis with the use of a second generation DES. The first one (STRIDES study: long-release polymer everolimus eluting stent: Abbott Vascular [ClinicalTrials.gov Identifier: NCT00475566]), was again not able to significantly reduce the restenosis rate (152), while the second one (ZILVER PTX study: polymerfree paclitaxel eluting stent: Cook Medical [ClinicalTrials.gov Identifier: NCT00120406]) was this time very convincing in term of restenosis rate reduction (153). Accordingly, the ZILVER PTX trial has shown that the DES was superior to the similar version of the BMS in terms of primary patency, and this in all studied sub-group analysis. Despite the fact that the longterm follow-up of the ZILVER PTX study is so far not available, this very promising stent is already regularly used in many catheterization laboratories in Europe.

3.3.1.3 Drug coated balloons or drug eluting balloons:

After being studies first for coronary lesions (154), the drug eluting balloon (DEB) has also made its appearance in the peripheral interventions domains. The hypothesis that by administrating for a relatively short period (1-2 minutes) a high concentration of antiproliferative drug, especially paclitaxel, at the vessel wall during the balloon inflation has proved its safety and efficacy in two randomized clinical trials.

The THUNDER trial randomly assigned 154 patients with femoropopliteal stenoses to treatment with paclitaxel coated angioplasty balloons, uncoated balloons with paclitaxel dissolved in the contrast medium, or uncoated balloons with contrast solution containing no paclitaxel (155). The primary end point of mean late lumen loss after six months was significantly lower in the coated balloon group than either the paclitaxel solution or control groups (0.4 versus 2.2 and 1.7 mm, respectively). The coated balloon group also had a significantly lower rate of target lesion revascularization at six months (4 versus 29 and 37%). These positive results were maintained at two years.

The findings of the THUNDER trial were confirmed in the similarly designed FemPac trial and the non-yet published LEVANT-1 trial. Accordingly, in the FemPac trial 87 patients undergoing angioplasty of femoropopliteal lesions were randomly assigned to either uncoated or paclitaxel-coated
balloons catheters (156). The primary end point of late lumen loss at six month follow-up angiography was significantly less in the coated balloon group (0.5 versus 1.0 mm).

So far, a lot of enthusiasm is associated with this DEB technology, because it combines an easy to use technology (i.e. balloon angioplasty) with an efficacious way to prevent restenosis (i.e. antiproliferative local drug delivery). The fact that after having delivered the drug no foreign body (e.g. stent) remains in the vessel is particularly attractive especially when dealing with SFA lesion, where stent fractures may be observed (157). Presently several larger randomized trials, including patients presenting with SFA lesions, as well as patients presenting with critical limb ischemia secondary to below the knee lesions are underway (158), and very soon more data supporting this very promising technology will be at our disposal, in order to widespread this DEB technology to more patients and more lesions’ subsets.

3.3.2 Endovascular Revascularization Outcomes

In order to better categorize outcome data, the following terminology is used (159):

- A graft or a stent is considered to have primary patency if there has been uninterrupted patency without a procedure being necessary or performed to deal with disease progression in the adjacent native vessel, such as transluminal dilatation or proximal or distal extension to the graft (159).

- The term primary assisted patency is used when a graft or a stent is developing a restenosis or an incipient re-occlusion, but patency, even in the absence of symptoms has been restored with an endovascular (e.g. PTA or stenting) or a surgical (e.g. anastomosis revision) intervention.

- The term secondary patency is used if the graft or the stent has become occluded but patency has been restored with thrombectomy, thrombolysis, or transluminal angioplasty, or if there are problems with the graft itself or one of its anastomoses that requires revision or reconstruction.

Table 4 shows the 2-5 years patency rates observed after different types of revascularization procedures - endovascular (angioplasty vs. stent) as well as the patency rates observed according to the level of revascularization procedure – iliac, femoro-popliteal, infra-popliteal. Finally, Table 4
suggests that according to the initial clinical scenario (e.g. claudication vs. CLI), as well as according to the complexity (stenosis vs. occlusion) and the localization of the treated lesion (in-flow vs. out-flow vs. below the knee), the awaited patency rates are reduced, and this independently of which type of revascularization procedure is performed (2).

### Table 4: estimated primary patency rate at 2-5 years [modified according to Bonvini RF et al. (160)]

* These primary patency rates for the different endovascular techniques vary according to the clinical status of the patient (claudication vs. CLI) and the degree of the vascular obstruction (stenosis vs. occlusion) (2, 139).

** These primary patency rates are observed for relatively simple lesions (short stenosis or occlusions) and need to be confirmed in larger trials (155, 156, 161)

<table>
<thead>
<tr>
<th>Endovascular Treatments</th>
<th>Primary Patency rates (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Iliac angioplasty</td>
<td>70%</td>
</tr>
<tr>
<td>Iliac stenting</td>
<td>80%</td>
</tr>
<tr>
<td>Femoro-popliteal angioplasty</td>
<td>30-60%*</td>
</tr>
<tr>
<td>Femoro-popliteal angioplasty with DEB</td>
<td>70-80%**</td>
</tr>
<tr>
<td>Femoro-popliteal stenting</td>
<td>60-70%*</td>
</tr>
<tr>
<td>Femoro-popliteal stenting with DES</td>
<td>70-80%**</td>
</tr>
<tr>
<td>BTK angioplasty +/- stenting</td>
<td>30-60%*</td>
</tr>
<tr>
<td>BTK intervention with DEB or DES</td>
<td>50-80%**</td>
</tr>
</tbody>
</table>
3.3.3 New Tools for Complex Endovascular Interventions

In the last decade the arrival of new endovascular material and tools has allowed us to perform percutaneous interventions more safely (complication rate <4%) (2), and especially more efficaciously (technical success rate >90 %). These improvements have led to a high penetration of different types of endovascular interventions in the vascular community, which now proposed this minimally invasive approach for the vast majority of lesions and patients subsets (2).

Herewith, a short summary of different types of specific endovascular tools actually at disposal of every endovascular specialists.

3.3.3.1 Crossing devices:

The oldest and the more studied crossing device for endovascular interventions is the Excimer Laser™ (Spectranetic, Colorado Spring, CO, USA, Figure 11). The Excimer Laser™ has been associated with a good technical success rate when dealing with long femoro-popliteal occlusions as well as BTK occlusions (162). Because the Excimer Laser™ does not guarantee an intraluminal recanalization (i.e. subintimal passage still possible and relatively frequently observed), is expensive, requires a special training, and finally because after a laser recanalization the restenosis occurrence may be as up as after a conventional balloon recanalization, this tool should be reserved for very high volume tertiary centers or for scientific purposes.

Figure 11: Excimer Laser™ (Spectranetic, Colorado Spring, CO, USA) [Reproduced from Bonvini RF et al. (160)]

More recently other crossing devices have arrived on the market: the Frontrunner™ XP (Cordis, Miami, FL, USA, Figure 12A) (163) and the Crosser™ (FlowCardia, Inc., Sunnyvale, CA, USA, Figure 12B) (164). The Frontrunner™ XP uses a micro-dissector, which creates an intraluminal channel in the occluded vessel, which will finally be dilated and stented in a standard fashion. The Crosser™ uses a system of high frequency ultrasound vibrations which generates a mechanical impact on the
occlusion’s stump. This vibrational effect should allow a more comfortable intraluminal passage in the occlusion. Despite, these theoretical benefits, so far the clinical results are quite disappointing, with a subintimal passage rate still elevated (164). Accordingly, both systems should be reserved, for the moment, for research purposes or for very selected patients or interventions.

3.3.3.2 Reentry devices:

When the intraluminal recanalization, especially of a long SFA occlusion, is impossible especially because of extensive calcifications, a subintimal recanalization may be attempted. This subintimal technique, firstly described by Bolia et al. in 1990 (165, 166), may be challenged especially when the reentry in the true lumen, distally the occlusion, is difficult to obtain (167, 168). Accordingly, an important step forward in the subintimal recanalization technique, was the arrival of different reentry devices. These reentry devices were aimed to facilitate the reconnection between the subintimal with the distal intraluminal space, in order that after the entry and the reentry points, as well as the entire subintimal passage may be dilatated or stented in standard fashion. The first reentry catheter which has proved its safety and efficacy was the Outback™ catheter (Cordis, Miami, FL USA, Figure 13)
(167, 169), followed few years after by the Pioneer™ catheter (Medtronic, Santa Rosa, CA, USA, Figure 14) (170).

![Image](image1.png)

**Figure 13A:** subintimal recanalization technique;  
**13B:** Outback™ reentry catheter (Cordis, Miami, FL; USA) [Reproduced from Bonvini RF et al. (160)]

![Image](image2.png)

**Figure 14:** Pioneer™ US-guided reentry catheter (Medtronic, Santa Rosa, CA, USA)  
[Reproduced from Bonvini RF et al. (160)]

Thanks to these reentry devices, nowadays the subintimal recanalization has become one of the most adopted recanalization techniques, especially by dealing with long SFA occlusions, because the creation of a subintimal passage is usually more easily obtained than to remain intraluminal, especially in case of severe SFA calcifications. Accordingly, in case of reentry failure with standard techniques, these catheters allow a rapid and safe reentry in more than 90% of the cases (167, 169).

The Pioneer™ catheter, thanks to an integrated ultrasound piece, is more sophisticated and expensive. This ultrasound piece allows a direct visualization of the reentry zone, thus allowing an ultrasound guided puncture as close as possible to the reentry zone. Conversely, the Outback™
catheter may be used only under fluoroscopic guidance and thus is sensibly easier to use and less expensive. Efficacy of both system is similar, even if a direct comparison has never been performed, and both systems may be used, with caution, also at iliac or infra-popliteal level.

3.3.3.3 Debubking devices:

The rational for using a debubking device, especially in the femoro-popliteal regions, is that the femoral and the popliteal arteries are very frequently severely diseased with a huge amount of atherosclerosis on the arterials’ walls. Accordingly, it is not surprising that during balloon angioplasty of such a long and diseased segments, intimal wall dissections, important elastic recoils or lesions underexpansion may oftenly occur, render conventional balloon angioplasty at that level frequently unsatisfactory. Atherectomy devices are aimed to debulk as much as possible of atherosclerotic material from the arterial wall, in order to obtain a significant lumen gain without the balloon angioplasty associated barotrauma, thus finally reducing the risk of dissection or other adverse events (Figure 15).

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**Figure 15: showing the theoretical advantages of atherectomy compared to balloon angioplasty or stenting [courtesy of Prof. Zeller Th., Bad Krozingen, Germany]**
Atherectomy may be performed in several ways with different atherectomy devices. Following a short summary of the most used atherectomy devices and techniques:

*Directional atherectomy* using the Silverhawk™ device (ev3, Paris, France, *Figure 16*), *rotational atherectomy with aspiration* using the Pathway PV Atherectomy system™ (Pathway medical, Redmond, WA, USA, *Figure 17A-B*), *orbital atherectomy* using the Diamondback 360° Orbital Atherectomy device (Cardiovascular system, StPaul, MN, USA, *Figure 17C-D*) and finally the *high speed rotational atherectomy* using the Rotablator system™ (Boston Scientific, Natick, MA, USA, *Figure 17E-F*).

![Silverhawk™ device (ev3, Paris, France)](image)

*Figure 16: Silverhawk™ device (ev3, Paris, France), with the collected atheroma [reproduced from Bonvini RF et al. (160)]*
So far the Silverhawk™ device is one of the most used atherectomy devices in high volume centers because efficacious by removing plaques (Figure 18) and relatively user friendly. Accordingly, it is considered by several experts as the first-line treatment in case of severly and diffuse SFA disease, for small size SFA and for all similar situations in which an extensive stenting strategy should be avoided and where a simple balloon angioplasty attitude would be associated with a prohibitive restenosis rate. By using the Silverhawk™ device, also in diffuse SFA lesions, the bailout stenting may be reduced to <10%, with a very promising restenosis rate especially for the « de-novo » lesions in diabetic patients (171, 172). The combination of an atherectomy device followed by a DEB angioplasty seems very attractive, and it is actually under investigation.
Figure 18 showing removal of different plaque material at the femoro-popliteal level

[courtesy of Prof. Zeller Th., Bad Krozingen, Germany]
3.4 PATIENTS SELECTION

The problem of claudication is almost entirely limited to patients with atherosclerotic disease who have symptoms related to the lower extremities. Claudication can also occur in large vessel vasculitides, such as Takayasu and giant cell arteritis, which typically involves the arms. The role of percutaneous intervention has been less well studied in these disorders and there is the belief that angioplasty in case of arterial narrowing secondary to an inflammatory disorder is associated with an increased risk of early and late recurrences.

3.4.1 Role of Revascularization for Claudication

Because of the variability of individual limb ischemic symptoms and variable impact of these symptoms on quality of life, patients should be selected for revascularization on the basis of the severity of their symptoms; a significant disability as assessed by the patient; failure of medical therapies; lack of significant comorbid conditions; vascular anatomy suitable for the planned revascularization; and a favorable risk/benefit ratio.

Patients selected for possible revascularization may then undergo additional imaging studies as required, such as duplex ultrasound, MRA or CTA, and/or catheter angiography, to determine whether their arterial anatomy is suitable for percutaneous or surgical revascularization.

3.4.2 Indications for revascularization

The ACC/AHA and the TASC II guidelines suggest that the following issues need to be addressed when considering either percutaneous or surgical revascularization in patients with intermittent claudication (2, 3):

- The patient has not had or is not predicted to have an adequate response to exercise rehabilitation and pharmacologic therapy,
- The patient is significantly disabled by claudication, resulting in an inability to perform normal work or other activities that are important to the patient. This criterion reflects the variability among patients of the symptoms of claudication and of the impact of these symptoms on the quality of life. Of note, before the final decision of a conservative or a revascularization attitude, one should remember that, there may be substantial differences between patient and physician assessments of the quality of life impairment caused by the claudication (173, 174).
• The patient is able to benefit from an improvement in claudication (i.e., exercise is not limited by another cause, such as angina, heart failure, chronic obstructive pulmonary disease, or orthopedic problems).
• The projected natural history and prognosis of the patient.
• The characteristics of the lesion permit appropriate intervention at low risk with a high likelihood of initial and long-term success.

3.4.3 Endovascular Treatment for Claudication

Endovascular techniques to treat peripheral arterial occlusive disease include PTA with balloon dilatation, stents, atherectomy, laser, cutting balloons, thermal angioplasty.

Endovascular (and surgical) treatments can be selected on the basis of morphological features that stratify lower extremity arterial anatomy into subgroups: - iliac lesions; - femoro-popliteal lesions; below the knee (i.e. infrapopliteal) lesions.

Outcomes of PTA and stents depend on anatomic and clinical factors. Durability of patency after PTA is greatest for lesions in the common iliac artery and decreases distally. Durability also decreases with increasing length of the stenosis/occlusion, multiple and diffuse lesions, poor quality runoff, diabetes, renal failure, smoking, and CLI (175-179).

Percutaneous transluminal angioplasty of vein bypass graft stenoses has also been reported, with 1- to 3-year patency of the treated site of approximately 60% (180, 181), comparable to that for surgical repair (180). Percutaneous transluminal angioplasty of multiple vein graft stenoses has a much lower 3-year patency suggesting that patient’s selection is the key in obtaining satisfactory outcomes (182).

Selection of lesions for endovascular versus conservative therapy is not well defined. An ilio-femoral stenosis is generally considered hemodynamically significant if the luminal stenosis on angiography is ≥70% (3). Stenoses of 50% to 70% diameter by angiography may or may not be hemodynamically significant, and intravascular pressure measurements have been recommended to determine whether these lesions are significant and to predict patient improvement if the lesion is treated (183). Unfortunately, there is no consensus on a diagnostic transstenotic pressure criteria or on methods to measure these pressures (184). The most used criterion utilizes a mean gradient – as measured with a 4F or 5F diagnostic catheter – of 10 mm Hg before or of 15 mm Hg after vasodilators (183, 185). Of note, the summation of multiple intermediate lesions (i.e. 50-70% of stenosis) may
cause an even more important pressure gradient than that observed in case of an isolated more severe stenosis (i.e. 90%).

3.4.4 Cost-effectiveness of Endovascular Treatments for Claudication

In order to remain cost-effective, especially by treating claudicant patients, the proposed treatment should be efficacious, durable, relatively inexpensive and associated to a low rate of procedural related complications. For all these reasons, the endovascular approach by claudicant patients, which most of the time may be performed in an ambulatory setting, seems very attractive.

Accordingly, a cost-effectiveness analysis compared PTA and bypass surgery with exercise therapy for treatment of claudication. The cost-effectiveness of PTA was $38'000 per quality-adjusted life year, which is in the range of other accepted procedures, while bypass surgery cost-effectiveness was $311'000 per quality-adjusted life-year (186).

Effectiveness is strongly affected by the severity of patient symptoms before revascularization and severity of disease. For femoral-popliteal disease, PTA was more cost-effective than surgical bypass for the treatment of claudication (stenosis and occlusion) and for treatment of CLI (stenosis only) while surgical bypass was more cost-effective for treatment of CLI for long SFA occlusions (187).

Selection of patients for femoral-popliteal artery PTA or stenting has been assessed in several randomized trials and meta-analysis of case series. The meta-analysis concluded that only for treatment of occlusions in patients with CLI was there a suggestion that stents were more durable than PTA alone (139). For all these reasons, a primary balloon angioplasty approach followed by a bailout stenting only in case of unsatisfactory results (i.e. extensive dissection, residual stenosis >50%, important elastic recoil, etc) seems reasonable for a first intervention for claudicant patients presenting with a femoro-popliteal disease (141).

Other techniques of endovascular revascularization have shown so far no advantages over PTA/stents (188-191), with only the almost abandoned endovascular brachytherapy which has shown to reduce restenosis rates of PTA and stenting in the femoral-popliteal arteries (192, 193), at the price of an increased risk of late acute thrombotic occlusions, especially in the presence of a stent (194).
3.5 THE TASC GUIDELINES

On the basis of the above-reported outcomes of PTA/stenting and surgery, consensus recommendations for selection of patients for endovascular therapy in the management of lower-limb peripheral arterial occlusion were made by an international panel (2, 3).

Selection of patients for endovascular therapy should be based on TASC anatomic classifications, as well as severity of patient symptoms, comorbid conditions, and risks of surgical revascularization.

To facilitate the physician decision, especially concerning the endovascular vs. surgical procedures, in the year 2000 followed by an update in 2007, specific vascular guidelines were proposed by an international group of specialists: the TASC and the TASC II guidelines (TASC = Trans-Atlantic Inter-Society Consensus) (1, 2).

According to the 2007 TASC II guidelines, TASC II A-B-C lesions, either at iliac or femoral level, should be firstly attempted by an endovascular approach, while TASC II D lesions are probably better approached by a surgical intervention. Accordingly, it is only recently, that, thanks to technical improvements of material and operators’ skill, also TASC II D lesions may be treated using an endovascular approach, obtaining a high degree of immediate technical success associated with a high patency rate at 2 years (134-136).

Figure 19 and 20 summarize the TASC II recommendations for aortoiliac and femoropopliteal lesions. Of note, infrapopliteal lesions are not well represented in these TASC II guidelines, suggesting that each case and lesion subsets should be discussed on a “case-by-case” basis.
The TASC II Guidelines:

Type A lesions

- Unilateral or bilateral stenoses of CIA
- Unilateral or bilateral single short (≤3 cm) stenosis of EIA

Type B lesions:

- Short (≤3 cm) stenosis of infrarenal aorta
- Unilateral CIA occlusion
- Single or multiple stenosis totaling 3–10 cm involving the EIA not extending into the CFA
- Unilateral EIA occlusion not involving the origins of internal iliac or CFA

Type C lesions

- Bilateral CIA occlusions
- Bilateral EIA stenoses 3–10 cm long not extending into the CFA
- Unilateral EIA stenosis extending into the CFA
- Unilateral EIA occlusion that involves the origins of internal iliac and/or CFA
- Heavily calcified unilateral EIA occlusion with or without involvement of origins of internal iliac and/or CFA

Type D lesions

- Infrarenal aortoiliac occlusion
- Diffuse disease involving the aorta and both iliac arteries requiring treatment
- Diffuse multiple stenoses involving the unilateral CIA, EIA, and CFA
- Unilateral occlusions of both CIA and EIA
- Bilateral occlusions of EIA
- Iliac stenoses in patients with AAA requiring treatment and not amenable to endograft placement or other lesions requiring open aortic or iliac surgery

Figure 19: TASC II recommendations concerning aortoiliac occlusive diseases [reproduced from the TASC II Guidelines (2)]
Type A lesions
- Single stenosis ≤10 cm in length
- Single occlusion ≤5 cm in length

Type B lesions:
- Multiple lesions (stenoses or occlusions), each ≤5 cm
- Single stenosis or occlusion ≤15 cm not involving the infrageniculate popliteal artery
- Single or multiple lesions in the absence of continuous tibial vessels to improve inflow for a distal bypass
- Heavily calcified occlusion ≤5 cm in length
- Single popliteal stenosis

Type C lesions
- Multiple stenoses or occlusions totaling >15 cm with or without heavy calcification
- Recurrent stenoses or occlusions that need treatment after two endovascular interventions

Type D lesions
- Chronic total occlusions of CFA or SFA (>20 cm, involving the popliteal artery)
- Chronic total occlusion of popliteal artery and proximal trifurcation vessels

Figure 20: TASC II recommendations concerning femoropopliteal - BTK occlusive diseases
[reproduced from the TASC II Guidelines (2)]
4.0 ENDOVASCULAR PROCEDURES ACCORDING TO THE LOCALIZATION

Balloon angioplasty, with or without stenting, is useful for symptomatic relief in many patients with peripheral arterial disease. Percutaneous transluminal angioplasty (PTA), results in a "controlled" dissection of the arterial media (195). Advancements in catheter, guidewire, and balloon design, and the development of intravascular stents have resulted in a dramatic increase in the number of percutaneous procedures performed worldwide.

Support for this change in management of claudicant patients came at the beginning of the nineties from an initial randomized trial that showed no significant difference in outcome after a median of four years between PTA and bypass surgery for iliac or femoropopliteal disease and for claudication or rest ischemia (196). However, the long-term success of PTA depends upon the site and length of the lesion. Lesions which display unfavorable anatomy and which might be better treated surgically have one or more of the following features:

- Long segments (>20 cm)
- Multifocal stenoses
- Long segment occlusions (>20 cm)
- Eccentric, severely calcified stenoses

PTA has been traditionally limited to the treatment of focal, short segment stenoses or occlusions. However, with advancements in technology, PTA is now routinely applied to more extensively diseased segments to attempt limb salvage before a distal surgical bypass; it can also be used in patients who are poor surgical candidates according to comorbidities or quality of the distal run-off.

Since patient symptoms and outcomes are closely related to the anatomic location of disease, each segment of the lower extremity circulation will be reviewed separately.
4.0.1 Lower Limb Arterial Anatomy

Figure 21 shows the typical vessel anatomy of the lower limbs. Several anatomical variants may be relatively frequently observed. These variants include most frequently the common femoral artery bifurcation (e.g. profunda femoral artery arising directly from the mid-SFA) and the distal popliteal bifurcation (e.g. anterior or posterior tibial arteries arising directly from the mid-segment of the popliteal artery). Indeed, operators have to be aware of these anatomical variants in order to immediately recognize them, to correctly understand their anomalous trajec, finally allowing to safely continue the scheduled revascularization procedure.

![Arterial tree of the lower limb](chart)

**Figure 21**: arterial tree of the lower limb [courtesy of Prof. Zeller Th., Bad Krozingen, Germany]
4.1 AORTOILIAC OCCLUSIVE DISEASE

The iliac vessels originate from the distal abdominal aorta (Figure 22). The common iliac artery (CIA) subsequently divides into the internal iliac artery (IIA) supplying the pelvic organs, and the external iliac artery (EIA), which continues to become CFA at the level of the inguinal ligament. The diameters of the CIA and the EIA range from 8 to 10 mm, and from 6 to 8 mm, respectively. Due to abundant collateral circulation through the inferior mesenteric artery, lumbar vessels, and the IIA, limb-threatening ischemia is rare, even in the presence of total occlusion of distal abdominal aorta as long as there is no associated severe femoro-popliteal or tibial disease.

![Figure 22: Aorto-iliac bifurcation [reproduced from Bonvini RF et al. (108)]](image)

Three distinct patterns of atherosclerotic involvement of the infrarenal aorta and the iliac vessels have been described (Figure 23) (197). Type I refers to exclusive involvement of the distal abdominal aorta and the CIA, is present in about 5-10% of patients with PAD, and is more frequently encountered among women. Type II involves the infrarenal aorta, CIA and EIA, and may extend into the CFA; this pattern may be observed in 35% of patients with PAD. Type III is the most common pattern, and involves the infrarenal aorta, iliac, femoral, and popliteal arteries as well as the infra-popliteal circulation.
4.1.1 Patient Selection for Aortoiliac Interventions

Patients with aortoiliac occlusive disease present most frequently with lifestyle limiting claudication. Whereas calf pain on exertion is the leading symptom in femoropopliteal arterial disease, patients with aortoiliac involvement may have less characteristic symptoms such as ambulatory back, buttock, hip, and thigh pain, in addition to calf pain. These conditions are frequently misinterpreted as representing pathology of the lower back or hip, delaying diagnosis for many years. Since the chronic progressive nature of the disease allows for the development of a robust collateral circulation, associated critical limb ischemia is rare provided the femoropopliteal and tibial vessels are patent. This is true even in the presence of a distal aortic occlusion (Leriche Syndrome).

The most important part of the physical exam in a patient with suspected iliac disease includes an assessment of the CFA pulses. An absent CFA pulse usually indicates either an occlusion of the ipsilateral iliac or CFA. The routine diagnostic work-up of patients with suspected aorto-iliac includes a
hemodynamic evaluation including ABI and exercise treadmill testing. The typical hemodynamic findings in patients with iliac disease include a decreased ABI. Exercise treadmill testing is particularly useful in patients with typical claudication symptoms suggestive of iliac disease (e.g., buttock claudication), but with a normal resting hemodynamic assessment.

Duplex ultrasound imaging is helpful for patients in which adequate visualization of the iliac arteries is possible. In cases of sub-optimal visualization of the pelvic region, assessment of the Doppler flow analysis in the CFA may offer useful information. The presence of a physiologic triphasic waveform in the CFA makes a hemodynamically relevant iliac artery stenosis unlikely.

Anatomic assessment of the aortoiliac vessels with CTA or MRA is highly effective. In addition to having high rates of sensitivity and specificity for the diagnosis of disease, these studies are invaluable in providing information to help guide percutaneous revascularization, if indicated.

Appropriate patient selection, taking into consideration the clinical status of the patient, the location, morphology and physiological significance of the aortoiliac lesion, as well as the operator’s experience, are key factors in determining the appropriateness of endovascular intervention.

According to the TASC II document, for simple lesions (TASC II A-B lesions), endovascular treatment is the therapy of choice and for very complex disease (TASC II D lesions) surgery is recommended. There is a lack of consensus regarding TASC II C lesions. For this lesion subset, the decision should be made on a case-by-case basis, depending on the clinical presentation, patient comorbidities, the lesion morphology, and operator experience (2).

Despite these general recommendations, the lack of randomized data comparing surgical versus endovascular revascularization and the continuous evolution in revascularization technique and equipment have resulted in marked variation in treatment strategies across institutions. In experienced centers, it is common to adopt an endovascular first approach to even complex aortoiliac disease, and to refer to surgery only those patients who either this endovascular approach fails or those who cannot be approached using standard endovascular techniques (e.g., complex aneurismal disease, significant CFA disease) (134, 198, 199).

4.1.2 Percutaneous vs. surgical approach for aortoiliac lesions

No study has randomized patients with exclusively aortoiliac obstructive disease to surgery versus endovascular intervention. Whereas there is general agreement that simple lesions should be
treated percutaneously, it remains source of debate what is the best approach for more complex disease (TASC II C/D lesions) (200).

To answer this debate, Sixt et al. have recently retrospectively compared the acute and long-term outcomes of endovascular therapy for TASC II A/B lesions versus TASC II C/D lesions in 375 patients with symptomatic aortoiliac disease (134). TASC II A/B, C and D lesions were present in 59%, 26%, and 15% of cases, respectively. Acute treatment success — defined as residual stenosis < 30% — was achieved in all TASC II A lesions, in 96% of TASC II B lesions, in 93% of TASC II C lesions, and in all TASC II D lesions. The 1-year primary patency rate was 86% for the entire study cohort with no differences among TASC classes (134).

Interestingly, in the TASC II A/B and C/D groups the 5-year event free survival was comparable (70% vs. 57%; p=NS). The clinical outcome, as measured by Rutherford stage and ABI, improved significantly in all TASC subgroups after successful intervention and was maintained up to 1 year. The placement of one or more stents during the procedure was identified as independent protective factor towards the development of restenosis (HR 0.51, P=0.008), finally suggesting that, in experienced hands, endovascular therapy of aortoiliac lesions can be successfully performed and is associated with favourable long-term outcomes across the whole spectrum of TASC II lesions.

Accordingly, in case of an isolated aortoiliac disease, it may be reasonable to attempt a percutaneous treatment first, as long as the lesion appears amenable and the operator has the necessary expertise, and to refer the patient to vascular surgery in case the endovascular approach has failed (134, 198, 199).

4.1.3 Angioplasty vs. Stenting for aortoiliac interventions

Endovascular interventions in the iliac territory are associated with high technical success rate (>90%), low periprocedural complication rate (<4%), and a favourable long-term primary patency rate (>80%) (201).

Angioplasty: PTA of an uncomplicated iliac stenosis has an initial technical success rate of approximately 90% (175). Long-term patency is directly influenced by the extent of disease. A commonly quoted five-year patency rate is 70% (195).

Stenting: Intravascular stents can be employed, usually for a suboptimal angioplasty result (e.g., residual stenosis >30%, residual gradient > 10mmHg, or significant dissection) (202). Although, initially iliac lesions were treated with a balloon angioplasty approach and stenting was reserved as
bailout indications (138, 203), some authors advocate using stents primarily when there is an iliac occlusion, an eccentric and calcified lesion or when the disease involves a long segment (204, 205).

A meta-analysis published in 1997 summarized the results of endovascular interventions for aortoiliac occlusive disease stratified for stent use (206). This analysis included six angioplasty studies enrolling a total of 1300 patients and eight stent series for a total of 816 patients. No difference was observed in terms of immediate technical success between PTA or stenting (91% and 96%, respectively). Overall, the systemic complications rate was 1%, the local complication rate 9%, and the rate of major complications necessitating treatment was 4%. The mean post-procedural ABI was significantly greater in the stent group compared with the PTA group (0.87 and 0.76, respectively). Indeed, most of the benefit of stenting was detected in patients presenting with CLI or iliac total occlusions (206).

In addition, later studies have shown that PTA alone is frequently unable to deliver an optimal hemodynamic result and that stenting may be necessary in up to 40% of patients (138) and that, stent placement during the iliac procedure was found to be an independent protective factor towards the development of restenosis (134).

Finally, the benefit of a primary stenting approach in iliac arteries has been definitively established in 2002-04, where several European and US series have confirmed the feasibility, safety and long term efficacy of stents in the iliac region (207-209).

For these reasons, the ACC/AHA as well as the TASC II guidelines recommend stenting in primary intention in common and external iliac arteries as class IB and class IC indication, respectively (2, 3).

The value of balloon pre-dilatation prior to planned stenting in aortoiliac interventions remains controversial. While some investigators routinely perform balloon pre-dilatation, other frequently proceed to direct stenting. Pre-dilatation with a slightly undersized balloon may be particularly helpful in ostial or severely calcified lesions, as it may facilitate stent placement and expansion. In addition, balloon inflation may convey important information for proper stent choice, such as lesion length, vessel size, and lesion characteristics.

A theoretical advantage of direct stenting, although not firmly demonstrated, is the reduction of the incidence of dissection and distal embolization. This observation may be particularly important in case of chronic total iliac occlusions, where it is difficult to predict the amount of organized thrombus
present at the occlusion site. In those cases, angioplasty alone with balloon size matching the vessel size and inflated at nominal pressure may be associated with a distal embolization risk of as high as 24% (210). Therefore, we recommend direct stenting whenever feasible in chronic total occlusions, followed by an adequate post-dilatation in order ensure adequate apposition of the stent. This strategy has been shown to be associated with distal embolization in as low as 1% of cases following recanalization of chronic iliac occlusions (211).

4.1.4 Different Stent Types

There are several different stent types and models. Stent may differ in the metallic composition of the struts (e.g. stainless steel, nitinol, cobalt-chromium), the geometric configuration of the struts (e.g. open cell vs. closed cell design), but most importantly, to the delivery system of the stent (e.g. balloon-expandable vs. self-expanding). Finally, several small differences may also be observed according to the company manufacturing the stent (e.g. Cordis, Abbott, Bard, Cook, ev3, Medtronic/Invatec, etc.). Herewith, a short summary of the main differences of several stent models

4.1.4.1 Balloon-expandable stents: (Figure 24):

The slotted tube stainless steel Palmaz stent is the prototype for balloon-expandable stents. These devices have several advantages in the aortoiliac circulation compared with self-expanding stents. Their high radial force makes them suitable for heavily calcified lesions. Minimal foreshortening at deployment and good visibility allow for precise placement in the treatment of ostial lesions. Finally, balloon-expandable stents may be further expanded (typically by 1-2mm) after initial deployment by using larger balloons until the desired diameter is achieved.

Currently, the vast majority of stents are pre-mounted on a balloon and stent flexibility has improved, allowing for stent delivery using the crossover technique. One of the potential disadvantages of these devices in the iliac circulation is their propensity to create edge dissections, in particular in heavily calcified vessels or if the stent diameter is oversized. Since balloon-expandable stents are not elastic, they may crush in the presence of extensive compressive forces. Therefore, these devices should not be placed in the common femoral artery and should also be avoided in the distal part of the EIA, where significant conformational changes may occur. Furthermore, several of currently available peripheral balloon-expandable stents are still made of stainless steel, thus causing significant artifacts (i.e., signal loss) on MRA.
4.1.4.2 Self-expanding stents: (Figure 25):

The most distinguishing features of self-expanding stents are their elasticity and flexibility. These devices expand to their nominal diameter when released from a constrained state within the delivery system. Typically, a slightly oversized stent (i.e. 1-2mm) is chosen to allow for optimal vessel wall apposition. The flexibility facilitates stent delivery using the crossover technique and allows for excellent trackability and conformability in tortuous iliac vessels. After stent release, post-dilatation is usually performed to achieve good stent apposition to the vessel wall. Disadvantages of self-expanding stents include suboptimal radial strength and varying degrees of foreshortening at the time deployment. Therefore, this stent type is less suitable for the treatment of ostial lesions. Self-expanding stents should be considered for the treatment of non-ostial lesions of the CIA and all EIA lesions.

While the prototype of this stent class (Wallstent) is made of stainless steel, newer generation devices (e.g., SMART [Cordis], Absolute [Abbott]) are composed of nitinol, an alloy of nickel and titanium. Compared with the stainless steel counterparts, nitinol stents allows for increased radial strength and minimal foreshortening at deployment. The radial strength of nitinol stents has further increased in third generation devices (e.g., Supera Stent [IDev Tech., Texas, USA]), allowing for optimal stent expansion also in severely calcified lesions. In addition, the superior conformability is important in vascular segments with abrupt changes in vessel diameter, as might be encountered at
the transition from the common and external iliac arteries. A further advantage of nitinol over stainless steel stents is their magnetic resonance compatibility, achieved however at the cost of a reduced x-ray visibility.

To our knowledge, only one randomized head-to-head comparison between different self-expanding stents in the iliac circulation has been performed. Between 1998 and 2001, the CRISP (Cordis Randomized Iliac Stent Project) trial randomized a total of 203 patients with symptomatic iliac disease and suboptimal results following angioplasty to treatment using a nitinol stent (SMART) or a stainless steel stent (Wallstent) (137). Acute procedural success was significantly higher with the nitinol stent compared with the stainless steel stent (98% versus 87%, respectively), however, the primary vessel patency at 12 months was comparable (95% and 91%, respectively).

Figure 25: self-expanding stent (Zilver PTX™, Cook Medical) [reproduced from the Cook Medical’s website]

4.1.4.3 Covered stents: (Figure 26-27):

Covered stents are composite devices consisting of a metallic skeleton covered with synthetic graft material (e.g. Dacron, ePTFE). Because of the bulky graft material, these devices require larger delivery systems. They are currently not FDA approved for iliac occlusive disease. Nevertheless, covered stents have been used in this vascular bed, mainly for the treatment of aneurysms but also for bailout of iatrogenic iliac ruptures or arteriovenous fistulas. Isolated aneurysm of the iliac arteries are relatively uncommon, accounting only for 2% to 7% of all intra-abdominal aneurysms (212).

The most frequently used covered stents in the iliac circulation include the self-expanding Wallgraft (Boston Scientific), the Viabahn (Gore) and the Fluency (Bard) stents, and the balloon-expandable iCAST (Atrium Medical, Hudson, NH, USA) stent. The self-expanding covered stents are
more flexible than the iCAST stent, but require larger caliber access sheaths for delivery. This can be particularly problematic when treating iliac perforations, where the clinical situation may not permit time to change access sheaths.

The iCAST balloon-expandable stent consists of a 316L stainless steel stent that is encapsulated with ePTFE such that the stainless steel is not exposed to the luminal wall. Although this stent is very stiff, it has the advantage over self-expanding covered stents that stents up to 10mm in diameter may be delivered through a 7Fr sheath. This stent is being used increasingly for the treatment of occlusive iliac disease, and preliminary data suggests that restenosis rates with this stent may be lower than with uncovered balloon-expandable stents.

![Figure 26: balloon-expandable covered-stent (iCAST™, Atrium)](image1)

Figure 26: balloon-expandable covered-stent (iCAST™, Atrium) [reproduced from the Atrium Medical’s website]

![Figure 27: self-expanding covered-stent (Viabahn™, Gore Medical)](image2)

Figure 27: self-expanding covered-stent (Viabahn™, Gore Medical) [reproduced from the Gore Medical’s website]
4.1.5 Technical Features according to the Specific Lesions Localization

In the current era, the interventional treatment of stenoses in the aortoiliac territory is usually straightforward for appropriately trained endovascular specialists, with a procedural success approaching 100%. These stenoses are easily crossed using 0.035" wires and treated using 0.035" balloon and stent systems. Although compelling data supporting stenting in all cases is lacking, most operators have adopted the practice of stenting all iliac lesions because of the predictability of the procedural result achieved with iliac stenting and the associated good long-term outcomes. The major considerations in the interventional strategy in treating stenotic disease of the aortoiliac territory relates to the location of the disease.

4.1.5.1 Distal abdominal aorta stenosis (Figure 28):

Localized stenosis of the infrarenal abdominal aorta is relatively infrequent and occurs predominantly in young and heavy smoker women (213). Currently, PTA ± stenting has become the treatment of choice for short abdominal aortic stenosis in the absence of significant iliac disease. Failures of angioplasty may be the result of elastic recoil, obstructive intimal dissection, or late restenosis. Technical success with angioplasty ± stenting may be achieved in up to 80% of the cases with a primary 3 years clinical and hemodynamic patency of 85% and 79% respectively (214) (215).

Although no prospective study has addressed routine versus provisional stenting in the distal aorta, primary stenting has been advocated for the treatment of complex lesions (e.g., irregular, eccentric, ulcerated, or calcified) and occlusions. Covering such lesions with a stent before balloon dilatation may minimize the risk of distal embolization by trapping the atheroma behind the stent struts and the vessel wall and may reduce the risk of vessel rupture by more evenly distributing the dilating forces against the arterial wall. It remains source of debate whether balloon expandable (e.g., Palmaz [Cordis]) or self-expandable stents (e.g., Wallstent [Boston Scientific], Smart [Cordis]) are the device of choice for the distal aorta. The advantages of balloon expandable stents include a more accurate positioning and the achievement of larger diameters. Self-expanding stents require smaller sheaths for access, may achieve further gradual expansion because of intrinsic radial force, thus allowing the use of smaller balloons thus minimizing the risk of acute vessel trauma (215).

Access is usually gained using single retrograde CFA approach. On occasion a bilateral retrograde CFA access may be used if balloon dilatation or stent expansion is performed with double balloon technique. The stenosis of the distal aorta is crossed with a 0.035" steerable guidewire, either
non-hydrophilic (e.g., Magic Torque [Boston Scientific]) or hydrophilic (e.g., angled Glide Wire [Terumo]), alone or in combination with an angled diagnostic catheter (e.g., angled Glide Catheter [Terumo], or Tempo [Cordis]). If a balloon expandable stent is chosen, the Palmaz XL [Cordis], which can be crimped on a balloon (e.g., XXL [Boston Scientific] with diameters ranging between 12 and 18 mm or MAXI LD [Cordis] with diameters ranging between 14 and 25 mm) is one of the most used ones. The sheath size required to deliver these devices ranges from 8 Fr to 12 Fr. Since large aortic balloons with diameters between 20 and 25 mm may allow only for low pressure inflations (i.e., 2-4 atmospheres), post-inflation using 2 balloons (e.g., 8-12 mm in diameter) should be performed to achieve optimal stent expansion in this location. For the purpose of double-balloon inflation (Figure 29), the contralateral CFA is accessed and the aortic lesion is crossed with the same equipment as described above.

Figure 29: single balloon and double balloon inflation techniques [reproduced from Bonvini RF et al. (108)]

Conventional self-expanding stents reach lower maximal expansion (e.g., 16 mm for the Easy Wallstent [Boston Scientific] or 14 mm for the Large SMART [Cordis]) and always require a post-inflation. Self-expanding stent should be sized 1-2 mm larger than the vessel diameter. However, using the 14 mm SMART stent with a post-dilatation with a 12mm balloon (e.g., PowerFlex P3, [Cordis]), the entire procedure can be safely performed through a single 7 Fr introducer sheath.
Figure 28: Distal abdominal aorta (Ao) stenosis treated with a self-expanding stent placed before the CIA origins and post-inflated using a single balloon technique [reproduced from Bonvini RF et al. (108)]

4.1.5.2 Distal abdominal aorta occlusion (Figure 30):

The Leriche syndrome refers to a total occlusion of the abdominal aorta, most of the time located in the infra-renal region. Usually, patients present life-limiting claudication because disease progression is slow allowing for the development of collateral circulation. However, in case of an acute occlusion, patients may present with bilateral CLI. Surgery is the treatment of choice for both acute and chronic Leriche syndrome. However, in dedicated centers a percutaneous attempt may be envisioned, especially in patients at high risk for surgery (216). Percutaneous recanalization normally consists of a brachial approach for the intraluminal recanalization associated to a femoral approach for the large-caliber stent placement.
Figure 30: Distal abdominal aorta occlusion (= Leriche syndrome: arrow) treated with an aortic stenting and a bilateral kissing iliac stenting (Ao= aorta, LA= lumbar artery, IMA= inferior mesenteric artery) [reproduced from Bonvini RF et al. (108)]

4.1.5.3 Ostial common iliac artery and abdominal aorta bifurcation stenosis (Figure 31):

PTA and stents have also been safely used for stenosis involving the aortic bifurcation. Because balloon dilation of the CIA ostium can displace the plaque across the aortic bifurcation and either worsen the contralateral stenosis or induce embolization of debris down the contralateral iliac artery, some authors suggest to favorize the kissing balloons or kissing stents technique in order to obtain an excellent immediate result, diminishing the risk of local complications (e.g., contralateral plaque shift or distal embolization), finally associating with an acceptable long-term patency rate (217).

Several series on kissing stenting for the reconstruction of the aortoiliac bifurcation have been published. The documented technical success may be up to 100%, the reported complication rates are low and most of the time conservatively or percutaneously managed and the 2 years patency
rates may be up to 92% with an amputation or lifestyle-limiting claudication-free survival rates of 100% and 92% respectively (218-220).

Ostial lesions of the CIA are best approached using an ipsilateral retrograde CFA access because an optimal stent placement using the crossover approach may result challenging. On a broader perspective, retrograde CFA access should be considered the standard approach for aortoiliac percutaneous revascularization, leading to success in >90% of iliac stenotic lesions.

Reconstruction of the aortic bifurcation is usually performed with kissing angioplasty/stenting technique using a bilateral retrograde femoral access. Simultaneous balloon inflation at the level of the aortic bifurcation is aimed to prevent plaque shift in patients with severe bilateral ostial iliac disease and sometimes also in patients with unilateral ostial lesion. Frequently, the procedure is followed by kissing stenting, which may be performed with balloon expandable stents, which are more easily positioned than self-expanding stents and have greater radial strength. To this purpose, a 6Fr or 7Fr 25-30 cm (e.g., Brite Tip [Cordis], Flexor [Cook]) sheath is introduced in a retrograde manner bilaterally. Kissing balloon angioplasty and stenting may be performed over a 0.018” or 0.035” wire.

In order to prevent plaque protrusion at the level of the bifurcation, stents should protrude slightly (i.e., 1-2 mm) into the distal aorta. It is crucial to minimize the amount of iliac stent protrusion into the distal aorta since this may compromise future lower limb access from the contralateral site. This observation is particularly relevant if balloon-expandable devices are used because protruding stents may be irreversibly damaged during crossover maneuvers.

In patients with previous complex endovascular reconstruction at the level of the bifurcation of the distal aorta, crossover maneuvers should be avoided and a retrograde ipsilateral or a brachial approach should be preferred. In the presence of associated severe disease of the distal aorta, the deployment of a large balloon-expandable or self-expanding stent (e.g. Smart 14/40mm, Cordis) in the distal aorta, as described earlier, should precede iliac kissing stenting at the level of the bifurcation.
Figure 31: Ostial common iliac artery (CIA) stenosis treated with the placement of two balloon-expandable stents at the abdominal aorta (Ao) bifurcation [reproduced from Bonvini RF et al. (108)]

4.1.5.4 Common iliac and proximal external iliac artery occlusions (Figure 32-33):

The crossover approach is preferred to the retrograde access for iliac total occlusions since it minimizes the risks of extensive dissections involving the distal aorta and allows more frequently for intraluminal recanalisation. However, this technique may not be used in the presence of ostial common iliac occlusion since back-up for advancing wires and catheters is often insufficient. To improve the pushability of guide-wires in ostial occlusions, it is recommended to place in the proximal occlusion edge a Simmons 1 or Simmons 2 5-6Fr (e.g., from Cordis) or other 6Fr diagnostic catheters, according to the aortic bifurcation anatomy and the presence or absence of a short stump. Alternatively the brachial approach utilizing a 6Fr 90cm introducer sheath should be considered.

The first step of the crossover technique is a retrograde puncture of the contralateral femoral site with the advancement of a 23 cm 6Fr or 7Fr sheath. Over a stiff 0.035" hydrophilic wire (e.g., stiff angled Glide Wire [Terumo]) a 5-6Fr diagnostic catheter (e.g., Hook, Sheperd-Hook, internal
mammary) is positioned at the aortic bifurcation. Subsequently the occlusion is passed with the stiff hydrophilic wire which is then positioned in the CFA. Especially, in the absence of a very proximal or ostial occlusion of the CIA, once the lesion is passed with the stiff hydrophilic wire and is positioned in the superficial femoral artery, a 5Fr hydrophilic angled catheter (e.g., angled Glide Catheter [Terumo]) can be passed through the lesion and then positioned in the superficial femoral artery. Intraluminal position can be ascertained by dye injection through the catheter. Subsequently, the hydrophilic wire can be exchanged over the catheter for a stiffer 0.035" wire (e.g., stiff Amplatz [Boston Scientific] or Supracore [Abbott vascular]). Then, a 6-7Fr 40 cm cross-over sheath (e.g., Flexor Balkin [Cook]) or Super Arrow-Flex [Arrow]) may be advanced just proximally to the occlusion. Then, the occlusion is predilated with a 5-7 mm balloon at low pressure (4-6 atm) and if, at this time, the stent can be easily positioned utilizing the crossover sheath the procedure can be completed with this contralateral approach.

In case of ostial CIA occlusion, optimal stent positioning at the CIA ostium is best achieved with an ipsilateral retrograde approach. Using the wire as a marker, the ipsilateral CFA is punctured under fluoroscopic guidance and a 6Fr or 7Fr 23cm sheath is introduced. At this point, the procedure can be continued as described above using the ipsilateral retrograde technique. Compared with the stent delivery using the crossover approach, stent placement using the retrograde access is more precise and allows for better support.

A third way to approach iliac total occlusions is using a brachial access. This approach is challenging and should be reserved to experienced interventionalists. The left brachial access is preferred because it allows for a more direct access to the descending aorta and at the same time it minimizes the risk of cerebral embolization while crossing the aortic arch. The brachial artery should be punctured in its distal part above the antecubital fossa, where effective hemostasis may be achieved by arterial compression against the humerus. After introducing a 5Fr short sheath, an exchange length 0.035" wire (e.g., Magic Torque, stiff angled Glide Wire) is advanced under fluoroscopy into the distal aorta. Subsequently, the 5Fr sheath is exchanged for a 90 cm long 6Fr sheath (e.g., Shuttle [Cook]), since most of current stents, even in larger diameters, are 6Fr compatible and a larger sheath size increases the risk of forearm ischemia. Additional contralateral CFA access is needed to perform kissing PTA or stenting. At the end of the procedure, the long
brachial sheath is exchanged for a short one which is then removed as soon as the level of anticoagulation allows for it and manual compression is applied.

**Figure 32**: Ostial common iliac artery (CIA) and abdominal aorta (A) bifurcation stenosis treated with a kissing stenting technique. → = pelvic collateralization
[reproduced from Bonvini RF et al. (108)]

**Figure 33**: Common iliac and proximal external iliac artery occlusions treated with a self-expanding stent
⇒ in panel B = catheter confirming the intraluminal passage in the IIA [reproduced from Bonvini RF et al. (108)]

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4.1.5.5 Distal external iliac or common femoral artery stenosis and/or occlusion (Figure 34-35-36-37):

In the presence of a stenosis located in the distal portion of the EIA or the proximal segment of the CFA, the retrograde approach should not be used due to the immediate proximity between the access site and the lesion. Therefore, access should be gained using a crossover technique. For lesions of the CFA surgery should be considered the therapy of choice, as it may be performed in local anesthesia, may yield good results, and does not jeopardize future access. If a percutaneous intervention is performed, the controlateral approach is mandatory and a debulking strategy with atherectomy devices (e.g. Silverhawk or Rockhawk devices, [ev3 Endovascular, Inc. Peripheral Vascular North Plymouth, MN, USA]) may be preferred in order to minimize the need of stent placement and to reduce any potential plaque shift into the profunda femoral artery.

Surgery of the CFA is mainly based on an endarterectomy which is frequently associated to an enlargement plasty of the profunda femoral artery. The technical surgical success exceeds 90% with a <20% of 1-year restenosis detected at duplex-scanning (221, 222). However the surgical related complication rate — local infection, hematomas, seromas, nerve damages — approximates 15% (221, 222).

The percutaneous treatment of the CFA remained long anecdotal and limited to small case series. The reported procedural success and survival free of amputation or repeat revascularization were high (>95%) (223). Very recently a retrospective series analyzing 360 consecutive endovascular CFA interventions performed at a single tertiary center over a 12 year period has demonstrated a high technical success rate (92.8%), a low major and minor complication rate (1.4%, 5% respectively) and acceptable 12-months restenosis and target lesion revascularization rates of 27.6% and 19.9%, respectively (224).
Figure 34: Distal external iliac artery stenosis (arrow) [reproduced from Bonvini RF et al. (108)]

Figure 35: CFA stenosis treated with a Silverhawk™ atherectomy at the CFA, BP and DFA ostial levels. DFA = deep femoral artery, BP = bypass [reproduced from Bonvini RF et al. (108)]
Finally, CFA stenosis or occlusions may be iatrogenic secondary to intimal dissection occurred during coronary or vascular angiography or intervention or secondary to a vascular closure device placement (Figure 37). This type of complication may be managed by surgery or by an endovascular approach including simple PTA, stent implantation or atherectomy (225).

Figure 36: CFA occlusion treated with PTA + final kissing balloon inflation [reproduced from Bonvini RF et al. (108)]

Figure 37: ostial SFA sub-occlusion caused by the collagen plug of an Angioseal™ device. The right panel shows the final result after a self-expanding stent placement [reproduced from Bonvini RF et al. (108)]
4.1.6 Complications of Aortoiliac Interventions (*Figure 38-39*)

Potential complications of aortoiliac interventions, similarly to other endovascular interventions, include flow-limiting dissection, abrupt vessel occlusion, perforation, and distal embolization. On a broader perspective, the incidence of complications is greater during recanalization of total occlusions compared with the treatment of non-occlusive lesions. Extensive iliac dissection (*Figure 38*) can usually be treated successfully with self expanding stents.

In the presence of vessel rupture (*Figure 39*), immediate balloon occlusion proximal to the perforation, followed by reversal of heparin with protamine and placement of a covered stent is mandatory. In the mean time, blood should be typed and crossed and vascular surgery notified in case the endovascular salvage fails. If distal embolization is suspected, immediate angiography should be performed and further treatment (e.g., prolonged heparinization, intra-arterial lytic therapy, endovascular clot-extraction, surgery) should be guided based on the angiographic and clinical findings.

If distal embolization should occur during an iliac intervention performed with an ipsilateral retrograde approach, it is recommended to access the contralateral CFA and to treat the complication with a crossover approach. Conversion from a retrograde to an antegrade approach through the same access, although technically feasible, should be discouraged because it may seriously damage the CFA at the access site. An alternative approach (i.e., in the absence of acute limb ischemia) is to treat the distal embolization the day after using antegrade access.

*Figure 38: Extensive iatrogenic EIA dissection (arrow) [reproduced from Bonvini RF et al. (108)]*
4.1.7 Long-Term Follow-Up

Following iliac intervention, all patients should receive life-long aspirin therapy. Clopidogrel is recommended for at least 4 weeks following stent implantation, despite the fact that some operators do not routinely prescribe this dual antiplatelet regimen after a non-complicated iliac stenting. Currently, there is no evidence that prolonged dual anti-platelet therapy (i.e., aspirin and clopidogrel) may favorably impact the prognosis of patients with PAD. During follow-up, patients should be screened for evidence of restenosis based on their symptomatology, CFA pulse exam, and ABI measurements. If any of these elements suggest restenosis, then further evaluation and treatment are warranted to maintain patency of the treatment site.

Since large series of aorto-iliac PTA with routine follow-up angiography are missing, the true incidence of restenosis in this vascular segment is unknown. Nevertheless, the lower rate of repeat revascularization and data from non-invasive studies suggest that restenosis is a marginal problem (i.e. <10% at 1 year). For that reason, drug-eluting stents have not been tested in aorto-iliac disease.
4.2 FEMOROPOPLITEAL OCCLUSIVE DISEASE

The femoropopliteal segment is the most common site for treatable arterial occlusive disease. Balloon angioplasty is usually performed without stenting, as the latter procedure has a significant reocclusion and restenosis rate and does not appear to improve outcomes after intervention especially of focal lesions (i.e. <10cm) (144-148, 227, 228).

Although contrast angiography, CTA or MRA are typically used to define the anatomy prior to intervention, however, all these imaging modalities carry a risk of acute renal failure that is greatest in patients with renal insufficiency and diabetes, which are commonly present in patients with PAD. In such patients, duplex guidance seems to be a safe and effective alternative that avoids the risk of contrast injection, because duplex ultrasound, if performed by experienced operators, allows to precisely locate the culprit lesion, thus to easily program the best revascularization approach (229).

4.2.1 Incidence of restenosis at the femoropopliteal level

Angioplasty for femoropopliteal disease has a lower rate of long-term maintenance of arterial patency than with aortoiliac disease (230). Accordingly, the overall technical success rate may be up to 90% with a higher success rate for stenoses than for occlusions (231). The two-year patency rates for balloon angioplasty alone may vary from 42 to 58% with a loss of initial patency secondary to restenosis (which usually occurs in the first six months) or to progressive atherosclerosis at the lesion site or elsewhere in the same vessel. The smaller vessel diameter at the femoropopliteal level associated with the unique extrinsic forces interacting between muscle and the vessels in this region are probably the major explanations for the higher rate of restenosis at this site compared to iliac disease.

Anatomic factors that adversely affect long-term patency include long or eccentric calcified lesions, occlusion instead of stenosis, and poor distal runoff (178, 231). Interestingly, repeat PTA has equivalent patency rates to first-time PTA (175). Endovascular interventions at femoropopliteal level are usually performed in patients presenting with systemic atherosclerosis. This suggests that PTA ± stenting may be particularly desirable in such patients, especially if one considers that 60 to 90% of these patients have concomitant coronary artery disease and PTA preserves saphenous veins for possible coronary artery bypass graft of future femoropopliteal bypass graft (232).
4.2.2 Complications of Femoropopliteal Interventions

Complications from PTA requiring some form of treatment occur in 1 to 4% of published cases (195, 233). Because a larger arteriotomy is needed for percutaneous interventions, direct arterial injury can lead to groin hematoma (2 to 4%) or the formation of a pseudoaneurysm (0.3 to 2%), or arteriovenous fistula (0.1 to 0.3%). Complications directly related to arterial dilatation include distal embolization (2%), thrombotic occlusion (2%), and, rarely, arterial rupture (233).

Femoropopliteal stents are prone to fracture, which is thought to be due to the dynamic forces imparted to the superficial femoral and popliteal arteries with knee flexion (234). Systematic reviews have identified a cumulative incidence of stent fracture in the femoropopliteal segment ranging from 2 to 65% (235, 236). The variability is likely related to heterogeneity in severity and length of stenosis treated, and type and number of stents deployed. The risk for stent fracture increases with treatment of longer lesions and multiple stent deployments (157, 235-237).

Stent fracture is associated with an increased risk of restenosis and late occlusion (157, 237). In one observational study of 239 patients, primary stent patency was significantly reduced in patients with stent fracture compared to those with no fracture at one and two years follow up (68 versus 83%, and 65 versus 75%, respectively) (237).
4.3 INFRAPOPLITEAL OCCLUSIVE DISEASE

The infra-popliteal run-off is composed by a tibio-peroneal trunk (TPT) which divides into the posterior tibial artery (ATP) and the peroneal or fibular artery (AP). The anterior tibial artery (ATA) arises, in the majority of the cases, from the distal segment of the popliteal artery before it becomes the TPT (Figure 40).

The infra-popliteal vessels have similar characteristics as the coronary vessels:

- They have the same vessel size (i.e. 2-4 mm),
- They often present some kind of bifurcational lesions,
- They may develop an important collateralization in case of multiple vessel occlusions.

For these reasons, it is admitted that the prevalence of BTK disease may be as high as that of CAD, especially if one considers that atherosclerosis favorizes small vessels with important arterial wall shear stress, which oftenly occurs in bifurcation regions. The main difference between BTK and coronary vessels is the length of the vessel. Accordingly, the disease lengths may vary from up to 10cm length for coronary vessels, to more than 40cm length for BTK vessels.

In general the last remaining patent vessel in the BTK region is the peroneal artery, which has a deeper course in the calf and which usually gives collaterals to the occluded ATA or ATP. These collaterals are essential to perfuse the pedal or the plantar arteries, which finally maintain the foot perfusion (Figure 41).
Figure 40: Tibial arteries anatomy [reproduced from Bonvini RF et al. (238)]

Figure 41: Foot vessel anatomy [reproduced from Bonvini RF et al. (238)]
There are few published data on the utility of PTA in the treatment of infra-popliteal arterial disease for patients presenting with claudication. Although, most of the series reporting the outcomes of infra-popliteal endovascular interventions combines patients presenting with CLI and a minority of them presenting with severe lifestyle-limiting claudication, infra-popliteal angioplasty for claudicant should be reserved to special cases and not being routinely performed.

Advances in wire and balloon design permit technical success rates >90% (239, 240), and despite a poor 40% patency rate observed at two years (240), small vessel angioplasty is an effective method to preserve limb viability in a patient with a threatened extremity, as two-year limb salvage rate of >85% may be obtained (239). Patency may be enhanced by the use of stenting, especially DES (161, 241), or more recently by the use of the DEB technology.

One group of particular concern is diabetics who often have nonhealing foot ulcers and gangrene that result in amputation (242). All these issues will be in deeply discussed in the “critical limb ischemia” section of the manuscript.
5.0 POST ANGIOPLASTY MEDICAL MANAGEMENT

Patients who have previously undergone revascularization procedures require careful long-term care and vascular follow-up to detect both the recurrence of disease at revascularized sites and the development of new arterial disease at remote sites.

In spite of increasing short-term success rates for both endovascular and surgical revascularization procedures, the possibility of recurrence remains throughout the lifetime of the patient. Early revascularization interventions for recurrent hemodynamic compromise are preferred, because delay in detection or treatment can lead to higher morbidity and poorer outcome (243, 244).

Participation in a follow-up surveillance program is imperative for patients undergoing both percutaneous and surgical revascularization. However, the recommended frequency of surveillance visits depends on the burden of disease in the individual patient, the specific procedure that was performed and its expected outcome, and the clinical syndrome for which the patient originally presented.

Aortic and common iliac arterial level procedures have greater durability than infrainguinal procedures and therefore require less frequent surveillance. In contrast, infrainguinal revascularization for CLI, either by surgical or percutaneous methods, is associated with higher restenosis and graft failure rates and therefore requires more intense surveillance (2).

Whereas the role of surveillance duplex imaging of autogenous and prosthetic grafts has been evaluated, the utility and role of duplex ultrasound and other noninvasive diagnostic modalities (MRA and CTA) for such routine surveillance of endovascular sites have yet to be determined.

For grafts as well as native vessels, a stenosis of less than 50% appears to be associated with favorable prognosis and patency. In contrast, a stenosis greater than 70% is a harbinger of poor long-term patency, and thus, reintervention may be warranted (245, 246).

Similarly of patients undergoing a surgical revascularization of the lower limbs, the surveillance program should include: - an interval history (i.e., new symptoms), a vascular examination (i.e., pulses palpation), an ABI measurement at rest and if possible a postexercise ABI measurement, as well as a duplex scanning of the treated vascular segment, with special attention to an increased peak systolic velocity suggesting the presence of a significant restenosis. This follow up examinations should be performed immediately after the intervention and at regular intervals (e.g., every six months) for at least two years (2).
5.1 MEDICAL TREATMENTS

5.1.1 Antiplatelet and Antithrombotic Drugs prior revascularization

The effect of antiplatelet therapy on cardiovascular events has been systematically reviewed by the Antithrombotic Trialists’ Collaboration (247). A meta-analysis comprising 287 studies compared the efficacy of antiplatelet therapy versus control in approximately 135,000 high-risk patients with vascular diseases manifested as acute and previous MI, acute and previous stroke, or other high-risk conditions, such as lower extremity PAD (247). Among those patients with PAD treated with antiplatelet therapy, there was a 22% odds reduction for adverse cardiovascular events, including MI, stroke, or vascular death. Similar benefits were realized by patients with intermittent claudication, those having peripheral angioplasty, and those having peripheral bypass graft procedures (247).

The antiplatelet therapy used in many of the lower extremity PAD trials was aspirin at different dosages; however, some included ticlopidine, a thienopyridine drug, and one included picotamide, a thromboxane synthase inhibitor (247).

The CAPRIE trial compared the efficacy of aspirin (325 mg daily) to the thienopyridine derivative clopidogrel (75 mg daily) in 19,185 patients with a history of MI, stroke, or PAD. Clopidogrel reduced the risk of adverse cardiovascular events by 8.7%. Among the 6,452 patients with PAD, clopidogrel reduced the risk of MI, stroke, or vascular death by 23.8% more than aspirin (50). The risks of intracranial and gastrointestinal bleeding in patients randomized to aspirin were 0.49% and 2.66%, and those randomized to clopidogrel, the risks were 0.35% and 1.99%, respectively.

It is recommended that patients with lower extremity PAD be treated with antiplatelet therapy to reduce the risk of MI, stroke, or vascular death. On the basis of the single comparative trial published to date, clopidogrel appears to be more effective than aspirin in preventing ischemic events in individuals with symptomatic PAD (50).

The combination of clopidogrel plus aspirin versus aspirin alone has been examined in patients who had presented with acute coronary syndrome. Combination aspirin and clopidogrel therapy was associated with a 20% relative risk reduction for MI, stroke, or cardiovascular death (248). To date, there is no evidence to support the efficacy of combined aspirin and clopidogrel treatment versus a single antiplatelet agent in patients with isolated lower extremity PAD.

Information regarding the efficacy of oral anticoagulants (i.e. coumarin derivatives) in reducing adverse cardiovascular events in patients with atherosclerosis is derived primarily from studies of
patients with coronary artery disease. Meta-analyses comprising 37 trials of anticoagulant therapy in more than 20'000 patients with coronary artery disease evaluated the efficacy and safety of oral anticoagulation (mainly warfarin) alone versus the control, stratified by intensity of anticoagulation, as well as the efficacy of warfarin versus aspirin in patients with coronary artery disease (249, 250).

For patients with lower extremity PAD in whom an additional indication for use of warfarin exists (such as individuals with lower extremity PAD and either atrial fibrillation or a prosthetic heart valve), the risk and benefit of therapy with an antiplatelet medication alone, warfarin alone, or their combination must be assessed individually.

5.1.2 Antiplatelet and Antithrombotic Drugs during revascularization

The optimal level of anticoagulation for peripheral interventions has not been defined. Some investigators feel comfortable to proceed at an activated clotting time (ACT) of approximately 200 seconds. Others administer fixed doses of unfractionated heparin (e.g., 2.500 - 5.000 units) without checking ACT. The fact that higher anticoagulation levels do not reduce the occurrence of thrombotic events, while significantly increase that of hemorrhagic events suggests that a ≤60U/Kg heparin dose targeting an ACT < 250 seconds may be recommended for peripheral interventions (251).

Less frequently used alternative anticoagulation strategies include the direct thrombin inhibitor bivalirudin and low molecular weight heparins (252, 253). The use of low molecular weight heparins should be discouraged for peripheral procedures because they have not been adequately studied, have a long half-life and the anticoagulation cannot be entirely reverted. This is particularly problematic in the presence of complications such as perforations or progressing puncture site hematomas.

Similarly, platelet glycoprotein IIb/IIIa receptor inhibitors have not been tested in aortoiliac interventions and cannot be currently recommended, while the administration of abciximab for complex femoropopliteal interventions seems to have a favorable effect on patency and clinical outcome at six months (254), despite that this favorable association remains controversial (255). However, these agents may be very useful as bailout strategy in case of periprocedural thromboembolic complications (e.g. distal embolization, acute vessel occlusion).

5.1.3 Antiplatelet and Antithrombotic Drugs after revascularization

All patients undergoing planned lower limb revascularization should be on an antiplatelet agent. If aspirin is not tolerated (e.g., allergy or gastrointestinal side-effects), clopidogrel may be used as an
alternative. In patients undergoing PTA not on antiplatelet drugs, 250-500 mg of oral aspirin (or 300-600 mg of clopidogrel in case of aspirin intolerance) may be given prior to gaining femoral access.

There is no consensus regarding the use of pre-procedural clopidogrel loading for patients undergoing PTA that are on chronic aspirin treatment. Dual antiplatelet therapy, if not mandatory for coronary reasons, should be avoided in patients undergoing recanalization of an iliac total occlusion because it might jeopardize surgical bailout of complications such as a perforation.

Following successful iliac or femoropopliteal stenting, in addition to lifelong aspirin, clopidogrel is frequently administered with a loading dose of 300-600 mg, followed with a maintenance dose of 75 mg/day for at least one month. In some centers, after iliac stenting, clopidogrel is not prescribed, especially in the presence of large iliac vessels or in patients at high bleeding risk, however, there is general consensus that after femoropopliteal stenting 1 month dual antiplatelet therapy is mandatory.

After having adopted some new antiproliferative technologies during the endovascular intervention, such as a DES or a paclitaxel DEB, there are no clear guidelines on how to manage the following dual antiplatelet regimen. The duration of this therapy must be tailored to the individual bleeding risk of the patient and the complexity of the performed intervention. Usually after the use of a DEB in the femoropopliteal or the BTK region, 1 to 3 months of dual antiplatelet regimen is prescribed, while after the use of a DES in the femoropopliteal or the BTK region, 3 to 6 months are recommended.
6.0 CRITICAL LIMB ISCHEMIA

Limb-threatening ischemia or newly defined critical limb ischemia (CLI) occurs when arterial blood flow is insufficient to meet the metabolic demands of resting muscle or tissue. It has been estimated that limb-threatening ischemia occurs in 1 to 2% of patients with PAD who are 50 years of age or older (2, 3).

According to the 2007 TASC II guidelines and those of the ACC/AHA published in 2006, a sudden decrease in limb perfusion that causes a potential threat to limb viability (manifested by ischemic rest pain, ischemic ulcers, and/or gangrene) in patients who present within two weeks of the acute event is defined as an acute limb ischemia (2, 3). Patients with similar manifestations who present later than two weeks are considered to have critical limb ischemia, which is by definition chronic.

The natural history of CLI usually involves inexorable progression to amputation unless there is an intervention that results in the improvement of arterial perfusion. This is in contrast to the often benign natural history of mild and moderate claudication.

Critical limb ischemia is defined as limb pain that occurs at rest or impending limb loss that is caused by severe compromise of blood flow to the affected extremity. The term "critical limb ischemia" should be used for all patients with chronic ischemic rest pain, ulcers, or gangrene attributable to objectively proven arterial occlusive disease.

Unlike individuals with claudication, patients with CLI have resting perfusion that is inadequate to sustain viability in the distal tissue bed. Although it may be challenging at times to ascertain the limb prognosis in patients presenting with lower extremity ischemic rest pain, ulceration, or gangrene, CLI is defined de facto by most vascular clinicians as that pathology in which the untreated natural history would lead to major limb amputation within 6 months.

Critical limb ischemia is usually caused by obstructive atherosclerotic arterial disease; however, it can also be caused by atheroembolic or thromboembolic disease, vasculitis, in situ thrombosis related to hypercoagulable states, thromboangiitis obliterans, cystic adventitial disease, popliteal entrapment, or trauma.

Factors that can contribute to the development or exacerbation of CLI include syndromes that are known to reduce blood flow to the microvascular bed, such as diabetes, severe low cardiac output...
states, severe renal failure and, rarely, vasospastic diseases (e.g., Raynaud’s phenomenon, cold exposure). Other conditions that accelerate or compound CLI include those in which demand for blood and nutrient supply is increased markedly, such as infection, skin breakdown, or traumatic injury (2).

Atherosclerotic arterial occlusive disease that precipitates CLI is most often diffuse or multisegmental, involving more than one arterial anatomic “level.” Frequently, because of the systemic nature of the atherosclerotic process and a predilection for symmetrical disease, the contralateral limb may also be affected by ischemic symptoms and may also demonstrate objective signs of ischemia on examination.

Patients with CLI present with a spectrum of clinical manifestations, depending on the degree of ischemia and the time course of its development. The Rutherford or the Fontaine clinical categories (described previously) are used to classify the degree of ischemia and salvageability of the limb.

Critical limb ischemia is associated with a very high mid-term morbidity and mortality. Patients with lower extremity PAD have a 3 to 5 times overall greater risk of cardiovascular mortality than those without this disease. Those with more advanced lower extremity PAD, as manifested by CLI, have even greater risk of experiencing cardiovascular ischemic events (15, 47, 256). Thus, care strategies for individuals with CLI must recognize the cardiovascular ischemic burden. Ideal care strategies for individuals with CLI will therefore include recognition of the possibility of severe coronary artery disease, cerebral vascular disease, or aortic aneurysmal disease and include the impact of these illnesses on patient outcomes with or without specific CLI interventions.

In addition, such long-term integrated care plans will offer risk factor modification for secondary prevention of cardiovascular ischemic events, to maximize the possibility of achieving an improved long-term morbidity and mortality (62).

6.0.1 Predictors of developing CLI

In addition to the classical cardiovascular risk factors, several other clinical predictors should be considered by evaluating the risk of developing a CLI. The severity of the PAD, in terms of decreased ABI, as well as the age of the patient are important co-factors by determinating the risk of a future CLI. However, the most powerful predictor of developing of a CLI remains the presence of diabetes, and especially that insulin-dependent (Figure 42).
Figure 42: magnitude of the effect of risk factors on the development of CLI [reproduced from the TASC II Guidelines (2)]

6.0.2 Prognosis of the Limb

The prognosis of the limb is determined by the extent of arterial disease, the acuity of limb ischemia, and the feasibility and rapidity of restoring arterial circulation to the foot. For the patient with chronic arterial occlusive disease and continued progression of symptoms to CLI (e.g., development of new wounds, rest pain, or gangrene), the prognosis is very poor unless revascularization can be established.

Few studies of the natural history of PAD have been performed to objectively quantify disease progression. Claudication symptoms usually remain stable and do not worsen or improve at rapid rates (56). The temporal progression of symptoms across arterial beds in patients with known atherosclerotic disease has also been studied on a limited basis (57).

According to the initial clinical findings, as well as the degree of the arterial compromise only 50% of the patients presenting with a CLI undergo a revascularization attempt (either percutaneous or
Indeed, due to the associated co-morbidities and the extent of the arterial disease, 25% of these patients are managed with a conservative attitude, which propose a medical treatment only, while the remaining 25% of the patients are managed with a primary amputation approach without any revascularization attempt (Figure 43).

In this CLI patients group, the one year outcomes are characterized by the occurrence of an up to 25% of mortality, mostly secondary to cardiovascular events. Thirty percent of these patients had undergo different degree of amputation, ranging from the minor ones (i.e. toes and for-foot amputations) to the major ones (including below and above the knee amputations). Finally, the remaining 45% of the patients are further divided into those in whom the CLI has resolved (25%) and those still presenting a persistent CLI (i.e. non-healing ulcer) (Figure 43).

Figure 43: Fate of the patients presenting with chronic CLI [reproduced from the TASC II Guidelines (2)]

6.0.3 Lower Limb Amputations

Once the patient undergoes a major amputation, he/she remains at increased risk of different cardiovascular events. Accordingly, the peri-operative mortality rate may be as high as up to 10%, and this is probably related to the fact that >50% of the performed amputations occur in the elderly (i.e.>
80 years old). Once over-pass the peri-operative phase, patients may present a sufficient wound healing process in up to 75% of the cases (i.e. 60% primary healing, 15% secondary healing), while the remaining 15% of the amputated patients, do not present a satisfactory cicatrization of the wound and thus they have to undergo several additional interventions (i.e. above the knee amputation) (Figure 44).

At two years, outcomes are even worse, if one considers that up to 1/3 of the patients died and that only 40% of these amputated patients regain a full mobility.

Figure 44: fate of the patients with a below the knee amputation [reproduced from the TASC II Guidelines (2)]
Critical limb ischemia occurs most frequently when 2 or more levels of the distal arterial tree are compromised by either hemodynamically significant stenoses or occlusion. Although this usually manifests in aortoiliac and femoral-popliteal segments or the femoral-popliteal and tibial segments, it may also occur in the setting of parallel arterial segments, such as superficial and deep femoral artery occlusions or an isolated infra-popliteal disease (3). Multiple levels of disease promote severe ischemia by reducing the effectiveness of collateral flow and by lowering distal systolic driving pressures. The major manifestations of limb-threatening ischemia are rest pain, ischemic ulcers, and gangrene.

The multiple levels of disease decrease the effectiveness of major autogenous collateral vessel flow and reduce systolic driving pressures in the periphery. As pressure is lowered in the distal arterioles, and occasionally also raised in the distal venules by inactivity and venous stasis, the pressure gradient across capillary beds is decreased, which reduces perfusion below the level required to sustain basal tissue metabolism. This results in slowly progressive tissue death and, ultimately, amputation if allowed to persist uncorrected.

6.1.1 Clinical Presentation

Patients with CLI usually present with limb pain at rest, with or without trophic skin changes or tissue loss. The discomfort is often worse when the patient is supine (e.g., in bed) and may lessen when the limb is maintained in the dependent position. There may be calf atrophy, dependent rubor and elevation pallor, loss of hair over the dorsum of the foot, thickening of the toenails, and shiny, scaly skin due to loss of subcutaneous tissue. Typically, narcotic medications are required for analgesia; the pain commonly may disturb sleep and render the patient severely disabled, often unable to walk. The quality of life for patients with severe CLI can be worse than that of patients with terminal cancer (2, 257), although some individuals with diabetes may present with severe CLI and tissue loss but no pain because of concomitant neuropathy.

Critical limb ischemia may develop in a small subset of individuals who are already being closely monitored within a medical practice for lower extremity PAD and claudication. However, severe limb ischemic symptoms may also be the initial presentation of lower extremity PAD, with rest pain, ulceration, or even frank gangrene serving as the first manifestation of lower extremity arterial
insufficiency. This acute onset of symptoms may suggest thromboembolic disease, sudden multisegmental in situ thrombosis, thromboangiitis obliterans, or an inflammatory arteritis.

The diagnosis of CLI may be obscured by associated neuropathic conditions. Individuals with baseline diabetic neuropathy may have impaired or absent sensation in the distal limb arterial territories most at risk for ischemia. Furthermore, susceptibility to infection and the presence of microvascular disease in individuals with diabetes makes it more likely that ischemia in these patients will progress rapidly.

Finally, the ischemic process itself can be primarily responsible for causing neuropathy: once gangrene is present, the patient’s sensory nerves may be damaged, and the patient may no longer feel the pain associated with ulceration. Tissue damage may thereby progress undetected or ignored.

6.1.1.1 History:

It is important for clinicians who evaluate patients with CLI to distinguish between ischemia that is acute versus chronic, because the diagnostic and therapeutic approaches and prognoses differ significantly. Acute limb ischemia requires urgent evaluation and intervention, whereas CLI usually does not. However, for individuals with CLI, it remains fundamentally important for the clinician to determine the time course of development of the ischemia. If the clinical history and physical examination suggest relatively rapid progression, then early or “semiurgent” revascularization may be required to prevent further deterioration and irreversible tissue loss. In addition to careful assessment of the time course of the ischemic syndrome, a vascular history should be obtained. This should include evaluation for arterial disease in other territories, assessment of global risk factors for atherosclerosis, and clarification of any specific precipitating factors or events (e.g., trauma, infection, surgical manipulation) that may have caused initial skin ulceration.

6.1.1.2 Rest pain:

Ischemic rest pain or diffuse pedal ischemia can be described as a severe pain which is not readily controlled by analgesics and which is typically localized in the forefoot and toes of the chronically ischemic extremity. The pain may also be felt more proximally; when this occurs, the pain usually does not spare the distal sites.

Ischemic rest pain is brought on or made worse by elevation of the lower extremity and is ameliorated or relieved by limb dependency. Thus, rest pain is often experienced at night or while
reclining (258). Diffuse pedal ischemia is commonly associated with systolic arterial ankle pressures below 40 mmHg and toe pressures below 30 mmHg (159).

6.1.1.3 Ischemic ulcers:

Ischemic ulcers often begin as minor traumatic wounds and then fail to heal because the blood supply is insufficient to meet the increased demands of the healing tissue (259). The ulcers are often painful and are associated with other manifestations of chronic ischemia including rest pain, pallor, hair loss, and nail hypertrophy.

Ischemic ulcers need to be distinguished from venous insufficiency and peripheral neuropathy, which are the other major causes of foot and leg ulcers.

- Ischemic ulcers typically form at sites of increased focal pressure such as the lateral malleolus, tips of toes, metatarsal heads, and bunion area. They are usually dry and punctate.
- Venous ulcers are more commonly located above the medial ankle and are frequently moist, superficial, and diffuse. They are often associated with hemosiderin pigmentation and other evidence of venous insufficiency such as varicosities and worsening symptoms with dependency.

Some patients may have combined arterial and venous disease and manifest signs of both arterial and venous insufficiency, while diabetic patients may have both arterial disease, which can involve both the microcirculation and large vessels, and peripheral neuropathy.

Ischemic ulcers, which most often involve the foot, can become infected and may lead to osteomyelitis. The clinical manifestations, diagnosis, and management of such infections are similar to that seen in diabetic foot infections. It is generally recommended that all diabetic patients with an ulceration be evaluated for PAD using objective testing (2).

6.1.1.4 Gangrene:

Gangrene is characterized by cyanotic, anesthetic tissue associated with or progressing to necrosis; it occurs when arterial blood supply falls below that necessary to meet minimal metabolic requirements (259). Gangrene can be described as either dry or wet.
• Dry gangrene is characterized by its hard, dry texture, usually occurring in the distal aspects of toes and fingers, often with a clear demarcation between viable and necrotic tissue. This form of gangrene is more common in patients with atherosclerotic disease and frequently results from embolization to the toe or forefoot. The patient may often give a history of associated claudication or foot and toe pain.

Once demarcation has occurred, the involved digit may be allowed to autoamputate without further proximal progression of gangrene. However, this is often a process which is both lengthy and disturbing to the patient. On the other hand, many patients with dry gangrene do not have adequate circulation to heal a distal amputation. As a result, most patients should be evaluated with angiography for possible distal revascularization in order to improve chances of healing a distal amputation and obtaining limb salvage.

• Wet gangrene is characterized by its moist appearance, gross swelling, and frequent blistering. It is a true emergency, often occurring in diabetics with decreased sensation who sustain an unrecognized trauma to the toe or foot. If sufficient viable tissue is present to maintain a functional foot, emergent debridement of all affected tissue often results in healing. If the wet gangrene involves an extensive portion of the foot, emergent guillotine amputation may be warranted, with revision to below knee or above knee amputation 72 hours later.

6.1.1.5 Blue toe syndrome: (Figure 45):

The blue toe syndrome is characterized by the sudden appearance of a cool, painful, cyanotic toe or forefoot in the often perplexing presence of strong pedal pulses and a warm foot. There may also be scattered areas of petechiae or cyanosis of the soles of the feet.

The blue toe syndrome is usually due to embolic occlusion of digital arteries with atherothrombotic material from proximal arterial sources. These episodes may lead to similar and more severe episodes in the future. Thus, identification and eradication of the embolic source is usually indicated (260). Expeditious evaluation by angiography is required to evaluate the source; complete exclusion and bypass of the diseased segment are indicated. However, caution is advised for performing angiography in patients who have other signs suggestive of multiple atheroemboli, such as livedo reticularis, since angiography may lead to further embolization.
Figure 45: Blue Toe syndrome [courtesy of Prof. Zeller Th., Bad Krozingen, Germany]
6.2 PATIENT EVALUATION AND NON-INVASIVE TESTING IN CLI

6.2.1 Physical Examination

Evaluation of patients for CLI requires systematic assessment of pulses and tissue perfusion to identify the level of obstructive lesions and potential involvement of other threatened extremities. Signs of chronic ischemia, including dependent rubor, early pallor on elevation of the extremity, and reduced capillary refill, should be confirmed. Peripheral manifestations of atheroemboli, such as livido reticularis, should be sought, as should their potential sources (e.g., abdominal aortic aneurysm).

Distinctions should be made between ulcers that are arterial and those that are venous or neurotrophic. In the absence of neuropathy, arterial ulcers are usually exquisitely painful and tender to palpation. Motor and sensory function should also be assessed in the lower extremities.

Patients with open ischemic ulcers involving the extremities often have associated local infection or cellulitis. In the diabetic population or in immunocompromised individuals, these infections tend to be polymicrobial and require systemic antibiotic therapy (2). Individuals who have had prior symptoms of CLI remain at future risk of development of recurrent symptoms or signs of CLI. Thus, regular surveillance during subsequent physical examinations should be performed, with thorough inspection of the feet, including the heels, toes, and interdigital spaces, to evaluate the patient for early signs of skin breakdown or ulceration.

6.2.2 Office Testing Strategies

The evaluation of patients presenting with CLI should include a complete blood count, chemistries (including fasting blood glucose and renal function tests), electrocardiogram, and ABI.

In the absence of noncompressible vessels, measurement of an absolute systolic blood pressure 50 mmHg or lower at the ankle and 30 mmHg at the toe will often imply that amputation may be required in the absence of successful revascularization (2). Individuals with CLI who present with clinical features to suggest atheroembolization should be evaluated for more proximal aneurysmal disease (e.g., abdominal aortic, popliteal, or common femoral aneurysms).

Atheroembolism is suggested by onset of signs and symptoms of CLI after recent endovascular catheter manipulation, the onset of associated systemic fatigue or muscle discomfort, symmetrical bilateral limb symptoms, livido reticularis, or rising creatinine values.

The vascular evaluation of a patient with CLI begins with a detailed history and careful physical examination. Almost all such patients have evidence of an underlying medical disease including heart
disease, diabetes, kidney disease, hypertension, chronic pulmonary disease, or extracranial cerebral vascular disease. Maximal therapy of these conditions must be provided before, during, and after the revascularization procedures to ensure the best possible outcome.

The physical examination should include a careful search for bruits, aneurysms, and malignancy. The extremities should be carefully evaluated for the presence and strength of pulses, tissue changes, and evidence of prior vascular intervention. The physical findings are neither specific nor sensitive enough to design operative therapy. As a result, all patients with evidence of peripheral ischemia should undergo objective testing. This includes either noninvasive tests (e.g. ABI, Duplex scanning, CTA, MRA) or contrast angiography.
6.3 DIFFERENTIAL DIAGNOSIS OF CLI

Before stating that a lower limb ulcer is secondary to a severe PAD, several differential diagnoses have to be actively excluded in order to not impair the ulcer healing process. Accordingly, a concomitant venous disease, an active infective process, a decompensated diabetic neuropathy, as well as other rarer causes (*Table 5*), have to be considered, before proposing any revascularization procedure.

<table>
<thead>
<tr>
<th>ETIOLOGIES</th>
<th>Differential Diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vascular</td>
<td>Atherosclerosis, venous insufficiency, embolic disease, thrombangiitis obliterans, diabetic microangiopathy, vasculitis, collagen vascular diseases</td>
</tr>
<tr>
<td>Hematologic</td>
<td>Sickle cell anemia, Polycythemia, Thalassemia, Leukemia, Thrombocytosis</td>
</tr>
<tr>
<td>Malignancy</td>
<td>Kaposi’s sarcoma, Squamous cell carcinoma, Lymphosarcoma, Metastasis</td>
</tr>
<tr>
<td>Infective</td>
<td>Leprosis, Mycosis</td>
</tr>
<tr>
<td>Miscellaneous</td>
<td>Gout, Pyoderma gangrenosum, Necrobiosis lipoidica, Vit B12 deficiency</td>
</tr>
</tbody>
</table>

*Table 5: Etiologic Classification of foot and leg ulcers [modified according the TASC II Guidelines (2)]*

The localization of the ulcer, may strongly suggest the origin of the ulcer. Accordingly, in the presence of a foot ulcer, the arterial, as well as the diabetic components are to be considered as first line etiologies of this type of ischemic ulcer (*Figure 46*).
In case of an arterial foot ulcer, which is typically observed in diabetic patients (diabetic foot), the localization of the ulcer may also vary from the distal toes, to the dorsal and the plantar regions of the foot, to the heel (Figure 47). These localizations may depend to the specific arterial occlusion of the BTK vascular segments, as well as the presence of a previous traumatic lesion (i.e., unadapted shoes, iatrogenic lesion, etc).
To further differentiate the etiology of a foot ulcer between an ischemic and a diabetic one, several clinical factors may be considered. Table 6 summarizes these different clinical scenarios, helping the physician in the diagnostic processus of the non-healing ulcer of the patient.

<table>
<thead>
<tr>
<th>SYMPTOMS OR SIGNS</th>
<th>Ischemic Ulcer</th>
<th>Neuropatic Ulcer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pain</td>
<td>Painful</td>
<td>Painless</td>
</tr>
<tr>
<td>Pulses</td>
<td>Absent</td>
<td>Normal</td>
</tr>
<tr>
<td>Margins</td>
<td>Irregular</td>
<td>Regular</td>
</tr>
<tr>
<td>Localization</td>
<td>Toes</td>
<td>Plantar</td>
</tr>
<tr>
<td>Callosity</td>
<td>Absent</td>
<td>Present</td>
</tr>
<tr>
<td>Sensation</td>
<td>Variable</td>
<td>Absent</td>
</tr>
<tr>
<td>Veins</td>
<td>Collapsed</td>
<td>Dilated</td>
</tr>
<tr>
<td>Temperature</td>
<td>Cold</td>
<td>Dry, warm</td>
</tr>
<tr>
<td>Color of the skin</td>
<td>Pale, cyanotic</td>
<td>Red</td>
</tr>
</tbody>
</table>

Table 6: symptoms and signs of ischemic versus neuropathic ulcers [modified according the TASC II Guidelines (2)]

In the presence of an above the foot ulcer (i.e., pre-tibial), other etiologies may be suspected and excluded before investigating and especially treating the arterial components. Special attention should be given to the presence of a concomitant venous disease. Accordingly, a chronic venous insufficiency, secondary to a previous deep venous thrombosis (i.e., post-thrombotic syndrome) or other pathologies, as well as the presence of troncular varices feeding the ulcer region have to be managed before approaching the arterial component of the ulcer (Figure 48).
However, in case of a confirmed CLI according to the clinical status (ischemic rest pain, minor/major necrotic lesions, widespread ulceration/gangrene, sign of infection, etc.), the non-invasive angiological work-up and the presence of one or more occluded vessel, the TASC II guidelines recommend the following approaches (2):

- If the patient is a good candidate for revascularization \(\rightarrow\) vascular imaging (i.e., MRA or CTA or invasive angiography) followed by surgical or endovascular revascularization as appropriate;
- If the patient is NOT a good candidate for revascularization and the pain or the lesions are stable \(\rightarrow\) medical management;
- If the patient is NOT a good candidate for revascularization and the pain or the lesions are NOT stable (e.g., local ± systemic infection) \(\rightarrow\) primary amputation.
6.4 CLI TREATMENT OPTIONS

The different therapies for CLI will be reviewed here, according to the site of the vascular lesion and the specific clinical setting.

6.4.1 General Approach to Management of CLI

Treatment of CLI is dependent on increasing blood flow to the affected extremity to relieve pain, heal ischemic ulcerations, and avoid limb loss. Individuals with minimal or no skin breakdown or in whom comorbid conditions prevent consideration of revascularization can occasionally be treated by medical therapies in the absence of revascularization. Such therapies are much more likely to be successful when CLI is detected promptly and tissue necrosis is minimal. To accomplish this, patients who are at risk for or have been treated for CLI should be informed that symptoms of CLI should be brought to medical attention promptly.

Medical care strategies have included the use of antiplatelet agents, anticoagulant medications, intravenous prostanoids, rheologic agents, and maintenance of the limb in a dependent position. However, none of these clinical interventions has been evaluated adequately or proven to offer predictable improvements in limb outcomes in prospective clinical trials.

Passage of time will sometimes be associated with adequate improvements in the arterial supply–demand balance to permit improvement in symptoms. For example, collateral vessels may form to enable resolution of CLI and reduction in pain.

Treatment of infection may decrease the metabolic demands that impede wound healing, and use of non–weightbearing orthotics may diminish the contribution of repeated trauma to skin breakdown.

6.4.2 Importance of Collaboration between Primary Care and Vascular Specialty Care in CLI patients

In the absence of revascularization, most patients with CLI are expected to require amputation within 6 months. Therefore, timely referral to a vascular specialist is indicated to expedite treatment, prevent further deterioration, and reverse the ischemic process. Such a referral, along with continued interactive long-term care collaboration, is essential if all potential options for limb salvage are to be considered and understood by the patient. For example, patients with ulcers, gangrene, or lower extremity rest pain (i.e., CLI) require full evaluation of the anatomic basis of the ischemia.
Detailed arterial mapping requires vascular expertise to identify the etiology of the ischemia and define the options available for revascularization. Patients with CLI often have concomitant severe coronary artery disease or cerebrovascular disease. This suggests an indication for performance of investigations to define potentially severe coronary artery disease or extracranial carotid artery disease and revascularization of these circulations.

The evaluation of the risk, benefit, and optimal timing of revascularization of multiple arterial circulations is among the most complex in medical decision making. It can be challenging to stage coronary or carotid revascularization procedures in individuals with CLI and a jeopardized limb who do not present with recent coronary or cerebrovascular ischemic symptoms. The diagnostic evaluation and treatment (whether percutaneous or surgical) of coronary or cerebrovascular disease to treat asymptomatic disease in CLI patients may lead to delay in performance of limb revascularization and may theoretically increase the risk of limb loss. Indeed, proof that preprocedural (coronary and carotid) revascularization lowers short-term cardiovascular ischemic risk of limb revascularization interventions is not yet available.
6.5 CLI AND TREATMENTS FOR LIMB SALVAGE

6.5.1 Revascularization Procedures

In addition to life style modifications, an optimal medical treatment, including at least one antiplatelet regimen and a meticulous control of the cardiovascular risk factors, the lower limb revascularization is an essential step by treating CLI patients. There are two different way to improve distal blood perfusion: the surgical and the endovascular approach. The aim of these procedures is to improve ischemic rest pain or to allow an ischemic ulcer to heal, finally avoiding major amputation.

Aortoiliac disease is also called inflow disease. Infringuinal disease is also called outflow disease. Among patients with both inflow and outflow (infrainguinal) disease, the ACC/AHA guidelines as well as the TASC II guidelines recommended that inflow lesions be addressed first, whether surgery or percutaneous intervention is performed (2, 3). After this has been accomplished, revascularization of outflow disease is warranted if there is persistent infection, ischemic ulcers, or gangrenous lesions, and the ABI remains less than 0.8 (261).

Until recently, the surgical options (e.g. femoropopliteal or femorotibial bypasses) were the only available approach in order to improve foot perfusion. These kind of limb-saving interventions are associated with an increased risk of morbidity and mortality, especially in this particular CLI patients’ subset (i.e., elderly and sick patients), and despite a relatively disappointing long-term patency rate of the performed intervention, surgery was very often proposed as first line treatment (2).

Accordingly, the BASIL trial has showed that in 450 patients presenting with a CLI due to an infra-inguinal arterial disease who were eligible for either procedure (surgical or endovascular), at 30 days, there was no difference in mortality between the two groups, but surgery was associated with a significantly higher rate of morbidity (57 versus 41%). Furthermore, there was no difference in the primary end point (survival without amputation) at one year (71% with endovascular versus 68% with surgery) and three years (52% versus 57%), with only a higher rate of reintervention in the endovascular group (26% versus 18%) (262).

Concerning the percutaneous approaches, it is since more the thirty years that vascular specialists have tried to decrease the aggressiveness of revascularization procedures, finally resulting in what is nowadays called the endovascular domain (131-133). Since several years, the endovascular approach is nowadays proposed as the first revascularization procedure to attempt in many different clinical scenarios. Due to the variety and complexity of these different techniques, often
a multidisciplinary approach involving all the different vascular specialists is required, in order to tailor the revascularization procedure to each single case.

In general the degree of aggressiveness should be less for claudicant patients, than for those presenting with acute or critical limb ischelmia, where more complex, thus more risky, procedures may be attempted.

Firstly described in 1997, the endovascular approach has emerged as an attractive alternative to surgery in CLI patients (242). In the first period of the endovascular experience in case of CLI, BTK or infra-popliteal interventions were always associated with some type of femoropopliteal revascularization procedure. The rational of combining a femoropopliteal intervention with BTK interventions was that of improving the distal run-off, thus potentially improving the long-term patency of the femoropopliteal intervention. It is only very recently, that special attentions were given to the infra-popliteal region and the isolated BTK interventions.

This “new” isolated BTK disease is often observed in very elderly patients (i.e., >80 years old) presenting with longstanding diabetes. Accordingly, CLI secondary to an isolated BTK problem is associated with normal or near-normal inflow (i.e., disease-free ilio-femoro-popliteal axes) and a very severely diseased BTK region, associating multiple long chronic total occlusions of one or more of the infra-popliteal arteries.

The introduction of BTK dedicated materials and the development of BTK dedicated revascularization techniques has broadened the type of patients who may benefit from such a revascularization procedure, but most importantly has allowed a significant improvement in the technical and the clinical outcomes of these high risk patients (140, 263). However, despite the actual technical success rate (i.e., final angiographic result with <50% residual stenosis) is very high (up to 90%) and the complication rate is very low (< 5%), the mid-longterm patency rate remains quite low (12 months primary patency rate of ≈ 50%).

Indeed, if a few months patent vessel is often sufficient to heal simple or small ulcers, more complex trophic lesions, as an infected ulcer or in the presence large necrotic zones, require more time before completely heal.

Accordingly, an early vessel restenosis or reocclusion will jeopardize the ulcer healing process, finally increasing the patient’s morbidity. For these reasons, a better patency rate at 12 months has become a priority also in CLI patients presenting with an isolated BTK disease. Thanks to the vast
armamentarium of devices and techniques at disposal of every endovascular specialist and especially thanks to clinical data reported in the literature, it is now admitted that infra-popliteal endovascular interventions are associated with an acceptable primary and secondary patency rate, an acceptable rate of ulcer healing and a significant decrease in the minor and major amputations rates (263).

For all these reasons, in many centers, an endovascular revascularization attempt in case of CLI is always proposed, especially in case of an amputation scheduled, and this also in very elderly patients presenting with very complex BTK diseases. However, despite, these considerations approximatively 200,000 new amputations are yearly performed in the United States, with almost half of them performed without neither an adequate vascular evaluation nor a revascularization attempt.
6.6 ENDOVASCULAR TREATMENTS FOR CLI

Strategies for management of patients with CLI have evolved considerably in the past decade, in step with the dramatic advances in endovascular technology and technique (264, 265).

Even complex arterial lesions, such as lengthy occlusions of the iliac, femoral, and tibial arteries, can often be addressed effectively by less invasive strategies (266, 267).

The optimal strategy for management of a patient with CLI must be determined on a case-by-case basis. Important issues to consider include the urgency of the clinical presentation, the presence of comorbidity, and the arterial anatomy.

First, the distinction must be made between patients presenting with acute limb ischemia versus limb-salvage situations that are subacute or chronic. The former require rapid intervention via endovascular or surgical means. Therapy for the latter can be planned in a staged, or even contingent, fashion. For example, less invasive techniques can often be attempted initially, with the contingency of open surgery should the endovascular attempt fail (264).

Other clinical scenarios will also dictate the initial approach to the patient with CLI. In patients presenting with late-stage or life-threatening ischemia, or in those presenting with gross infection with septic or gas gangrene, emergency amputation of the extremity may be necessary to prevent catastrophic or life-threatening circulatory collapse. The requirement for revascularization in patients undergoing limb removal will depend on whether perfusion to the amputation site is sufficient to enable healing.

Percutaneous intervention, as with PTA, is a less invasive alternative to surgery in patients with CLI. As mentioned above, PTA is associated with less morbidity than surgery but a higher rate of reintervention (262). As a result, it has been suggested that PTA be offered first to patients with significant comorbidities who are not expected to live more than one to two years (262). For patients expected to live longer who are relatively fit, the reduced intervention rate and possible improved durability with bypass surgery could outweigh the short-term increase in morbidity. However, it should be stressed that the more distal the arterial disease is located (i.e. BTK) the poorer the surgical outcomes are, in terms of long-term patency. Accordingly, it is now admitted that in case of BTK intervention, an endovascular attempt, whenever feasible, should always be proposed as first line treatment, and that distal femoro-tibial bypass be reserved only for these cases where the endovascular approach has failed.
6.6.1 Dedicated BTK Material and Techniques

Balloon angioplasty, is, and probably will remain, the main stem approach for BTK interventions. The advantages and the drawbacks of this technique are well known since more than 30 years. Accordingly, one of the main limitations of the balloon only approach is the elastic recoil of the treated lesion, the intimal dissection, the vessel perforation or rupture, and last but not least the restenosis. All these concerns have forced the endovascular community and especially the medical industry to develop some alternative to the plain old balloon angioplasty.

Table 7 summarizes the different techniques and devices actually used during BTK interventions. For the moment, the more complex revascularization techniques, as the directional, orbital and rotational atherectomy or these more expensive techniques as the cryoplasty or the cutting balloon angioplasty were associated with neither a significantly improved technical success rate, nor an improved long-term patency rate nor an improved limb salvage rate.

<table>
<thead>
<tr>
<th>DEVICES</th>
<th>PROS</th>
<th>CONTRAS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Balloon angioplasty (PTA)</td>
<td>Easy to use and not expensive</td>
<td>High restenosis rate</td>
</tr>
<tr>
<td>PTA with drug eluting balloon (DEB)</td>
<td>Easy to use with favorable restenosis rates</td>
<td>Relatively expensive</td>
</tr>
<tr>
<td>Bare metal stent (BMS)</td>
<td>To be used in case of PTA failure (dissection, recoll)</td>
<td>Expensive + relatively high restenosis rates</td>
</tr>
<tr>
<td>Drug eluting stent (DES)</td>
<td>To be used in case of PTA failure with better restenosis rates</td>
<td>Very expensive</td>
</tr>
<tr>
<td>Cryoplasty</td>
<td>To be used in order to avoid stent implantation</td>
<td>No better outcomes compared to PTA</td>
</tr>
<tr>
<td>Cutting and Scooring Balloons</td>
<td>To be used in order to avoid stent implantation</td>
<td>No better outcomes compared to PTA</td>
</tr>
<tr>
<td>Atherectomy (directional or orbital)</td>
<td>In case of a severe and diffuse PAD</td>
<td>To be used only by experienced operators</td>
</tr>
<tr>
<td>Atherectomy (rotational)</td>
<td>In case of a severe calciﬁed BTK lesions</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>TECHNIQUE</th>
<th>PROS</th>
<th>CONTRAS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sub-intimal angioplasty</td>
<td>It allows very long SFA recanalization</td>
<td>Re-entry may be difficult</td>
</tr>
<tr>
<td>Distal retrograde puncture</td>
<td>In case of antegrade failure</td>
<td>To be used only by experienced operators</td>
</tr>
<tr>
<td>Pedal-plantar loop Technique</td>
<td>It improves foot perfusion in case of antegrade PTA failure</td>
<td>To be used only by experienced operators</td>
</tr>
<tr>
<td>Trans-collatérale Technique</td>
<td>It allows to visualize the entry point of the occlusion</td>
<td>Risk of « donor-vessel » damage</td>
</tr>
</tbody>
</table>

Table 7: devices and techniques used by performing BTK intervention [modified according to Bonvini RF et al. (238)]

Since several years, the use of stents is regularly performed also for BTK lesions. All type of stents, from the bare metals stents (BMS), balloon-expandable or self-expanding, to the last
generation of drug eluting stents (DES) or even from the bio-absorbable stents, have already been tested in retrospective, in prospective and even in randomized controlled trials in patients presenting with a CLI secondary to an isolated BTK disease. The major drawbacks of stents implanted at the infra-politeal level include: stent compression, fracture, restenosis and occlusion (268, 269).

6.6.2 Technical Aspects of BTK Interventions

Once the CLI is retained based on clinical ground and the non-invasive arterial evaluation, usually an endovascular approach has to be preferred compared to the more aggressive surgical options. Usually an antegrade approach of the ipsilateral common femoral artery should be preferred because of a better pushability and torqueability of the material using this approach and the possibility to reach also very distal lesion in case of necessity (i.e. below the ankle interventions).

The exact vascular anatomy, as well as the exact disease extension should be obtained with a selective injection directly in the distal segment of the popliteal artery, and at that moment the best revascularization strategy should be planned. Due to the frequency of the presence of a multivessel and multilevel disease, the initial revascularization strategy should be carefully evaluated, because it is often not possible to completely revascularize all the three diseased vessels. The aim of every BTK revascularization attempt is to restore a pulsatile direct flow to the foot and preferentially to the part of the foot presenting the ischemic ulcer. This angiosome concept (see below) is of paramount importance because in order to give all the chances to an ulcer to heal it is mandatory to reopen the target vessel perfusing the diseased part of the foot (270, 271). Accordingly, it seems not reasonable to treat an easier to treat vessel, which is not targeting the ulcer and leave the completely occluded target vessel untreated.

Furthermore, it is also of capital importance to assure a sufficient distal foot perfusion and not to establish a perfect three vessels recanalization just to the ankle and leave the below the ankle foot perfusion untreated. This is essential in order to improve ulcer healing as well as to improve BTK vessel patency, because the BTK vessel reocclusion rate is increased in case of a bad distal foot runoff (272).

Once revascularized at least one BTK vessel straight down to the foot, it is mandatory that this unique vessel remains patent sufficiently long, in order to allow the ulcer to heal. Accordingly, in case of a single vessel runoff, the use of more expensive devices, assuring a better longterm patency
seems reasonable (e.g., DES or DEB), as well as the attempt of more complex thus more risky, revascularization techniques.

6.6.2.1 The trans-collateral approach: *(Figure 49):*

This technique, very similar to that used for the coronary retrograde recanalization approach, is aimed to better visualize the entry zone of the occluded vessel. The retrograde wire will give a better target for the antegrade wiring (i.e. “kissing wire technique”), which may safely and more rapidly be performed also using dedicated, thus more aggressive, recanalization wires. Furthermore, in case of antegrade wiring failure, the retrograde wire may be also used as the primary recanalization wire, creating a microchannel from retrograde, thus facilitating the balloon passage and the entire revascularization procedure. The most developed collateral branch has to be preferred, because through this collateral it might be necessary to advance different type of microcatheters of balloon catheters (273, 274).

*Figure 49: Trans-collateral approach to recanalize an occluded posterior tibial artery (ATP) through a collateral arising from the peroneal artery (AP)*

Black arrow = sub-intimal antegrade wire - White arrow = PTA through the collateral  
[reproduced from Bonvini RF et al. (238)]
6.6.2.2 The retrograde approach via the direct puncture at the foot level: (Figure 50):

This technique, similarly to that of the trans-collateral approach, facilitates the connection between both patent segments proximally and distally the occlusion. This retrograde approach should only be used in case of a failed previous antegrade attempt (275). The rational of using this approach is that often the retrograde intraluminal recanalization is more easily obtained than that performed antegradely which relatively often turn in a sub-intimal recanalization failure. Indeed, once the vascular access is obtained at the level of the foot, the intra-luminal connexion is secured and than the chance of failure decreases significantly (276, 277).

Usually the ATP or the pedal artery in the distal ATA’s segment at the level of the ankle should be used, because at this level these arteries are easier to puncture and especially are easy to compress obtaining adequate hemostasis. However, in case of necessity, the direct puncture of the peroneal artery may be attempted, with special considerations at the end of the procedure while attempting hemostasis (i.e. blood pressure cuff at site of puncture and rigours local and hemodynamic surveillance during the first six hours post-procedure).

Figure 50: posterior tibial artery (ATP) puncture for a retrograde ATP recanalization
White arrow = micro-needle puncturing the distal ATP; APL = plantar artery;
Black arrow = wire and balloon directly inserted through the foot skin [reproduced from Bonvini RF et al. (238)]
6.6.2.3 The pedal-plantar loop technique: *(Figure 5)*:

As mentioned above, this technique may be very useful in order to increase the foot perfusion when the disease is extending the below the ankle region and there is the impossibility to reopen the occluded vessel targeting the ischemic lesion. Accordingly, the plantar arch is dilated up to the contralateral vessel, in order that the single open vessel arriving to the foot is able to perfuse, thanks to an improved plantar arch, also the contralateral part of the foot (278). This re-established loop between the plantar arch and the pedal artery should allow a better fingers perfusion, thus finally improving ulcer’s healing process (279, 280).

*Figure 51*: plantar arch angioplasty through the dorsalis pedis artery (ADP) in order to improve the plantar artery perfusion (APL)

White arrows = sub-occlusion before and after angioplasty [reproduced from Bonvini RF et al. (238)]
6.6.3 Evidence Based Therapy for BTK – CLI Endovascular Revascularization

The number of publications evaluating the efficacy and safety of an endocascular approach in case of CLI and BTK lesions has exponentially increased in recent years. Although the number of large prospective randomized trials is still low; several well conducted ongoing studies will soon give us a lot of answers concerning the best endovascular approach in case of CLI and BTK lesions.

Accordingly, different techniques and devices have already been studied and interestingly the reported technical success rate of these procedures was very high (up to 99%). The mean primary patency rate at one year was also quite encouraging (73%), but the most interesting data were the obtained mean one year limb salvage rate, which was of 88.8% (161, 238).

By analyzing the subgroup of patients receiving a stent for a BTK lesion, Biondi-Zoccai et al. (161) have recently reported an interesting meta-analysis including 18 BTK studies with more than 600 patients. In this meta-analysis, including a follow-up period ranging from 6 to 24 months, the reported restenosis rate was of 26%, with a mean primary patency rate of 79% and a mean target lesion revascularization rate of only 10%. The functional class improvement was of 91% of the analyzed patients, while the one year limb salvage rate of 96%.

The direct or the indirect comparison between BMS and DES has suggested a better patency rate by using DES (especially sirolimus eluting stents), however, without any significant benefit in term of one year limb salvage.
The lifetime risk of a foot ulcer for patients with diabetes (type 1 or 2) may be as high as 25% (281). Diabetic foot ulcers are a major cause of morbidity and mortality, accounting for approximately two-thirds of all nontraumatic amputations performed in the United States (282, 283). This observation illustrates the importance of prompt treatment of foot ulcers in patients with diabetes.

### 7.0.1 Wound Classification

The first step in managing diabetic foot ulcers is classifying the wound. Classification is based upon clinical evaluation of the extent of the lesion and, in some classification systems, an assessment of the vascular status of the foot. The intensity and duration of treatment can be determined after clinical evaluation of the ulcer.

A widely used classification of diabetic foot ulcers is that proposed by Wagner (284, 285):

- **Grade 0** — No ulcer in a high-risk foot
- **Grade 1** — Superficial ulcer involving the full skin thickness but not underlying tissues (*Figure 52*)
- **Grade 2** — Deep ulcer, penetrating down to ligaments and muscle, but no bone involvement or abscess formation (*Figure 53*)
- **Grade 3** — Deep ulcer with cellulitis or abscess formation, often with osteomyelitis (*Figure 54*)
- **Grade 4** — Localized gangrene (*Figure 55*)
- **Grade 5** — Extensive gangrene involving the whole foot (*Figure 56*)
Figure 52: **Wagner Grade 1** = Superficial ulcer involving the full skin thickness

Figure 53: **Wagner Grade 2** = deep ulcer, penetrating down to ligaments and muscle

Figure 54: **Wagner Grade 3** = Deep ulcer with cellulitis ± abscess formation ± osteomyelitis

Figure 55: **Wagner Grade 4** = Localized gangrene

Figure 56: **Wagner Grade 4** = Extensive gangrene involving the whole foot

[Figures 52-53-54 are courtesy of Prof. Zeller Th., Bad Krozingen, Germany]
The Wagner classification is based upon clinical evaluation (depth of ulcer and presence of necrosis) alone and does not account for the vascular status of the foot. A modified system that is frequently used by orthopedic surgeons individually scores the components of wound depth and ischemia (286). The International Working Group on the Diabetic Foot proposed classifying all ulcers according to the following categories: perfusion, extent, depth, infection, and sensation (PEDIS classification) (287).

The treatment of diabetic foot ulcers begins with a comprehensive assessment of both the patient's general medical condition and the wound. Evidence for the presence of underlying neuropathy, bony deformity, and PAD should be actively sought. A standardized system for classifying foot ulcers should be used to document initial presentation and plan appropriate treatment.

Extensive debridement, good local wound care, relief of pressure on the ulcer by mechanical off-loading, and control of infection (when present) are believed to be important components of therapy for grade 1 and 2 foot ulcers. There are few data comparing methods of debridement (sharp, enzymatic, autolytic, mechanical, and biological).

There are several methods to achieve mechanical off-loading, including total contact casts, cast walkers, wedge shoes, and bedrest. Local wound care is an important component of therapy. Dressings are selected based upon wound characteristics including the presence of heavy exudate, desiccation, or necrotic tissue. Antibiotics are administered when infection is present. Following wound debridement or partial foot amputation, negative pressure wound therapy to manage the open wound is often proposed. Residual necrotic tissue or osteomyelitis must be debrided from the wound prior to using these devices.

In order to determine optimal therapy for patients with Wagner grade ≥3 ulcers, it is necessary to assess for peripheral artery disease and/or bony involvement. In patients with Wagner grade ≥3 ulcers and CLI, revascularization is recommended. Patients with Wagner class 4 and 5 ulcers require immediate surgical consultation, especially in case of sign of symptoms of local ± general infection.

While a revascularization attempt is mandatory in case of CLI associating an ischemic ulcer of the lower limb with a severe PAD, the attitude in case of a non-healing ulcer associated with only a mild PAD has not yet being defined. Even if in some center it is recommended that revascularization
interventions should be performed in every patient with any degree of limb ischemia and a non-healing ulcer, this attitude is based on any clinical evidence.

Accordingly, it results very difficult to exactly establish the clinical relevance of a mild PAD in the presence of an ulcer of mixed origin. Indeed, the presence of a mix ulcer (i.e. arterial + venous + neuropathic) may be as frequent as up to 20% (288) and this mixed origin was found to be a significant predictor of slow ulcer healing process (289, 290).

Several important therapeutic issues are associated with ulcers of mixed origin, because in the presence, even of mild PAD, an aggressive compression stocking for the venous component may be contraindicated. Furthermore, so far, there is no evidence that by performing a revascularization procedure of a mild concomitant PAD may facilitate the ulcer healing process of these mixed ulcers.
7.1 ANGIOSOME CONCEPT (*Figure 57-58-59*)

The angiosome concept was firstly described by Taylor and Palmer in 1987 (291). It divides the body into three-dimensional vascular territories which are supplied by specific arteries and drained by specific veins (291). In the lower limbs, they defined five distinct angiosomes which are fed by the medial sural artery, the lateral sural artery, the posterior tibial artery, the anterior tibial artery, and peroneal artery. The foot and ankle areas have six distinct angiosomes arising from the posterior, the anterior and the peroneal arteries (291).

**Posterior Tibial Artery**: the posterior tibial artery supplies the medial ankle and the plantar portions of the foot. Arising from the posterior tibial artery, the calcaneal branch supplies the medial heel, the medial plantar artery supplies the instep, and the lateral plantar artery supplies the lateral midfoot and forefoot.

**Anterior Tibial Artery**: the anterior tibial artery becomes the dorsalis pedis artery, which supplies the dorsum of the foot.

**Peroneal Artery**: The two branches of the peroneal artery supply the anterolateral portion of the ankle and rear foot. The anterior perforating branch supplies the lateral anterior upper ankle, and the calcaneal branch supplies the lateral heel.

**Toes’ perfusion**: The dorsum side of the toes and foot are fed by the anterior tibial artery and dorsalis pedis artery, while the plantar side of the toes and foot without the lateral heel are fed by the posterior tibial and the plantar arteries.

Despite the fact that the angiosome concept helps the interventionist to better target the most important vessel to the healing process of the ulcer, several anatomical considerations should be known before performing any type of endovascular intervention. Accordingly, any significant stenosis (i.e. >70% lumen narrowing) at the ilio-femoro-popliteal level will be considered hemodynamically relevant and thus will be treated before attempting any further infra-popliteal revascularization procedure.

In case no significant “in-flow” lesion is detected at the ilio-femoro-popliteal level, the patient must present at least one stenotic/occluded vessel of the below the knee arteries (i.e. anterior and posterior tibial arteries, peroneal artery) in order to be considered having a clinically relevant PAD. In
the situation of the PAD being secondary to an isolated BTK disease and the patient presents a CLI, according to the angiosome concept, the target vessel perfusing the ulcer region will be preferentially treated (see CLI chapter) (270, 271, 292).

Accordingly, the anterior tibial artery will be responsible for the antero-lateral pre-tibial region, while the posterior artery for the postero-medial region. In case of the technical impossibility to treat one of these two vessels, or in case of a diffuse ulcer region involving more the one region, the peroneal artery will also be treated if presenting with a significant stenosis. Here detailed the vascular territories perfusing the different tibial and foot regions according to the angiosome concept:

**Anterior tibial artery:**

**Peroneal artery:**

**Posterior tibial artery:**

![Figure 57: Angiosome concept: calf's level](adapted from Galliano RD (293))
Figure 58: Angiosome concept at the foot's level [reproduced from Iida O et al. (294)]

Lateral plantar artery: Medial plantar artery:

Figure 59: Angiosome concept at the foot’s level according to vessel anatomy

[adapted from Galliano RD (293)]
7.2 PRIMARY AMPUTATION

The vast majority of patients presenting with even critical ischemia can be offered a reasonable attempt at limb salvage. Overall, only about 25 percent of patients with critical limb ischemia undergo amputation within one year (2, 3).

The ACC/AHA and the TASC II guidelines identified the following as risk factors for amputation in patients with limb-threatening ischemia (2, 3):

- Significant necrosis of weight-bearing parts of the foot in ambulatory patients
- An uncorrectable flexion contracture
- Paresis of the extremity
- Ischemic rest pain
- Sepsis
- Limited life expectancy due to comorbid disease

One such setting is when gangrene extends into the deeper tissues of the tarsal region of the foot or myonecrosis involves the lower leg; primary amputation at the below knee level is probably indicated in such patients.

If the patient is reasonably healthy, a well fitting prosthesis will provide excellent functionality. The functional outcome following below knee amputation is far better than that following amputation at the ankle. This is due in large part to the better fit at the leg as opposed to the ankle, and excellent cosmesis of modern prosthetics.

An above knee primary amputation should be considered when the patient is unable to ambulate, communicate, or provide self care. Relative disadvantages of below knee amputations in this situation include a lesser likelihood of healing than more proximal amputation and the development of severe contractures. Figure 60 schematically shows the different level of amputations.
Figure 60: level of amputation [modified according the TASC II guidelines (2)]:
- **Below the knee amputations (blue lines)** = toe; fore-foot; infra-genicular amputation;
- **Above the knee amputations (red lines)** = supra-genicular amputation; hip desarticulation
7.3 OTHER MEDICAL APPROACHES IN DIABETIC FOOT AND CLI PATIENTS

7.3.1 Pharmacologic therapy

There are no data to support the routine use of primary pharmacologic therapy in patients with CLI, and the best therapeutic options are revascularization with surgery or PTA. However, many patients are poor candidates for either procedure because of concomitant diseases or unfavorable anatomy. Medical therapies would be desirable in such patients.

7.3.1.1 Prostaglandin E1:

Prostaglandin E1 (PGE1) is a vasodilator and inhibitor of platelet aggregation. However, it is rapidly inactivated in the lungs, and must be given intra-arterially or intravenously using large doses. One study randomly assigned 1560 patients with chronic CLI (rest pain for ≥2 weeks or foot ulceration or gangrene) to treatment with intravenous PGE1 (alprostadil) or no PGE1 for 28 days (295). At hospital discharge, the combined end point (death, amputation, persistence of CLI, acute myocardial infarction, or stroke) was significantly lower in the treated patients (64 versus 74% for no treatment, p<0.001). However, there was no long-term clinical benefit and at six months with no significant difference in the evaluated end points (53 versus 58%). For this reason, the 2007 TASC II consensus document does not recommend to systemically use PGE1 or any other prostanooids for the management of limb-threatening ischemia (2).

7.3.2 Stimulation of angiogenesis

Stimulation of angiogenesis is an investigational approach to the therapy of CLI. Two modalities have been studied: therapeutic angiogenesis and autologous implantation of bone marrow mononuclear cells. Therapeutic angiogenesis is also being evaluated in patients with intermittent claudication and refractory angina.

Therapeutic angiogenesis involves the administration of angiogenic growth factors, as recombinant protein or naked DNA, to augment the collateral circulation and enhance blood flow to ischemic tissues (296). The intravenous or intramuscular gene transfer of naked plasmid DNA, encoding for vascular endothelial growth factor, can induce marked improvement in endothelial function, flow reserve, collateral vessel development, healing of ischemic ulcers, and limb salvage,
eliminating the need for amputation in some patients (297, 298), however, these are not yet proven interventions and are not available as established therapies (299).

The possible efficacy of *autologous implantation of bone marrow mononuclear cells* to stimulate angiogenesis was evaluated in a study of 45 patients with CLI (including rest pain, nonhealing ischemic ulcers, or both) who were not candidates for surgical or nonsurgical revascularization (300). Injection with bone marrow mononuclear cells was associated with significant improvement in several measures of limb ischemia compared with either injection of peripheral blood mononuclear cells or saline, including the ABI, rest pain, and pain-free walking time. These improvements were sustained at 24 weeks. In a similar study of seven patients, endothelium-dependent vasodilation was enhanced by bone marrow cell implantation (301).

Similar benefits may be achieved by multiple intramuscular injections of *autologous granulocyte colony-stimulating factor* mobilized peripheral blood mononuclear cells into ischemic limbs. In a pilot randomized trial of 28 diabetic patients with critical limb ischemia, this approach compared to controls was associated with improved lower limb perfusion, as demonstrated by Doppler studies and an increase in the mean ankle-brachial pressure index and a doubling of the rate of healing of ischemic ulcers (14 of 18 versus 7 of 18) (302).

### 7.3.3 Spinal cord stimulation

Initial uncontrolled studies suggested that spinal cord stimulation was effective for pain relief and might prevent or delay amputation and improve limb survival (303, 304). However, a controlled trial that randomly assigned 120 patients to spinal cord stimulation in addition to best medical therapy or to best medical therapy alone found that the rates of survival and amputation were the same in both groups (305). Pain scores were also similar although the spinal cord stimulation group was able to reduce pain medications by approximately 50%.

### 7.3.4 Distal venous arterialization

Although patients with critical ischemia who are not suitable for revascularization generally undergo amputation, this is associated with a high morbidity and mortality, particularly in older adults. One novel approach for these patients is the use of the disease-free venous bed as an alternative conduit for perfusion of the peripheral tissues with arterial blood; this process is called distal venous arterialization. In the absence of any substantial forward flow from the arterial circulation into the
capillaries, blood fed into the venous system at arterial pressure should be able to backflow into the nutritive capillary vessels and provide adequate local oxygenation.

The efficacy of this approach was evaluated in a study in which 18 patients underwent a bypass procedure to the venous bed of the foot; the most distal satisfactory patent artery, generally the common femoral or popliteal artery, was used for inflow into the graft, which was most often the ipsilateral or contralateral long saphenous vein or a synthetic graft (306, 307). After a follow-up of 17 months, three grafts failed early and there was one late failure; three patients required amputation while 15 patients had relief of symptoms and had healing of ulcers and gangrene resulting in an overall limb-salvage rate of 83%.
8.0 ACUTE LIMB ISCHEMIA

Acute limb ischemia (ALI) arises when a rapid or sudden decrease in limb perfusion threatens tissue viability. This form of ischemia may be the first manifestation of arterial disease in a previously asymptomatic patient or may occur as an acute event that causes symptomatic deterioration in a patient with antecedent lower extremity PAD and intermittent claudication (308).

The severity of ALI depends on the location and extent of arterial obstruction and the capacity of the collaterals to perfuse the ischemic territory. Severity may be influenced by the status of systemic perfusion (cardiac output and peripheral resistance). Acute limb ischemia is often associated with thrombosis due to atherosclerotic plaque rupture, thrombosis of a lower extremity bypass graft, or lower extremity embolism originating from the heart or a proximal arterial aneurysm.

When embolic occlusion affects a vascular bed not previously conditioned by collaterals, the resulting ischemic syndrome is typically severe. Collateral development in relation to the severity and chronicity of pre-existing ischemia due to atheromatous obstructive arterial disease lessens the severity of ischemia when acute thrombotic arterial occlusion develops. Arterial embolism is more likely than arterial thrombosis to cause sudden, severe, limb-threatening ischemia.

The hallmark clinical symptoms and physical examination signs of ALI include the 5 “Ps” that suggest limb jeopardy: pain, paralysis, paresthesias, pulselessness, and pallor. Some clinicians would also include a sixth “P,” polar or prostration, to indicate a cold extremity or the patient’s sufferances respectively. In certain clinical settings, however, arterial embolism can occur without symptoms, whereas thrombosis can produce sudden, severe limb ischemia.

The clinical diagnosis of arterial embolism is suggested by (a) the sudden onset or sudden worsening of symptoms, (b) a known embolic source (including atrial fibrillation, severe dilated cardiomyopathy, left ventricular aneurysm, atheromatous plaque in the aorta or proximal limb arteries, or mural thrombus lining the wall of an aortic or arterial aneurysm), (c) the absence of antecedent claudication or other manifestations of obstructive arterial disease, or (d) the presence of normal arterial pulses and Doppler systolic blood pressures in the contralateral limb.

Arterial emboli typically lodge at branch points in the arterial circulation where the caliber of the arterial lumen diminishes (i.e., bifurcations). Embolism to the aortoiliac bifurcation (“saddle embolus”) may produce bilateral lower-limb ischemia occasionally associated with reversible paraplegia and a high mortality rate (308, 309). Embolic occlusions at sites of arterial bifurcation may cause more
profound ischemia when collaterals of perfusion are interrupted, as occurs when the profunda femoris artery is compromised by embolism to the more proximal common femoral artery.

Acute limb ischemia may also occur as a result of acute arterial thrombosis superimposed on a stenotic atherosclerotic plaque. A common site of thrombosis is the superficial femoral artery, although occlusion may occur anywhere from the aorta to the digital arteries. Rarely, an extrinsic local factor such as popliteal entrapment, cystic adventitial disease, or repetitive trauma may be the precursor of arterial thrombosis. The location of the obstruction in relation to other axial arteries in the region of the obstructed vessel and the collateral flow they provide also affects the severity of ischemia. The longer the obstructive lesion, the more collateral pathways that are interrupted. Thrombosis tends to propagate proximally in an artery, up to the next large side branch. The low flow state distal to the obstructing thrombus also encourages distal propagation of thrombus. This is the rationale for treating patients promptly with systemic anticoagulation.

Typically, pulselessness, pallor, paresthesias, paralysis, and coolness characterize acutely ischemic limbs, and assessment of these features is aided by comparison with the contralateral limb. Evaluation of “capillary” return, which reflects the emptying and refilling of subpapillary venules, is subject to considerable environmental and interobserver variation, but capillary return is usually slow or absent in ALI. Some, but not all, patients with sensory loss describe numbness or paresthesias, but pre-existing sensory deficits in diabetic patients can lead to confusion. Motor deficits indicate advanced, limb-threatening ischemia, in part because foot movement is produced mainly by more proximal muscles. Dorsiflexion or plantar flexion of the great toe is produced by muscles that originate just below the knee that are innervated by the peroneal nerve that passes through the anterior tibial compartment.

Persistent pain, sensory loss, and toe muscle weakness are among the most important findings that identify the patient with threatened limb loss. Muscle rigor, tenderness, and pain on passive movement are late signs of advanced ischemia predictive of tissue loss.

According to the TASC II guidelines, ALI is defined as a sudden decrease in limb perfusion that causes a potential threat to limb viability (manifested by ischemic rest pain, ischemic ulcers, and/or gangrene) in patients who present within two weeks of the acute event (2). Patients with similar manifestations who present later than two weeks are considered to have CLI, which is by definition chronic.
The management of acute arterial occlusion remains a challenge for vascular specialists. Surgical thromboembolectomy and bypass grafting were the mainstays of therapy for many years (310). Subsequently, thrombolytic therapy ± thrombectomy procedures ± PTA ± stenting have become treatment options for selected patients.

Despite these advances, the morbidity, mortality, and limb loss rates from acute lower extremity ischemia remain high. Thus, regardless of the treatment modality used, early diagnosis and rapid initiation of therapy are essential in order to salvage the ischemic extremity.
8.1 ETIOLOGIES

Acute arterial occlusion can be the result of emboli from a distant source, acute thrombosis of a previously patent artery, or direct trauma to an artery.

8.1.1 Arterial emboli

Eighty percent of arterial emboli originate in the heart and travel to the extremities; the lower extremities are affected much more frequently than the upper extremities. The majority of these emboli occur in patients with significant underlying cardiac disease; the severity of the patient's underlying cardiac condition may increase the risk of surgery, and limit the options available for restoring blood flow to the ischemic extremity.

Potential sources of emboli from the heart include left ventricular thrombus formation following myocardial infarction, and atrial thrombus in patients with atrial fibrillation. Up to 75% of patients with emboli to the lower extremities have a history of recent myocardial infarction or atrial fibrillation.

Arterial to arterial embolization of thrombus or plaque originating from aneurysms or atherosclerotic lesions is another well described occurrence and accounts for 20% of peripheral emboli.

Emboli typically lodge where there is an acute narrowing of the artery, such as an atherosclerotic plaque or a point where the vessel branches (i.e., bifurcations): the common femoral, common iliac, and popliteal artery bifurcations are the most frequent locations. In a large series of arterial embolism, for example, the following frequencies were noted:

- Femoral — 28%
- Arm — 20%
- Aortoiliac — 18%
- Popliteal — 17%
- Visceral and other — 9% each

In comparison to clot emboli, atheroemboli are less likely to produce symptoms of acute arterial occlusion. Atheroemboli are typically nondistensible and irregularly shaped; as a result, they tend to
produce incomplete occlusion with secondary ischemic atrophy. One exception is the blue toe syndrome (see above).

8.1.2 Arterial thrombosis

Thrombosis of a previously patent but stenotic artery is a well-known complication of atherosclerosis. Occlusion of atherosclerotic vessels may occur by two mechanisms:

- Progressive atherosclerotic narrowing of the artery, with resultant low flow, stasis, and finally thrombosis
- Plaque’s rupture with consequent intraplaque hemorrhage and local hypercoagulability leading to thrombosis.

The ischemia resulting from arterial thrombosis in the face of underlying atherosclerosis is usually less severe than that following an acute embolus. This difference is primarily due to the collateral circulation that develops over time in patients with atherosclerosis and chronically narrowed vessels. Collaterals are frequently so extensive that patients notice no change or only a mild increase in their symptoms of chronic ischemia when a major atherosclerotic vessel becomes occluded.

Arteritides, ergotism, and hypercoagulable states can also result in arterial thrombosis, occlusion, and acute extremity ischemia. While these conditions most frequently affect the venous circulation, certain hypercoagulable states favor arterial thrombosis (e.g., antiphospholipid antibodies and hyperhomocysteinemia).

8.1.3 Arterial trauma

Acute arterial occlusion complicating vascular or cardiac diagnostic and interventional procedures has become a more frequent cause of acute extremity ischemia. The incidence of arterial complications following interventional cardiac catheterization (including hematomas, arteriovenous fistulae, pseudoaneurysms, arterial occlusion, and cholesterol emboli) has been reported to range from 1.5 to 9% (311). Although acute arterial occlusion occurs in less than 1% of interventional catheterization procedures, this complication demands immediate surgical or endovascular management (312). Intimal flaps and dissections are frequently the cause of the occlusion, and an endovascular repair of the vessel is often required. Thromboemboli can also develop at the sheath site or catheter tip, with embolization occurring during sheath removal.
8.1.3.1 Differential Diagnosis of Acute Limb Ischemia:

The differential diagnosis of ALI involves exclusion of conditions that mimic arterial occlusion, identification of non-atherosclerotic causes of arterial occlusion, and differentiation of ischemia caused by an arterial thrombosis from embolism.

Non-atherosclerotic causes of ALI include arterial trauma, vasospasm, arteritis, hypercoagulable states, compartment syndromes, arterial dissection, and external arterial compression, such as occurs with a popliteal cyst.

Other conditions that may mimic arterial occlusion are acute deep venous thrombosis, especially when associated with features of phlegmasia cerulea dolens; and acute compressive peripheral neuropathy.
8.2 CLINICAL EVALUATION

A thorough history and physical examination is the first step in the evaluation of the patient with acute extremity ischemia (313). The five "P's" of acute ischemia or large vessels are:

- Pain
- Pulselessness
- Pallor
- Paresthesias
- Paralysis

In addition, small vessel occlusion can cause the blue toe syndrome.

**Pain** — Pain associated with acute ischemia is usually located distally in the extremity, gradually increases in severity, and progresses proximally as the length of ischemia increases. Later, the pain may decrease in severity due to progressive ischemic sensory loss.

It is essential to determine if the patient had symptoms of chronic ischemia before the acute event occurred. Patients with an embolus usually have no pre-existing ischemic symptoms, and can frequently pinpoint the exact time that symptoms began. Thus, the sudden and dramatic development of ischemic symptoms in a previously asymptomatic patient is most consistent with an embolus, while gradually increasing symptoms in a patient with chronic ischemia is indicative of thrombosis.

**Pulse** — The quality and character of the peripheral pulses must be evaluated. If pulses are not palpable, a hand held Doppler should be used. It is rare to have acute limb-threatening ischemia without a major pulse deficit.

The status of the pulses in the contralateral extremity is also important. The presence of a pulse deficit in an asymptomatic contralateral extremity is an indication of underlying chronic arterial occlusive disease and suggests that acute thrombosis of an already diseased vessel is the most likely cause of the acute occlusion. By contrast, the presence of normal pulses in the contralateral extremity suggests the absence of chronic occlusive disease, and increases the likelihood that an embolus is the etiology of acute occlusion.
**Skin** — The skin of both the normal and affected extremity should be examined for temperature, color, and capillary refill. The skin of the ischemic extremity is typically cool and pale with delayed capillary filling. The level of arterial obstruction is usually one joint above the line of demarcation between the normal and ischemic tissue. Both extremities should also be examined for signs of chronic ischemia such as ulcers, atrophy of the skin, hair loss, and thickened nails.

**Neurologic examination** — A careful neurologic examination must be performed. Subjective sensory deficits such as numbness or paresthesias are signs of early nerve dysfunction secondary to ischemia. Major loss of sensory or motor function is indicative of advanced ischemia. The anterior compartment of the lower leg is most sensitive to ischemia, and sensory deficits over the dorsum of the foot are often the earliest neurologic sign of vascular insufficiency.

**Blue toe syndrome** — The blue toe syndrome is characterized by the sudden appearance of a cool, painful, cyanotic toe or forefoot in the often perplexing presence of strong pedal pulses and a warm foot. There may also be scattered areas of petechiae or cyanosis of the soles of the feet. The blue toe syndrome is usually due to embolic occlusion of digital arteries with atherothrombotic material from proximal arterial sources. These episodes lead to similar and more severe episodes in the future, thus, identification and eradication of the embolic source is usually indicated (260).
8.3 CLASSIFICATION

The following clinical categories of ALI have been proposed (Table 8) (3, 314):

- **Viable** — Viable limbs are under no immediate threat of tissue loss. There is no sensory loss or muscle weakness and both arterial and venous Doppler signals are audible.

- **Marginally threatened** — Marginally threatened limbs are salvageable if treated promptly. There is minimal (in the toes) or no sensory loss, no muscle weakness, arterial Doppler signals are often inaudible, and venous Doppler signals are audible.

- **Immiscibly threatened** — Immiscibly threatened limbs are salvageable with immediate revascularization. Sensory loss involves more than the toes and may be associated with rest pain. There is mild to moderate muscle weakness, arterial Doppler signals are usually inaudible, and venous Doppler signals are audible.

- **Irreversible (nonviable)** — Irreversible limbs have major tissue loss and/or permanent nerve damage. Sensory loss is profound, muscle weakness is profound with paralysis and possible rigor, and arterial and venous Doppler signals are inaudible. These nonviable extremities require major amputation regardless of the therapy that is instituted, however, revascularization may be required to permit healing of the amputation or amputation at a lower level.

<table>
<thead>
<tr>
<th>CATEGORIES</th>
<th>Sensory loss</th>
<th>Muscle Weakness</th>
<th>Arterial Signals</th>
<th>Venous Signals</th>
<th>Prognosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Viable</td>
<td>None</td>
<td>None</td>
<td>Audible</td>
<td>Audible</td>
<td>Not immediately threatened</td>
</tr>
<tr>
<td>Threatened Limb (marginally)</td>
<td>Minimal (toes) or none</td>
<td>None</td>
<td>Often inaudible</td>
<td>Audible</td>
<td>Salvageable if promptly treated</td>
</tr>
<tr>
<td>Threatened Limb (immediately)</td>
<td>More than toes, rest pain</td>
<td>Mild or moderate</td>
<td>Usually inaudible</td>
<td>Audible</td>
<td>Salvageable if immediately treated</td>
</tr>
<tr>
<td>Irreversible</td>
<td>Profound, anesthetic</td>
<td>Profound paralysis</td>
<td>Inaudible</td>
<td>Inaudible</td>
<td>Amputation unavoidable</td>
</tr>
</tbody>
</table>

*Table 8: clinical categories of ALI [modified according to Katzen BT (314)]*
8.4 DIAGNOSTIC TESTS

Despite more and more non-invasive imaging modalities (e.g., CTA, MRA) are performed to confirm the arterial origin of an ALI, arteriography remains the diagnostic procedure that provides the most useful information in the setting of acute arterial occlusion. In addition to demonstrating detailed arterial anatomy, arteriography can usually distinguish between thrombosis and embolism.

- An embolus will often demonstrate a sharp cutoff with a rounded reverse meniscus sign. The embolus may also be visible as an intraluminal filling defect if the vessel is not completely occluded. Other findings which are most consistent with an embolus include the presence of otherwise normal vessels, the absence of collateral circulation, and the presence of multiple filling defects.
- Arterial thrombosis is usually visualized as a sharp or tapered, but not rounded, cutoff on arteriography. Diffuse atherosclerosis with well developed collateral circulation is generally present.
8.5 TREATMENTS

Acute limb ischemia is a situation that requires prompt diagnosis and treatment to preserve the limb. Early treatment is also necessary to prevent systemic illness and/or death that might result from the metabolic abnormalities associated with tissue necrosis. Although the technical ability to recanalize or revascularize occluded arteries that perfuse ischemic tissues has improved significantly, the pathophysiology of the local and systemic clinical sequelae associated with reperfusion of an ischemic limb is only partially understood. Revascularization of an ischemic extremity may be complicated by reperfusion injury (i.e., reperfusion syndrome) to the damaged tissues and may precipitate systemic responses, including cardiac, renal, and pulmonary dysfunction.

It is difficult to compare published results of the treatment of acute extremity ischemia because of different methods used to describe the severity of ischemia and differences in the duration of ischemia. However, it is clear that acute extremity ischemia is associated with high hospital morbidity and mortality and high rates of limb loss. Limb loss rates as high as 3% and hospital mortality as high as 20% have been quoted in surgical series. Cardiopulmonary complications account for the majority of the deaths, underscoring the severity of the baseline medical condition of these patients.

**Heparin** — The best defense against limb loss is prompt initiation of therapy. Thus, once the diagnosis of acute arterial occlusion has been made by history and physical examination, the 2008 American College of Chest Physicians (ACCP) guideline on antithrombotic therapy for peripheral artery occlusive disease and the 2007 TASC II consensus document on the management of PAD recommend that the patient should immediately receive intravenous heparin followed by a continuous heparin infusion (2, 315).

Anticoagulation will prevent further propagation of thrombus, and inhibit thrombosis distally in the arterial and venous systems due to low flow and stasis. Time is crucial; the decision to administer heparin is based upon the clinical evaluation and should not be delayed while waiting for diagnostic procedures to be performed.

Following the initiation of heparin, treatment then varies depending upon the viability of the limb. Options include surgery and endovascular options including thrombolytic therapy, thrombectomy procedures as well as angioplasty ± stenting.
8.6 PATIENTS WITH THREATENED EXTREMITIES

Patients with a threatened extremity should undergo emergent surgical or percutaneous revascularization. The majority of these patients have had an embolic event, and irreversible changes can occur within as little as four to six hours of profound ischemia. While pharmacologic thrombolysis may successfully dissolve the embolus (see below), the time required is usually too long to allow this to be an acceptable alternative to surgery. For this reason and since several years many centers used as adjunctive treatment modality including different type of thrombectomy procedures (e.g. rheolytic, aspiration, fragmentation).

At surgery, an embolus will be found in the majority of patients. Embolectomy (e.g., Fogarty procedures) is usually all that is required to relieve the occlusion and provide adequate blood flow to the extremity. Most surgeons perform an intraoperative completion arteriogram after the embolectomy to evaluate the adequacy of distal blood flow. Intraoperative thrombolytic therapy may also be used if there are small emboli in the distal runoff vessels. Depending upon the length and severity of the ischemia, a fasciotomy may be required to prevent the development of a compartment syndrome.

The 2008 American College of Chest Physicians (ACCP) guidelines on antithrombotic therapy recommended the use of oral anticoagulation to prevent recurrent embolism after embolectomy (315).
8.7 PATIENTS WITH VIABLE EXTREMITIES

Intraarterial thrombolysis is an alternative to surgical therapy in patients with ischemic but viable extremities (316, 317). The usefulness of thrombolytic therapy is limited by the severity and duration of the ischemia, and the length of time required to achieve dissolution of the thrombus.

8.7.1 Thrombolytic therapy versus surgery

Thrombolysis utilizes lytic agents that act on fibrin (thus, eliciting “fibrinolysis”), and thrombectomy uses direct techniques to remove clot. The terms “thrombolysis” and “thrombolytic” are synonymous with the terms “fibrinolysis” and “fibrinolytic”.

After initial observational studies suggested efficacy (317), randomized trials compared surgical revascularization to intraarterial thrombolytic therapy in the treatment of acute ischemic but viable lower extremities (318-321). The results from the TOPAS and STILE trials illustrate the range of findings.

A randomized, prospective, double blind study of thrombolysis or peripheral arterial surgery (TOPAS) was performed in 544 patients who had acute lower extremity ischemia for 14 days or less (318, 319). Phase 1 of this trial compared three different doses of catheter directed recombinant urokinase (rUK) and found that a dose of 4000 IU/min for four hours, followed by 2000 IU/min for a maximum of 48 hours provided the maximum lytic efficacy at a minimal bleeding risk (318); recanalization was achieved in 80% and complete lysis of thrombus in 68% (319).

The phase 2 included 544 patients with acute arterial occlusion of less than 14 days in duration who were randomly assigned to the above rUK regimen or surgery (319). The following findings were noted:

- There was no significant difference between the groups in amputation-free survival rates at six months (72% vs. 75% with surgery), which was the primary end point, or one year (65 vs. 70%).
- Among patients treated with thrombolytic therapy, the amputation-free survival rates were better with bypass graft compared to native vessel occlusion.
- There was no significant difference between the groups in mortality at six months (16% vs. 12% with surgery) or one year (20% vs. 17%).
• Major (including intracranial) hemorrhage was more common with rUK (12.5% vs 5.5%, respectively).

• Among the patients who received rUK, 40% required subsequent surgery at six months. However, there was a reduced requirement for open surgical procedures after thrombolytic therapy at six months (315 versus 551 in those assigned to surgery).

The STILE trial consisted of 393 patients with nonembolic arterial and graft occlusion who presented with new or progressive symptoms of limb ischemia symptoms of up to six months duration (320, 321). The patients were randomly assigned to treatment with surgery or intraarterial catheter-directed thrombolysis with recombinant tissue plasminogen activator (rt-PA) or urokinase. Failure of catheter placement occurred in 28% of patients assigned to thrombolytic therapy.

Patients with ischemia of 14 days or less who were treated with thrombolysis had a significantly lower rate of amputation (6% vs. 18%) and shorter hospital stays compared to the surgical group. By contrast, patients with ischemia for longer than 14 days did better with surgical revascularization with significant reductions at one year in the rates of major amputation (0% vs. 10% with thrombolytic therapy) or recurrent ischemic events (35% vs. 65%) (321).

For the patients receiving thrombolysis who subsequently required surgery, the magnitude of the surgical procedure was reduced (compared to those not receiving prior thrombolytic therapy) in 56%. Factors associated with a relatively poor outcome after thrombolytic therapy included femoral-popliteal occlusion, diabetes, and critical limb ischemia (321).

These trials demonstrate that thrombolytic therapy is a safe and effective alternative to surgery in certain subsets of patients. Figure 61 proposes a therapeutic algorithm in case of confirmed ALI.
A Cochrane review evaluated the best approach to thrombolytic therapy when this form of treatment is chosen (322). Intraarterial rather than intravenous administration of the drug results in a better clinical outcome and reduced incidence of bleeding complications. The angiographic catheter should be placed within the thrombus for optimal results. High dose and forced infusion techniques result in more rapid thrombolysis, but may increase bleeding risk and do not appear to improve clinical outcomes.
8.7.2 Endovascular mechanical thrombectomy procedures

While thrombolysis in case of an ALI for less than 14 days has proven safety and efficacy, new percutaneous thrombectomy procedures has recently emerged in the endovascular field as an attractive complementary modality of the lytic therapy.

The aim of all of these procedures and techniques is to accelerate the revascularization process, which by adopting the thrombolysis alone may take several hours (e.g., over-night thrombolysis). The fact that by this way an early initial reperfusion of the threatened limb is obtained in most of the cases, allow to gain the necessary time to adequately perform the thrombolytic regimen, in a patient that is already partially reperfused, thus not anymore in an emergency (i.e., <6 hours) situation. Accordingly, once the acute occlusion is recanalized and there is an initial distal perfusion leading to an immediate symptoms regression, the thrombolytic catheter may be safely introduced directly inside the partially recanalized occlusion and left at least 12 hours. During this time period the patient should be closely monitored for symptoms and complications, because while compartment syndrome rarely occurs, puncture site bleedings are quite frequently observed.

The next day the patient should undergo again an arteriography though the lytic catheter and the underlying problem has to be fixed by standard endovascular means. Of interest, in case of an acute in-situ occlusion (e.g., by an underlying PAD) there is virtually always a stenosis that is responsible for the acute occlusion (e.g., plaque rupture [Figure 62] or tight stenosis [Figure 63]), while in case of an arterial embolus, the underlying native vessels are disease free and there is generally no need to further perform an endovascular procedure, because the lytic regimen has “cleaned” all the thrombotic material (Figure 64).

The following Figures describe different clinical scenarios of ALI (e.g., in-situ thrombosis, arterial embolization, etc), all treated with different types of thrombectomy procedures ± in-situ thrombolysis.
Figure 62 showing a distal SFA acute occlusion (left panel), which was recanalized by a mechanical thrombectomy procedure (central panel: 6Fr Rotarex device™), finally showing the underlying unstable plaque which has caused the acute occlusion (right panel).

Figure 63 showing an acute prosthetic bypass occlusion from the proximal (CFA) to the distal (ATA) anastomosis.

After a mechanical recanalization (8Fr Rotarex device™), angiography shows the underlying proximal bypass stenosis which has caused the acute occlusion and the persistence of important thrombi.

After having stented the proximal stenosis and after 12 hours of in-situ thrombolysis, there are no more residual thrombi in the bypass.
Figure 64 shows disease-free femoral arteries (left panel) with an acute embolic occlusion of the distal popliteal artery at the level of the tibial vessels trifurcation (central panel). The right panel shows a normal flow of the disease-free three tibial vessels after the successful aspiration thrombectomy.

Figure 65 showing an acute common femoral stent occlusion (left panel) treated in a “one-session intervention” by an 8Fr Rotarex Device (central panel) without the need of ballon angioplasty or other endovascular manipulations
There are different ways to perform mechanical thrombectomy procedures. Table 9 summarizes the most adopted devices and techniques by performing a mechanical thrombectomy procedure in the peripheral vascular tree in case of ALI.

<table>
<thead>
<tr>
<th>TECHNIQUE and DEVICES</th>
<th>MECHANISM OF ACTION</th>
<th>PROS and CONTRAS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aspiration Thrombectomy (AT)</td>
<td>By simply positioning the aspiration catheter in front of the thrombus and aspirate it. The catheter contains a steel spiral powered by an electric motor and rotating at 40,000-95,000 rpm. The rotating spiral produces a continuous vacuum and the thromboembolic material &quot;drilled&quot; by the tip is drawn into the catheter, where it is fragmented and transported to the collecting bag.</td>
<td>In case of large thrombus burden several passages are needed. Only the Rx systems allow to leave the wire in place, while by using the OTW systems one needs to regain every time the initial position. In case of very distal embolization the usual shaft length may be too short and the standard catheter may be too bulky to reach the distal thrombus. In this case a inner lumen of standard OTW balloon may be used.</td>
</tr>
<tr>
<td>Rheolytic Thrombectomy (RT)</td>
<td>By using a high-speed saline jet, the thrombus is fragmented. Finally thanks to the Bernoulli/Venturi effect the macerated thrombus is immediately aspirated. With some devices a low-dose lytic therapy may be directly injected in the thrombus, in order to facilitate the fragmentation process (= power-pulse spray technique)</td>
<td>Rheolytic thrombectomy devices are less aggressive than other thrombectomy devices (especially the FT devices). However, they may produce significant hemolysis leading to bradycardia and hypotension, especially if used in the coronary-pulmonary circulation.</td>
</tr>
<tr>
<td>Fragmentation rotational Thrombectomy (FT)</td>
<td>The catheters contain a steel spiral powered by an electric motor and rotating at 40,000-95,000 rpm. The rotating spiral produces a continuous vacuum and the thromboembolic material &quot;drilled&quot; by the tip is drawn into the catheter, where it is fragmented and transported to the collecting bag.</td>
<td>These devices are very useful in case of the thrombus begin to be organized (i.e., &gt;14 days), because thanks to their rotational head or internal spiral the thrombus is efficaciously fragmentated. Being more “aggressive” in the native vessels (Rotarex &gt; Aspirex), they may cause dissection or vessel rupture especially if used in small caliber vessels.</td>
</tr>
<tr>
<td>Ultrasound enhanced Thrombolysis</td>
<td>This Infusion Catheter System is to enhance catheter-directed thrombolysis by accelerating the fibrinolytic process with the application of ultrasound</td>
<td>This system is very efficacious in facilitating the lytic therapy to dissolve clots, however it needs several hours to reestablished sufficient blood flow, thus being too slow for emergency limb-saving interventions</td>
</tr>
</tbody>
</table>

Table 9: different thrombectomy devices, their mode of action and several pros and contras
These pictures (Figure 66) represent the most used thrombectomy devices for PAD interventions [all the following pictures are reproduced from the respective companies' websites]:

10Fr Pronto Catheter™ (Vascular Solutions)

Angiojet Rheolytic catheter™ (Medrad/Possis)

Tips of the 6Fr-8Fr Rotarex Device™ (Straub Medical)

Tips of the 8Fr-10Fr Aspirex Device™ (Straub Medical)

Thromcat XT™ (Kensey Nash Corp.)

EKOS Endowave system™ (EKOS Corp.)
Of interest, despite these mechanical thrombectomy procedures are performed in order to allow a following regular lytic therapy, it seems that frequently (≈ 50%) these procedures may immediately remove most of the thrombotic material, thus unmasking the underlying problem, finally allowing to complete the revascularization in a one-session procedure. This is of particular interest, because with these one-session procedures, there will be no increased bleeding risks associated with thrombolysis and both, patient’s comfort and catheterization laboratory’s logisitic, were significantly improved (Figure 65).

So far, no randomized controlled trial has established the superiority of these mechanical thrombectomy devices compared to surgery or in-situ thrombolysis and only several retrospective registry or case series are reported in the literature (323-332). Furthermore, very few direct comparisons between the different thrombectomy devices are available in human trials, thus challenging the decision of which device may be superior to the others (333-335).

Accordingly, as suggested by many operators, one should learn and use as few as possible devices, in order to well recognize their device-related pitfalls or complications, as well as being able to anticipate the aspiration capabilities of the specific used device.

In general, more “aggressive”, thus more powerful devices, such as the fragmentational devices, are preferred in case of large thrombus burden or in diseased vessel (e.g., prosthetic bypass, atherosclerotic SFA), while more “physiological” devices, such the rheolytic devices, should be preferrend in small caliber and diseased free vessels (e.g., vein bypass, embolic infra-popliteal occlusions). Finally aspiration catheters may be reserved by very distal embolization, where no other thrombectomy device may arrive, or in case other devices are contraindicated or not available.
8.8 RECOMMENDATIONS IN CASE OF ALI

The issue of thrombolytic therapy is primarily limited to patients with ALI and viable extremities present for less than 14 days. Based in part upon the observations in TOPAS and STILE, the following recommendations have been made by major society guidelines:

- The 2005 ACC/AHA and the 2007 TASC II guidelines on PAD, which were produced in collaboration with major vascular medicine, vascular surgery, and interventional radiology societies, concluded that there was general agreement that catheter-based thrombolytic therapy is effective and beneficial and is indicated in patients with ALI of less than 14 days duration (2, 3). The evidence was considered less well established for patients with ALI of more than 14 days duration.

  The guidelines also concluded that the weight of evidence was in favor of mechanical thromboembolectomy as adjunctive therapy of ALI resulting from peripheral arterial occlusion.

- The 2008 ACCP guideline on antithrombotic therapy for peripheral arterial disease suggested catheter-based thrombolytic therapy in patients with acute limb ischemia of less than 14 days duration who had a low risk of myonecrosis and ischemic nerve damage during the time required to achieve revascularization (315).

Although many patients treated with thrombolytic therapy will subsequently require surgical or percutaneous revascularization, the magnitude and complexity of the procedure required to revascularize the extremity is frequently less than in those not receiving prior thrombolytic therapy.

Thus, patients found to have an ischemic but viable extremity on clinical examination should undergo urgent arteriography in order to plan surgical or medical revascularization. There are several findings on arteriography which are used to determine if thrombolytic therapy, PTA, or surgical revascularization is the most appropriate treatment. These include:

- The presumed etiology (embolus versus thrombus)
- The location and length of the lesion
- The duration of symptoms
- The availability of autologous vein for bypass grafting
- The suitability of the patient for surgery
As an example, a proximal embolus at the bifurcation of the common femoral artery is an ideal lesion for surgical embolectomy. On the other hand, embolus to a distal vessel (e.g., to the tibial artery) may be best treated with a thrombolytic agent. Angioplasty ± stenting is then performed in case of an underlying lesion which became apparent after the clot has been lysed with thrombolytic therapy.

8.1.1 Patients with Nonviable Extremities

Patients with nonviable extremities should undergo prompt amputation. Arteriography is usually not necessary, since the level of amputation is determined by clinical findings and by the viability of tissues at the time of surgery. Every effort should be made to preserve as many joints as possible, in order to decrease the work of ambulating with prosthesis and to improve the chances for successful rehabilitation. Delays in amputation of a nonviable extremity can result in infection, myoglobinuria, acute renal failure, and hyperkalemia.

According to the initial clinical scenario and the emergency of the amputation, arteriography ± a revascularization procedure may be performed in order to improve the distal perfusion, thus allowing a lower amputation level (e.g., below the knee instead of above the knee) and a better healing process of the amputated limb.
9.0 PAST - PRESENT - FUTURE AND PERSONAL PERSPECTIVES

Considering the tremendous evolution that the endovascular techniques have achieved in the last 40 years, it is not surprising that many vascular specialists daily dealing with atherosclerosis are now focusing their attention and efforts in the development of new treatment options for patients suffering of a PAD.

Indeed, the cardiovascular community and medical industry have passed through at least three major eras of the percutaneous interventions.

9.1 THE PAST

At the very beginning (i.e., end of the seventies - early eighties) all new techniques or devices were first evaluated in the peripheral arteries and only after having proved their safety and efficacy, they were adopted also for the coronaries, in which complications might have led to fatal issues.

The main problem of the balloon angioplasty alone was related to the abrupt coronary occlusion due to the presence of an extensive intimal dissection. It is only ten years later (i.e., 1987), that the first vascular stent was successfully applied in a femoral artery and immediately after also during coronary interventions. The impact of stents was immense, because it allowed to successfully finish the coronary intervention, avoiding sending patients for an emergency coronary by-pass once an occlusive coronary dissection has occurred after the balloon angioplasty. The stent era had then begun and at the beginning of the nineties many studies have finally confirmed the safety and the efficacy of stents.

Once the angioplasty and the stenting techniques allowed for a safe and efficacious treatment of lower limb, renal and coronary stenosis, the cardiovascular community was then confronted with one of the most difficult problems to solve – the restenosis –.

Indeed, balloon angioplasty and in-stent restenosis occurred in up to 50% of the cases according to the disease extension and the performed intervention. This was not acceptable for the endovascular community, especially if one considered that the surgical alternatives (e.g., femoropopliteal and artocoronary bypasses) had a far better one-year patency rate.

Because the vast majority of the patients presenting with an in-stent restenosis belong to the coronary domain (i.e., coronary patients >> peripheral patients), for the first time the peripheral endovascular domain was “sacrificed” in order to leave the entire cardiovascular community to find a solution to the coronary in-stent restenosis. Many medications (systemic and intra-coronary) and intra-
coronary devices (e.g., atherectomy, cutting balloons) were studied for the next ten years, but all of them without any significant impact on restenosis.

It is only in September 2001, when the results of the first drug-eluting stent study were presented at the ESC congress in Stockholm, that for the first time a safe and very efficacious treatment modality significantly reduced the incidence of the in-stent restenosis. From that moment and for the upcoming ten years the medical industry as well as the cardiovascular community performed a tremendous effort in order to improve and optimize this drug-eluting stent technology. During this period (i.e., 2002-2010) no major evolution was attempted in the peripheral vascular medicine and this especially because the financial drive/interest was at that moment in the coronary arteries.

9.2 THE PRESENT

It is only since few years, and only once the coronary in-stent restenosis has reached an acceptable threshold (i.e., <10% at one-year), that the cardiovascular community has returned its attention to the lower limbs. Indeed the up to 50% restenosis rate after a SFA intervention was longtime accepted, and this because no other options were at disposal or were in the pipeline of ongoing prospective studies.

Furthermore, it is probably secondary to the continuous aging of the population and the increased prevalence of diabetes that the incidence of patients presenting with CLI has dramatically exploded in the last decade. Accordingly, if one considers that CLI leads to amputation and that amputation may lead to death, this PAD natural evolution was again “unacceptable” for the cardiovascular community.

Faced with this “new” challenge (i.e., avoid amputation, improve the quality of life), the cardiovascular community woke up and exited from this period of peripheral scientific “stagnation”, finally starting the actual era of innovations in the endovascular treatment of PAD. Indeed, as I have tried to summarize with this thesis, there are a lot of new techniques and new devices which broadened the spectrum of the endovascular interventions.

Of interest, as already adopted in many centers, it is not just one medical speciality that takes care of PAD patients, but rather a multidisciplinary team of endovascular specialists. This new figure, which may be represented by an angiologist (e.g., in Germany and Switzerland), by a cardiologist (e.g., in the USA and Italy), by a vascular surgeon (e.g., in the USA and France) or by an
interventional radiologist (e.g., in the rest of Europe), has a main common goal: "try to achieve the same good surgical results without performing open vascular surgery".

Accordingly, the most remarkable increase of the endovascular procedures performed worldwide is observed in the surgical community, which is trying to propose to their patients a single operator package of all possible revascularization modalities (Figure 67) (336).

![Figure 67: Peripheral Arterial Interventions: Trends by Specialty in the United States](image)

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(VS = Vascular Surgeon, IC = Interventional Cardiologist, IR = Interventional Radiologist)

[reproduced from Eslami MH et al. (336)]

The second group, which is now fully dedicated to the development of the peripheral endovascular interventions and techniques, is that of the cardiology community (Figure 67). Accordingly, interventional cardiologists, who are now able to achieve good longterm results after coronary interventions, try to bring their knowledge and skill in the fight of atherosclerosis and restenosis also in the lower limb. It is not surprising that a lot of drug-eluting technologies (i.e., DES and DEB) are now firstly applied in the femoral arteries as well in the BTK vessels, by interventional cardiologists. This is particularly true by treating BTK vessels, which have many similar aspects to the coronary arteries (e.g., same diameter, bifurcation lesions) and are treated with very similar dedicated techniques and devices (e.g., 0.014” wires, low-profile balloons, retrograde recanalization techniques).
9.3 THE FUTURE

What I the future will bring to the fight of PAD is difficult to predict. However, I’m convinced that because all the cardiovascular communities, including vascular surgeons, angiologists, cardiologists and radiologists, are now working together in the development of new techniques and devices and especially thanks to the financial support of the industry by performing multicenter prospective highly scientific trials, the future of PAD patients will be bright.

One of the keys of success will be based on the scientific evidence that a specific revascularization procedure with a specific dedicated device will first not harm the patient, second will be associated with a technical/clinical success rates high enough to counterbalance the inherent procedural/device related complication rates, and finally will be associated with acceptable long-term patients’ outcomes. In this modern era, where every new medical device is tried to be put on the marketplace as soon as possible, should warn every interventionists to be cautious on trying new “sophisticated” procedure/device in clinical settings before robust evidence of safety and efficacy is available (337, 338). For that reason, teaching hospitals and some pioneering cardiovascular centers must concentrate their effort on producing high level scientific trials, in order to facilitate the governmental institutions towards the final acceptance of these new endovascular procedure/devices (337, 338).

If one considers that the number of patients suffering from atherosclerosis remains stable in the last decades, the main effort which the cardiovascular community has to perform in the upcoming years will be mostly to improve all the revascularization procedures in terms of safety, immediate and long-term efficacy and especially in terms of minimal-invasiveness (i.e. endovascular), in order to allow more and more patients to benefit (even in an ambulatory setting) from the most adapted revascularization procedure, which will finally probably improve the quality of life and hopefully also the amputation-free survival (Figure 68) (339).
Concerning the aortoiliac diseases the endovascular results already achievable with the present technologies (i.e., balloon angioplasty + stenting) are good enough, so no dramatic improvements are to be awaited in the upcoming years.

Conversely, at the femoropopliteal level, after many years where balloon angioplasty with a bailout stenting approach was the only available technology, thanks to the arrival and especially the combination of different techniques and devices, a lot of improvements will be observable in a near future. Accordingly, despite the initial encouraging results of the second generation femoral paclitaxel eluting stents, the future of femoropopliteal diseases will not be the stent. Indeed, stents, with their metallic components, disrupt the complex physiology of the femoral artery, suggesting that probably a stent-less solution will be more suitable for this delicate region. So far, absorbable femoral stents are at the very beginning of their development, while paclitaxel-eluting balloons, maybe in combination with some debulking pre-treatment (e.g., directional atherectomy), are already used in daily practice, with several promising trials evaluating the combination of these technologies actually ongoing.

At the infrapopliteal level, there is already a clear consensus that stents should be used strictly as a bailout situation, especially because the main advantage brought by stents (especially DES) in BTK vessels is related to a better patency rate, with no significant advantages in terms of limb salvages of these elderly and sick patients. Once dedicated BTK drug-eluting balloons are less expensive, probably this kind of technology will become the first line treatment of every CLI patient.
10.0 CONCLUSIONS

The medical approach of patients presenting with a PAD is firstly associated with the optimal management of the cardiovascular risk factors, in order to significantly decrease the cardiovascular and cerebrovascular related mortality rate.

This medical approach should include at least one antiplatelet medication (e.g. Aspirin), a lipid lowering drug (e.g. statine) and an ACE-inhibitor regimen. Once this medical step is optimized, but the patient still remains symptomatic, the need for a more invasive treatment may be considered. The type of an arterial revascularization (i.e. endovascular vs. surgical) should be evaluated according to the clinical scenario (claudication vs. CLI, vs. ALI), the disease extension, the patient’s co-morbidities and last but not least the local expertise.

10.1 CLAUDICATION

Concerning claudicant patients, the indications for endovascular therapy have gradually expanded over the last two decades. While discrete stenosis may be easily treated, the endovascular management of long total occlusions or advanced disease remains challenging. Depending on the localization and type of the lesion, as well as the anatomy of the diseased vessels, different access techniques may be chosen. The retrograde CFA approach ± crossover maneuver, is the easiest and least traumatic and leads to success in the majority of patients.

Regarding stent type, the high radial strength of balloon-expandable stents and the lack of foreshortening make them suitable in particular for ostial or severely calcified iliac lesions. The greater flexibility and conformability of self-expanding stents apply well to long lesions in tortuous ilio-femoro-popliteal segments. With respect to CFA interventions, stenting should be avoided whenever possible, in order to prevent crushing and to preserve future vascular access.

Based on the low incidence of major complications as well as good long-term results, percutaneous revascularization has replaced surgery for most of the lower limb occlusive conditions. According to the TASC II recommendations, TASC II A-B lesions should be managed percutaneously, TASC II C lesions should be treated percutaneously or surgically according to the anatomical characteristics and the local expertise, and TASC II D should be reserved for a surgical management. Thanks to improvements in the equipment and in the expertise of the interventionists recent reports suggest that also TASC II D lesions may be safely and efficaciously treated with an endovascular approach.
Accordingly, this was further emphasized by the very recently published Guidelines of the European Society of Cardiology (340). Indeed, in these recent Guidelines one of the major modifications compared to the 2007 TASC II Guidelines, was that concerning the first revascularization option in case of complex lesions (i.e., TASC II C-D). The ESC Guidelines recommend that TASC II C lesions should be preferentially treated by an endovascular option first and managed surgically only in case of an endovascular failure or in case of recurrences. While TASC II D lesions remain a surgical domain, the ESC Guidelines stressed the importance that even such complex lesions may be approached by experienced interventionists in dedicated endovascular centers with a percutaneous attempt first. This minimally invasive approach may be nowadays attempted as first-line treatment, because of the good technical success rate achievable also in TASC II D lesions, the acceptable medium-long term patency rate and especially because patients presenting with TASC II D lesions are more and more elderly (i.e., >80 years old), with more and more associated severe co-morbidities (e.g., cardiovascular, pulmonary).

10.2 CRITICAL LIMB ISCHEMIA AND BTK INTERVENTIONS

The endovascular infra-popliteal interventions are usually performed in patients presenting CLI. This type of intervention may be attempted in case of an isolated BTK disease or after a previously performed femoro-popliteal revascularization procedure (surgical or endovascular).

Patients presenting with a CLI are very often very elderly, severely diseased in term of BTK vessel occlusions, as well as in terms of impaired general conditions.

In case of CLI, the clinical success is much more important than the immediate or longterm angiographic result, because ulcer healing and limb salvage and not the vessel patency should be the main goal of every BTK intervention. Despite the number of the published trials randomizing different devises or techniques is still weak, the preliminary results of the reported retrospective and prospective studies are very promising, with a limb salvage rate of almost 90% at one year.

Because the BTK endovascular approach is associated with a far below complication rate than what reported with a femoro-tibial bypass, this less invasive alternative should be proposed as first line treatment in any case where the main vascular problem is located at the level of the infra-popliteal region. Furthermore, if performed with caution, even an endovascular failure, does not compromise a future surgical limb-salvage intervention, which may be postponed until all endovascular options (e.g. antegrade, retrograde, trans-collateral, etc) were attempted.
10.3 ACUTE LIMB ISCHEMIA

Acute limb ischemias are medical emergencies, because in case of prolonged ischemic lower limb tissue damages, the rates of major amputations or other ischemic related morbidities are exceedingly high. Based on the clinical history and the non-invasive diagnostic work-up, most of the time it is possible to differentiate an ALI secondary to an embolic event (e.g., cardio-embolic) from one secondary to a local thrombotic event (e.g., unstable occlusive plaque). Accordingly, while the treatment modalities remain similar, the degree of emergency may vary considerably (i.e., embolic events often associated with profound and severe ischemia).

Local thrombolysis is now the preferred revascularization modality in order to “physiologically” restore distal blood perfusion. The main drawbacks of this approach are the increased bleeding risk associated with the lytic regimen and the time necessary in order to adequately reperfuse the lower limb (i.e., several hours). Thanks to the arrival of different types of mechanical thrombectomy devices, it is now possible to initiate the endovascular procedure in virtually all ALI cases. Accordingly in approximately 50% of the cases, this mechanical thrombectomy procedure may unmask the underlying stenosis, which may be treated in a one-session procedure. In the rest of the cases, where the thrombotic material cannot be completely removed, the mechanical thrombectomy procedure is able to restore a sufficient distal blood perfusion, in order to continue with the over-night thrombolysis, allowing finishing the endovascular procedure in the next morning.

10.4 CONCLUSIONS

The very important evolution of material and techniques in the last decade, suggests that an increasing proportion of lesions may be firstly attempted with an endovascular approach. The choice of which technique or device may be used to deal with a specific situation (claudication, CLI, ALI) should be left to the operators’ discretion, who will choose the most adapted device or technique according to his personal experience, as well as according to the expected associated success rate and the long-term patency rate. Thanks to a huge financial investment from the medical industry, as well as an important interest of the scientific endovascular community, - including vascular surgeons, interventional angiologist-cardiologist-radiologists -, several well-conducted studies have been so far published and many more are underway and will be published in a near future. This upcoming scientific evidence, will finally allow us to put into the perspective all the different tools and techniques at disposal of every endovascular specialist.
11.0 REFERENCES


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12.0 ORIGINAL ARTICLES PUBLISHED IN THE FIELD OF THE
ENDOVASCULAR TREATMENTS OF PAD

Late Acute Thrombotic Occlusion After Endovascular
Brachytherapy and Stenting of Femoropopliteal Arteries
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OBJECTIVES The aim of this article is to underline the importance of this complication after endovascular
brachytherapy (EBT) and intravascular stenting of the femoropopliteal arteries occurring in a running randomized
trial.

BACKGROUND Endovascular brachytherapy has been proposed as a promising treatment modality to reduce
restenosis after angioplasty. However, the occurrence of late acute thrombotic occlusion (LATO) in patients receiving EBT after stenting is of major concern.

METHODS In an ongoing prospective multicenter trial, patients were randomized to undergo EBT
(30 Gy or 4 Gy at a depth of the vessel plus 2 mm) after percutaneous recanalization of femoropopliteal obstructions. Of the 204 patients who completed the six
month follow-up, 94 were randomized to EBT.

RESULTS Late acute thrombotic occlusion occurred randomly in 6 of 22 patients (27%) receiving
EBT after intravascular stenting and always in combination with reduction of antithrombotic
drug prevention (aspirin). Conversely, none of the 13 patients with stents and without EBT (9.6%; p < 0.05) and none of the 72 patients (9.6%; p < 0.02) undergoing EBT
after simple balloon angioplasty presented LATO.

CONCLUSIONS Late thrombotic occlusion occurs not only in patients undergoing EBT after percutaneous
coronary recanalization but also after stenting of the femoropopliteal arteries and may compromise the benefit of endovascular implantation. The fact that all our cases with LATO
occurred concurrently with stopping drug therapy may indicate a possible relevant mecha-
nism. An intensive and prolonged antithrombotic prevention is probably indicated in these
patients. (J Am Coll Cardiol 2002;41:809–12) © 2003 by the American College of
Cardiology Foundation.

The phenomenon of restenosis after angioplasty was anticip-
ated by Gruntzig and Hopf (1). 30 years ago at the time
they first applied balloon angioplasty for lower limb arteries.
Further large clinical series after angioplasty of the lower
limb arteries, and numerous reports during the last two
decades involving patients undergoing percutaneous trans-
cutaneous coronary angioplasty (PTCA), have confirmed the
clinical and economical impact of restenosis. The magni-
tude of restenosis after PTCA and after angioplasty of the lower
limb arteries varies according to the diagnostic method-
ods used (clinical, quantitative angiography, intravascular
ultrasound) and has been reported in a range between 15%
and 50% (2–6). Through introduction of coronary stents, the
incidence of restenosis after PTCA has only been moderately reduced to 20% to 30% (7). The use of in-
travascular stenting at the femoropopliteal level to prevent
restenosis remains controversial (8–11).

In animal studies and in patients, one of the most
promising modalities to reduce restenosis seems to be the
application of endovascular brachytherapy (EBT) (12,13).
Although EBT was also first applied after angioplasty of
the lower limb arteries in the early 1990s (12), few perspec-
tive studies have been published on the efficacy of brachy-
therapy after angioplasty of the femoropopliteal arteries as a
strategy to prevent restenosis. In a recently published ran-
momized trial on EBT after angioplasty of very long
obstructions of the femoropopliteal arteries, the incidence
of restenosis at six months follow-up could be signifi-
cantly reduced from 52% to 28% in the group of patients receiving endovascular gamma-irradiation (14). The phenomenon of late acute thrombotic occlusion (LATO) has been reported
in larger PTCA trials with an incidence of 6% to 9% (15,16), and in one single randomized pilot study
of patients undergoing EBT after femoral stenting (17).

We decided to report on LATO in femoropopliteal
arteries in relation to EVBT and stenting based on the
results of the preliminary analysis of our ongoing, random-
ized, four-arm, multicenter trial, because of the high rele-
ance of this phenomenon which may challenge the bene-
fit of vascular radiation.

METHODS

The aim of our ongoing multicenter trial is to evaluate the
effect of a combined prevention strategy (physical and

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chemically on restenosis after percutaneous recanalization of the femoropopliteal arteries. The protocol included a randomized, unblinded comparison of the efficacy of EVBT (n = 192) performed immediately after angioplasty and a blinded comparison of a medical prevention using protocol randomized versus placebo (18).

All patients >50 years, with chronic occlusion (Fontaine II A and B), and with arterial stenosis >50% or total occlusion at the femoropopliteal level, who are referred to our four vascular centers were eligible for the trial. Utilization of stenting during the angioplasty procedure because of unstable dissection or unsatisfactory results after balloon dilatation is left to the discretion of the interventionist.

Following the initial notification of the Food and Drug Administration in 1996 of cases with LATO in patients undergoing intracoronary stenting and brachytherapy (19), our protocol mandates that patients receiving stenting and EVBT are treated with a double balloon angioplasty (sponge 100 mg and clopidogrel 75 mg/day) for an unlimited time after the procedure. The appropriate institutional review boards approved the protocol, and all patients gave written informed consent.

High-dose rate EVBT was performed using gamma-irradiation with a 60Co-source. A 5F closed-tip, noncanted catheter (Nucletron, Veenendaal, The Netherlands) was advanced through the 6F sheath and placed in the balloon-treated lesion so that the tip of the catheter reached 1.5 cm distal to the distal end of the interventional length (IL). The active source length corresponded to the IL plus 1.5 cm on the distal and proximal end. The dose distribution was calculated by means of a computer-assisted planning system (Pantak-BFS, version 13.2, Nucletron) with a 2.5-mm stepping source. The reference dose of 14 Gy was applied in a depth from the source given by the radius from the center of the dilated segment plus 2 mm. Marks on the dummy were defined the IL and the length of the irradiated segment. After its definition, the dummy wire was removed. The application catheter was connected to the irradiodose, and the source was advanced into the applicator.

Follow-up examinations include clinical, noninvasive examination (ankle-brachial pressure index) as well as duplex scanning after one day, at two and six months after intervention.

Duplex scanning, a well validated method to measure significant vascular obstructions at the femoropopliteal level, is performed according to the criteria of Jager et al. (20) by the same operator in each of the four vascular centers, using an Acuson Sequoia 256 (Mountain View, California) unit, and measuring the ratio between the peak systolic Doppler velocities of the dilated segment and at two cm proximal to the lesion.

The primary endpoint of the trial is to quantify the incidence of >50% restenosis at six months follow-up. Late acute thrombotic occlusion is defined as an acute occlusion of the dilated vascular segment occurring beyond the three months follow-up in a patient without any evidence of progression or restenosis at the preceding duplex scanning. Statistical comparison between the occurrence of LATO in the different subgroups was calculated by the Student t test.

## RESULTS

A total of 204 patients have reached the predefined six months follow-up period and are available for an interim analysis of the unblinded part of the protocol (EVBT vs. no EVBT). Of the 204 patients, 94 underwent EVBT immediately after angioplasty. Of these 49 patients, 22 patients with EVBT needed reintervention. The LATO of the dilated segment occurred in 6 of the 22 patients (27%). Conversely, none of the 13 patients (0%; p < 0.05) undergoing stenting without EVBT presented LATO. Furthermore, none of the 72 patients (0%; p < 0.01) undergoing EVBT after only balloon angioplasty and none of the 67 patients (0%; p < 0.01) without EVBT presented LATO. Late acute thrombotic occlusion was not seen in any of the patients taking clopidogrel and undergoing EVBT after stenting.

Figure 1 shows the restenosis rate at six months and the corresponding proportion of LATO in the two groups of patients undergoing stenting with and without EVBT. The restenosis rate in patients undergoing stenting with and without EVBT was similar (41% and 49%, respectively). Late acute thrombotic occlusion occurred exclusively in patients receiving EVBT after stenting (Fig. 1, black area), with major impact on the rate of restenosis in this group of patients. If LATO could have been avoided in these patients with stent and with EVBT, given the absence of an underlying restenotic process after thrombus extraction and/or lysis, as indicated in the following text, the restenosis rate would have decreased from 40% to 12% (Fig. 1).

Late acute thrombotic occlusion occurred at 16, 17, 18, and 23 weeks after stenting and EVBT. In a further case, LATO occurred 68 weeks after percutaneous recanalization. All cases of acute occlusion occurred concomitantly with the withdrawal of the antithrombotic drug prevention, because of gastric side effects (three patients) or noncompliance (three patients). Clopidogrel was stopped between two and six weeks before the sudden occlusion of the stented segment. Late acute thrombotic occlusion was associated with reappearance of claudication and was documented by angiography and in one case by duplex ultrasound. Four patients underwent thrombolysis with urokinase infusion overnight; another patient was treated with thrombus extraction followed by glycoprotein IIb/IIIa infusion. All five patients
had a final result of complete patency with no evidence of restenosis and no need of re-angioplasty. The sixth patient with minor symptoms was treated medically.

All six patients with LATO had three patent run-off vessels, compared with a mean value of two patent run-off vessels for the whole trial. The baseline severity and length of the obstruction varied between 75% and 100% and from 4.0 to 6.5 cm, respectively, and were comparable to that in the overall study population.

**DISCUSSION**

The preliminary analysis of our randomized, multicenter trial shows that the benefit of EVBT may be challenged by the occurrence of LATO, which in our series was observed exclusively in patients treated by stenting and EVBT. To our knowledge, this is the first report that demonstrates in a large randomized trial the impact of LATO on the long-term follow-up after EVBT in patients undergoing stenting of the lower limb arteries.

There is limited experience with intravascular stenting after angioplasty of the femoropopliteal arteries, with controversial results (8–11), in contrast to the positive experience for coronary stenting, which moderately reduces the restenosis rate compared with simple balloon angioplasty (7).

Endovascular brachytherapy may be a promising treatment modality to reduce restenosis after angioplasty, as recently reported in some randomized coronary trials (13) and in one randomized trial on peripheral percutaneous transluminal angioplasty (14).

An unusual rate of LATO after brachytherapy was first reported in 1998 in the interim analysis of the first trials of patients undergoing EVBT after intracoronary stenting (15,16), and was recently reported in a pilot study at the femoropopliteal level (17). The pathogenesis of LATO after stenting and EVBT is probably related to the same mechanism of action intended to reduce restenosis (i.e., reduction of neointimal proliferation). The same mechanism prevents endothelial regeneration to cover the stent struts, which usually occur within two to three weeks after stenting without lysis. The fact that five of our patients with LATO could be treated by either thrombolysis or thrombus aspiration confirms the hypothesis that these occlusions may be attributed to thrombosis. This hypothesis is supported by the fact that all these patients with LATO presented normal patent run-off vessels.

To avoid this vascular complication after brachytherapy, the interventionist may limit the application of EVBT in nonoccluded arteries. Alternatively, a more intensive and prolonged antithrombotic prevention should be prescribed, as recently proposed for coronary recanalization (16–22). In fact, if LATO could have been avoided in our group of patients undergoing brachytherapy after stenting, the restenosis rate would have fallen from 40% to 29% (Fig. 1). Because stenting was usually used in patients with suboptimal results after balloon angioplasty, we cannot exclude that these patients were prone to LATO due to the complication of the intervention. This consideration may be applicable also to the unusually high rate of restenosis found in the subgroup of patients with intravascular stenting without EVBT.

All our cases of LATO occurred concurrently with a reduction of the antithrombotic drug prevention and may indicate that platelet recruitment and thrombus formation which occur in non-re-endothelialized uncovered struts are not prevented sufficiently (23). Our finding of a case with acute occlusion immediately after stopping clopidogrel 68 weeks after intravascular stenting and EVBT leaves open the question of the necessity of a double antithrombotic prevention beyond the six-month threshold after EVBT (22). Further randomized studies are needed to clarify this problem. Patient compliance and side effects of this long-term secondary prevention may be limiting factors, as observed in our cases.

Our findings of a high incidence of LATO after stent and
EVBT may have clinically relevant implications; therefore, interventionists should be aware of this important complication which occurs also in the peripheral circulation, especially when a long-term double antiplatelet prevention with aspirin and clopidogrel is not assured.

The crucial answer to the question whether our combined physical and chemical prevention strategy still has a relevant impact on restenosis will be available only at the time of complete inclusion and follow-up of our randomized trial.

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REFERENCES


APPENDIX

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Preoperative Embolization of Collateral Side Branches: A Valid Means to Reduce Type II Endoleaks After Endovascular AAA Repair

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Purpose: To report the results of preprocedural embolization of collateral branches arising from abdominal aortic aneurysms (AAA) scheduled for endovascular repair.

Methods: Twenty-three consecutive AAA patients (14 men; mean age 73 years, range 56–82) had coil embolization of patent lumbar and inferior mesenteric arteries (IMA) in a staged procedure prior to endovascular repair. Embolization with microcoils was attempted in 27 of the 52 detected lumbar arteries and 14 of 15 inferior mesenteric arteries. Follow-up included biplanar abdominal radiography, spiral computed tomography, and duplex ultrasonography at 1, 6, 9, and 180 days after the stent-graft procedure and at 6-month intervals thereafter.

Results: Successful embolization was obtained in 24 (65%) of lumbar arteries, while all 14 (100%) IMAs were occluded with coils. No complication was associated with embolotherapy. Over a mean 17-month follow-up of 22 patients (11 intraoperative death), there was only 1 (4.5%) type II endoleak from a patent lumbar artery, with no sac expansion after 2 years. There were 4 (18%) type I and 1 (4.5%) type III endoleaks.

Conclusions: The embolization of side branches arising from an infrarenal aortic aneurysm before endovascular repair is feasible, with a high success rate; this maneuver may play a relevant role in reducing the rate of type II endoleaks, improving long-term outcome.

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Keywords: abdominal aortic aneurysm, endovascular repair, stent-graft, complication, endoleak, lumbar artery, inferior mesenteric artery, coil embolization

The most frequent mid and long-term complications observed after endovascular repair of abdominal aortic aneurysms (AAA) are endoleaks,1–5 which occur in up to 45% of cases. Patients with aortic endografts require regular surveillance with computed tomography (CT), duplex ultrasonography, or magnetic resonance imaging (MRI).6–11 When endoleaks are found, additional endovascular interventions or even conversion to open repair may be needed,6–10 which drives up the overall costs of AAA treatment.

White and colleagues10–12 in Australia first categorized endoleaks as types I through IV,
but the focus of our report is on type II, which refers to retrograde perfusion through collateral branches. Although type II leaks may resolve spontaneously,17 they may also lead to further expansion of the aneurysm sac, perpetuating the risk of rupture.18-20 Type II endoleaks can transmit pressure to the aneurysm sac,18,20 and several authors have noted that even a minor type II endoleak inhibits sac shrinkage.5,21,22 On the other hand, we were able to find only 2 patients with type II endoleaks who died after sac rupture.21-24

Development of a type II endoleak after endovascular aneurysm repair (EVAR) seems to be correlated with the number of collateral branches present before the operation,17,18,20 although this explanation is not unanimously accepted.22,24,27 We conducted a study to examine the hypothesis that meticulous preoperative microcoil or embolization of patent collateral branches in endograft candidates could significantly reduce the postoperative incidence of type II endoleaks.

**METHODS**

Under a protocol approved by our ethical committee, we obtained informed consent to embolize patent side branches from 23 consecutive AAA patients (all men; mean age 73 years, range 65-82) undergoing EVAR between March 1999 and December 2001. The patients' cardiovascular risk factors and comorbidities included hypertension (13, 56%), hyperlipidemia (6, 30%), diabetes (4, 17%), coronary artery disease (6, 39%), peripheral arterial disease (8, 35%), mild renal failure (11, 48%), and mild to severe pulmonary disease (5, 22%). The aneurysms were categorized according to the EUSTAR classification15 as type A (4, 17%), type B (18, 78%), and type D (1, 4%).

Preoperative spiral CT was performed with a Tomoscan Advantage scanner (Philips Medical Systems, Best, The Netherlands) at 5-mm slice thickness, 10-mm table speed, with 5-mm reconstruction intervals during bolus injection of 150 mL of Optiray 300 (Guerbet, Paris, France) at a 9-mL/s flow rate and scan delay of 30 seconds. Postprocessing was performed on a workstation (Philips Medical Systems) to obtain multiphase reconstructions (MPR) and maximum intensity projections (MIP) of the entire aorta.

Digital subtraction angiography was performed with a standard angiography unit (Integris V 3000; Philips Medical Systems). A 5-F catheterized pigtail catheter (Philips Medical Systems, Stenloge, Denmark) was positioned in the abdominal aorta, and examinations of the aorta and pelvic arteries were made in anteroposterior, left and right anterior oblique, and lateral views with multiple 20-mL injections of Hexabrix 300 (Guerbet) at a flow rate of 20 mL/s. The total amount of contrast medium varied from 120 to 150 mL.

According to the study plan, all patent infrarenal mesenteric arteries (IMA) were to undergo coil embolization in staged procedure prior to EVAR. The threshold for treating patent lumbar arteries (LA) was an arteriographically-measured diameter >2.5 mm or >2.0 mm without ostial stenosis; LAs with a diameter <2.0 mm were not treated, nor were LAs arising from the proximal or distal neck in the event they would be covered by the prosthesis.

The preoperative examinations identified 52 patent LAs arising from the aneurysm sac in 18 patients, but only 37 met the diameter criterion. Fifteen patent LMAs were found in 15 patients. One patent IMA arose distal to the aneurysm sac and therefore was not embolized because it would be covered by the prosthesis. In 2 cases, there was no patent LA, and 8 patients had an occluded IMA.

Embolization was performed in a separate session ~15 days before endovascular AAA repair. The coaxial catheterization technique employed a microcatheter (Transit, Cordis, Johnson and Johnson AG, Spritenbach, Switzerland; or Turbo Tracker, Boston Scientific, Solothurn, Switzerland) and a 4 or 5-F diagnostic catheter as the guiding catheter (Sim1, Sim2, C1, C2, C3; Cordis or Cook, Sorigo, Switzerland). The time for the procedure varied from 0.75 to 2.5 hours depending on the number of the vessels to be embolized (Figure).

For subsequent aneurysm exclusion, 19 bifurcated stent-grafts (14 Talent [Medtronic World Medical, Suresnes, FL, USA] and 5 Excluder [W.L. Gore and Associates, Flagstaff, USA]) were deployed with special attention to the aneurysm neck and proximal neck. The overall technical success rate was 100%.
AZ, USA) were used in addition to 2 aorto-
monolitic prostheses (Talent) with crossover bypass and 2 tube endografts (Talent). Bilat-
eral abdominal radiographs, duplex ultrasound
scans, and abdominal spiral CT scans were
performed at 1, 30, 60, and 180 days after the
procedure and at 6-month intervals thereafter.
The same operator (R.T.) always performed
the duplex studies using a Sequoia 256 scanner
(Acucor Mountain View, CA, USA) to
identify endoleak and measure the diameters
of the aneurysm sac. The CT scan was per-
formed at 6-mm thickness, 10-mm table
speed, pitch 1:2, and 3-mm reconstruction in-
tervals using a triphasic technique: before and
then during contrast injection (160 mL of
Hexabrix 300 at a 3-mL/s flow rate and a scan
delay of 30 seconds) and 2 minutes after in-
jection. If sac shrinkage was documented af-
fter the first year, then only duplex imaging
and abdominal radiography were done at the
6-month examinations.

RESULTS

In embolization sessions performed 2 to 21
days before stent-graft implantation, 24 (86%)
of 27 LAs identified for embolized were suc-
cessfully occluded. The 13 failures were due
to an inability to catheterize the vessel. All 14
(100%) patent IMAa were successfully embo-
lished. This produced complete collateral
branch embolization in 9 (36%) of 23 patients; another 9 (36%) had only partial branch oc-
cclusion owing to procedural failure in 5 (22%)
or to small LAs in 4 (17%). The other 5 (22%)
patients presented with spontaneous occlu-
sion of the LA and IMA. No complications oc-
curred during or after the embolization pro-
cedure.

There was 1 (4.3%) death related to the
EVAR procedure; the patient sustained an iliac
tartery rupture and died of multiorgan failure
subsequent to hemorrhagic shock. The re-
main ing 22 patients were followed for a mean
17 months (range 3–36). There were 4 (18%)
type I endoleaks, 3 detected immediately after
EVAR and 1 diagnosed a year later. According
to the guidelines proposed by Gorich et al.,3
2 of these type I endoleaks originated from
the proximal anastomosis (type IA, one early
and one late), 1 at the distal anastomosis
(type IB, early), and the fourth from the iliac
artery occluder (type IC, early). At the 3-
month CT scan, 2 early IA and IC had sealed
spontaneously. The other 2 late IA, early IB
were still present at 3 months and so were
treated with transcatheter embolization. How-
ever, despite embolization, the aneurysm with
the type IB endoleak showed continuous ex-
pansion, and a second bifurcated stent-graft
was implanted. A type II endoleak was found
in this patient 1 year later.

Only 1 (4.5%) type II endoleak was seen on
the 1-day postprocedural CT scan; the mini-
mal posterior contrast enhancement indicated
a lumbar artery etiology. This patient had only
partial preprocedural branch embolization
(IMA successful, but only 3 of 6 LAs embo-
lized). This type II endoleak was treated con-
ersatively since there was no evidence of sac
expansion during the 2-year follow-up.

In 8 (30%) AAAa, the sac reduced in diam-
eter from an average of 64 × 61 mm preop-
eratively to 51 × 53 mm postoperatively; the
remaining 13 (43%) AAAa demonstrated no
significant change in diameter. Among the 8
patients with sac shrinkage, 4 had complete
collateral occlusion (2 embolized, 1 with spn-
taneous occlusion). Three had only partial
embolization due to technical failure, and 1
had no embolization because of a small LA.
The only instance of sac expansion was the pa-

cient mentioned above who underwent a
secondary stent-graft procedure after embo-
lization failed to resolve a type IB endoleak.

DISCUSSION

The incidence of type II endoleaks persisting
beyond 6 months is reported in the range of
3.5% to 22%,2,5,6,7,14,15,16 and it may be respon-
sible for increased EVAR-related morbidity
with potential risk of rupture.5,14,15,16 This po-
tential risk, in association with sac expansion,
is equivalent to procedural failure and is of
major concern.8,16,19,24,31,32 Some authors re-
ported sac expansion or rupture in the face of
a type II endoleak.25,26,31 Others advised an
aggressive attitude be assumed in cases of
sac expansion even without evidence of en-
doleak28 or stated that sac shrinkage is the
only parameter that indicates successful
EVAR.29 For this reason, many authors have
used a variety of percutaneous procedures to treat these postoperative endoleaks, including sac embolization with coils, glue, or thrombin, or retrograde catheterization to occlude the IMA or LA.

The best treatment modality, however, is still a question of debate. Furthermore, all these techniques are often time-consuming and are not uniformly successful.21, 22, 26–28 Recently, the translumbar approach has been proposed by some authors as the first-choice treatment strategy for type II endoleaks.24

Other authors suggest that LA occlusion by injection of gelatin sponge in the aneurysm sac during the EVAR may reduce the development of side branch-related endoleaks.27

However, Gould et al.27 suggested that preoperative embolization of collateral branches had no beneficial effect on type II endoleaks. Their incidence of early type II endoleaks in patients with or without preoperative embolization was 28% and 25%, respectively, with similar results at 6 months (10% incidence of type II for both groups). On the other hand, Parry et al.5 performed preoperative embolization of the sac feeders (IMA and LA). They found no type II endoleak among 13 patients who had occluded side branches at baseline or 14 patients who underwent successful IMA or LA embolization. Conversely, 8 of 13 patients with patent LAs developed a type II lumbar endoleak.

To avoid or at least to reduce the occurrence of endoleaks, we prospectively performed meticulous preoperative microcoil embolization of patent collateral branches in a consecutive series of EVAR candidates. Every patent IMA arising from the aneurysm sac was embolized, whereas the decision on which LAs required embolization was at the discretion of the interventionist. Arterial criteria (>25-mm diameter or >20 mm if no ostial stenosis existed) were established because large LAs are easier to catheterize and embolize; microcoil embolization was attempted even in the presence of a thrombotic crown in the aneurysm sac.

This approach proved feasible in our relatively small prospective series, achieving a high success rate. In follow-up, we observed only a single (4.5%) type II endoleak, which we believe supports the hypothesis that preoperative embolization of collateral branches can reduce the number of type II endo-
leaks. To our knowledge, only Hovsepian et al. have reported a lower incidence of this complication (3%).

Type I endoleaks were found more frequently than type II in our series, but half of these sealed spontaneously within a 3-month period, which may mean that type I endoleak is also associated with patent collateral branches present preoperatively, as recently reported by Fan et al.

Major limitations of our study are the relatively small patient population and a midterm follow-up averaging 17 months. This short observation period could explain why only a relatively small percentage of patients had significant sac shrinkage. Moreover, endoleaks may occur even beyond 1 year after EVAR, especially in cases where preoperative side branch embolization has not been performed. Another shortcoming to the study was the absence of a control group without preoperative embolization.

Despite these limitations, the 4.6% incidence of type II endoleak is very low compared to previous reports and may support our preventive strategy if corroborated by further studies with a larger number of patients. We believe that preoperative side branch embolization is safer and easier to perform preoperatively than after the EVAR procedure. This maneuver may contribute to a reduction in the rate of type II endoleak and improve the long-term outcome after EVAR.

REFERENCES


Percutaneous Retrieval of Intravascular and Intracardiac Foreign Bodies with a Dedicated Three-Dimensional Snare: A 3-Year Single Center Experience

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INTRODUCTION

The presence of symptomatic or asymptomatic intravascular/intracardiac foreign body (FB) is under-reported in the literature, but it is more commonly encountered in clinical practice. The implantation of long-term venous catheters and the number of technical challenging endovascular procedures are both constantly increasing. Thus, the number of reported FBs will also increase, becoming a serious concern, especially once associated with a cardiovascular complication.

We report the analysis of 22 patients in whom an intravascular/intracardiac FB retrieval was attempted. The details of the procedure have been described in depth emphasizing the technical aspects of the utilized dedicated three-dimensional snare device. The technical feasibility, safety, and efficacy of the retrieval procedure were then analyzed. Results: We divided our patients into two groups. Group 1 included 12 patients in whom the FB had already migrated in the right heart or in the pulmonary circulation. Group 2 included 10 patients with an intravascular FB (intravenous or intracardiac). Technical retrieval success rate was 95.5% (21/22), with a 30-min procedural mean time and no in-hospital procedure-related complications.

Conclusions: Our data confirm that different kinds of FBs lodging in different sites of the cardiovascular system can safely and efficaciously be percutaneously retrieved by utilizing a dedicated three-dimensional snare device. This, therefore, suggests that this minimally invasive intervention should be rapidly attempted, thus anticipating several serious complications. © 2009 Wiley-Liss, Inc.

Key words: foreign bodies; intravascular; intracardiac; 3-dimensional snare

INTRODUCTION

For more than 60 years, physicians have been confronted with the presence of intravascular foreign bodies (FBs), which, at that era, could only be retrieved by a surgical approach. However, in the mid-60s, an efficacious and less invasive endovascular retrieval alternative appeared [1, 2].

In the presence of an intravascular FB, before starting to discuss the best retrieval methodology, one should be aware of the fact that the natural history of an asymptomatic intravascular FB is presently unclear [3], and that a large spectrum of FB related complications has already been reported. The myocardial perforation, myocardial infarction, valvular perforation, arrhythmias, and cardiac arrest are the most feared serious complications [4, 5, 6, 7, 8]. Some authors also suggest that intravascular FBs may act as a “migrating” thrombus formation leading to recurrent pulmonary embolism, or for bacteria leading to infective endocarditis, mycotic aneurysm, and pulmonary abscess [4–7].

Even if not formally confirmed, it seems that FBs lodging in the right heart chambers are more prone to cause

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some late complications than those observed in the superior/inferior cava veins (SCV/ICV) or those already fixed in the pulmonary circulation [8].

One of the most typically reported intravascular/intracardiac FB scenario, is the distal migration of a broken port catheter introduced for prolonged infusion therapy (e.g. chemotherapy). The chronic material fatigue, caused by the prolonged use of port catheters placed in the subclavian vein, and by the friction between the subclavian bone and first rib (Pinch-off syndrome), is thought to be the principal cause contributing to in situ catheter fractures leading to distal embolization [9,10]. Catheter fractures may also occur during implantation of the port system (e.g. technical problems) [10]. Large patients’ series have already reported an incidence of central catheter distal embolization of 0.1–2.6% [11–15]. In 1998, Biffi et al. [16] prospectively confirmed this 1.5% incidence rate of broken catheters after a mean time of 237 days (180–732 days) after insertion.

Several case reports have already described many types of lost intravascular FBs. However, only few case series report the experience of retrieving different FBs utilizing different techniques, and these series included, most of the time, only venous or right heart lost FBs [3,17–22].

Herein, we report our single center experience of all FBs retrieval attempts during a 3-year period (12/2004–1/2008), highlighting the safety and the efficacy of the utilized technique, especially if adopting a dedicated snare device, which is specifically built for facilitating this kind of intervention.

MATERIAL AND METHODS

From a prospectively maintained database, from December 2004 onward, we have retrospectively analyzed all the patients in whom an intravascular/intracardiac FB retrieval procedure was attempted at our tertiary Heart Center. The aim of this retrospective analysis was to establish the feasibility, the technical success rate (= n° of retrieval attempts/n° of successful procedures), and the safety (i.e. n° of procedural related and intraoschocital complications) of the adopted retrieval technique. No informed consent was required to include the patients in this retrospective analysis.

We further divided the analyzed patients according to their initial clinical condition, the type and location of the FB, the time period from the insertion to the breaking of the catheter, the utilized retrieval technique, and if measurable, the necessary time of the complete retrieval intervention.

Our study includes a selected group of patients directly sent to our angiography division for the retrieval intervention. Thus, those patients presenting with an intravascular/intracardiac FB conservatively or surgically treated have not been included in this manuscript. Finally, patients presenting with an intraoschocal FB were also excluded from the analysis.

Retrieval Procedure

The utilized dedicated three-dimensional retrieval snare (Entrino snare™, Bard, Murray Hill, NB) features three interlaced loops combining a good vessel coverage for small, medium, and large vessels. This kind of snare offers a sufficient handling to capture, retrieve, or manipulate objects. The elastic nitinol wire of this snare provides an ideal combination of flexibility, torque ability, and high-resistance also in tortuous vessels. Several models are at disposal, ranging from small coronary snare wires (2–4 mm, 3 Fr compatible), to standard vascular ones (9–15 mm, 6 Fr compatible), to very large ones (27–45 mm, 7 Fr compatible). In our experience, the 9–15 mm snare system is a good compromise for the retrieval of FBs lodging in the pulmonary circulation or in the right heart chambers. The larger snare should be preferred for retrieving FBs lodging in very large vessels such as the SCV and the ICV (up to 35 mm in diameter).

A standardization retrieval procedure was performed by an experienced operator in case of an elective retrieval attempt of a broken port catheter. In case the lost FB occurred as a complication of other vascular peripheral interventions, according to the clinical situation, the most appropriate retrieval technique was adopted by the interventionist. In both situations (elective and urgent), the Entrino snare™ was utilized. Three to five thousand units of heparin were given at the beginning of the procedure.

The elective retrieval procedure of intravenous (i.v.) or intracardiac (i.c.) port catheters started by placing a 6 Fr introducer sheath in the right common femoral vein (CFV), which has a sufficient large diameter to allow the retrieval also of larger FBs. Before attempting the retrieval maneuver, we initially mobilized the FB with a normal diagnostic catheter to detach it from a possible anchor site and also to gain a free FB’s tip, which thereby could be better snared. For this purpose, we utilized a Simmons 1 or 2 catheters, according to the size of the chamber where the FB was anchored. This maneuver was also done to displace the free tip of the FB into the IVC. In this manner, we obviated manipulating the snare in the right cardiac chambers, where any catheter’s manipulation could create ventricular arrhythmias as well as injury to the papillary muscles, the chorda tendinae, and the mitral valve. Once the FB was removed from its anchoring site, the

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TABLE 1. Characteristics of Patients According to Clinical Conditions/Foreign Bodies Type—Location—Time/Retrieval Technique

| Pt | Age | Gender | Clinical condition | Foreign bodies | Location | Since when | Retrieval technique | Adjourn Th. | Proc. Time |
|----|-----|--------|-------------------|----------------|----------|-----------|-------------|---------------|------------|------------|
| 1  | 42  | Female | Breast cancer     | Port (t)       | RA       | 2 m       | 9–15 mm snare | None         | 20°        |
| 2  | 29  | Female | Breast cancer     | Port (t)       | RA       | 1 m       | 9–15 mm snare | None         | 25°        |
| 3  | 30  | Female | Breast cancer     | Port (t)       | RA       | 1 m       | 9–15 mm snare | None         | 25°        |
| 4  | 36  | Female | Breast cancer     | Port (id)      | RA       | 4 m       | 9–15 mm snare | None         | 25°        |
| 5  | 71  | Male   | Lymphoma          | Port (t)       | RA       | 3 y       | 9–15 mm snare | None         | 20°        |
| 6  | 25  | Female | Appendix cancer   | Port (id)      | RA-RV    | 2 y       | 9–15 mm snare | None         | 25°        |
| 7  | 64  | Male   | Colon cancer      | Port (t)       | RA-RV    | 3 m       | 9–15 mm snare | None         | 25°        |
| 8  | 93  | Male   | Colon cancer      | Port (id)      | RA-RV    | 5 m       | 9–15 mm snare | None         | 35°        |
| 9  | 31  | Male   | Colon cancer      | Port (id)      | RA-RV    | 2 + 9–15 mm | CFV-CathSph  | 96°         | 35°        |
| 10 | 78  | Female | Colon cancer      | Port (t)       | RA-RV    | 7 m       | 9–15 mm snare | Staged CFV  | 35°        |
| 11 | 63  | Female | Sigma cancer      | Port (id)      | LPA      | 1 m       | 9–15 mm snare | None         | 25°        |
| 12 | 49  | Female | AVR/heart         | LPA NA        | LPA NA   | 9–15 mm snare | Staged CFV  | NA          |

Vascular group (n = 3 Versus 7 Arteries):

| 13 | 75  | Male   | ICM—ICD          | 0.018" wire   | RV        | NA        | 9–15 mm snare | None         | NA         |
| 14 | 76  | Male   | DCM—ICD          | 0.035" wire   | RV        | Undac    | 9–15 mm snare | None         | 40°        |
| 15 | 75  | Female | Breast cancer    | Port (t)      | LV        | 7 y       | 9–15 mm snare | None         | 40°        |
| 16 | 84  | Female | PAD IVDIE         | 0.018" wire   | SFA       | NA        | 9–15 mm snare | None         | NA         |
| 17 | 68  | Male   | PAD IVDIE         | 0.018" wire   | SFA       | NA        | 9–15 mm snare | None         | NA         |
| 18 | 63  | Male   | PAD IVDIE         | 0.018" wire   | CIA       | NA        | 9–15 mm snare | None         | NA         |
| 19 | 57  | Female | PAD IV           | 0.018" wire   | CIA       | NA        | 9–15 mm snare | None         | NA         |
| 20 | 75  | Female | PAD IV           | 0.018" wire   | CPA       | NA        | 9–15 mm snare | None         | NA         |
| 21 | 78  | Male   | PAD IV           | 0.018" wire   | TST       | NA        | 9–15 mm snare | None         | NA         |
| 22 | 70  | Male   | Kidney failure    | 0.018" wire   | RA-A-A-A  | NA        | 9–15 mm snare | Stent in ICA | NA         |
circulation. This group mostly presented a ruptured port catheter lodging in the SCV/CVC reaching into the right atrium/vein (Fig. 1). In the same group, there are also some patients in whom the broken catheter or other FBs had already migrated into the pulmonary circulation. These broken catheters were found in normal routine chest X-ray, in case of the port system malfunction, or during the surgical port system removal (i.e., once the port catheter was no longer necessary). In one case (Patient 10), the broken port catheter lodging in the right ventricle had caused several episodes of sustained ventricular heart arrhythmias, compromising the hemodynamic of the patient, who had to be intubated and transferred to our center for an emergency FB retrieval.

The second group includes 10 patients (45.5%) in whom the FB lodged in the peripheral vascular tree. This group includes some patients in whom the FBs were observed in a vein (distal IVC and jugular vein), and others in whom the FBs were in the arterial tree. These arterial FBs all came from some kind of complication occurred during different types of peripheral vascular interventions (e.g., renal stenting, iliofemoral angioplasty + thrombectomy, below the knee revascularization).

As also shown in Table 1, the adopted retrieval technique utilizing this dedicated three-dimensional snare was sufficient to successfully retrieve 21/22 of the lost intravascular or intracardiac FBs (95.5% success rate). In fact, the only patient from whom the FB could not be successfully retrieved was Patient 22 in whom a renal revascularization for a chronic total occlusion of the left kidney artery was attempted (Fig. 2A). After having placed a balloon-expandable (BE) stent at the renal ostium, we decided to treat the main renal artery body (with dissection and residual stenosis) with a self-expanding (SE) Stent (640 mm Schütz Stent™, Abbott Vascular, Redwood City, CA). During the stent implantation, we noticed that the stent significantly slipped back finally lodging half in the renal artery and half in the aorta (Fig. 2B). After having changed the 6 Fr introducer sheath for an 11 Fr one, we attempted the retrieval procedure of the lost SE-stent with the snare. Despite the stent could be snared and placed in the external iliac artery (EIA), it could not be retrieved outside of the common femoral artery (major friction with the sheath). It then had to be jailed with another BE-stent (8/38 Onda Stent™, Invatec, Roncadelle, Italy) at the EIA arterial wall (23), without flow impairment (Fig. 2C and D). Afterwards, a second SE-stent was finally correctly implanted in the main renal artery body without further complications.

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In another three cases (13.6%), adjunctive techniques were also necessary to finally succeed in the retrieval intervention: in two cases (6.1%), the intended FB could not be retrieved from the 6 Fr CPV introducer sheath (i.e., catheter node) and a vein surgical cut-down was necessary (Patients 10 and 12); in one case (4.5%), two snare from two different vascular approaches (femoral + antecubital) were necessary to correctly snare the broken Port catheter (Patient 9).

No procedural related complications were observed during the retrieval intervention and up to the hospital discharge.

If we finally specifically analyze only the patients referred to our center for the retrieval intervention and not those on whom the retrieval maneuver was performed during another vascular or cardiological intervention, we found that the elective retrieval maneuver was performed safely and rapidly with a procedural mean time of 35 min (21–96 min), including the puncture of the femoral vein.

DISCUSSION

By attempting a retrieval procedure in patients presenting with a broken port catheter in the right heart, one should be aware that the difficulties to more intracardiac FBs are mostly caused by the fact that these FBs can be fixed somewhere in the heart chamber, that the FBs constantly move with the heart beats and that with the two-dimensional fluoroscopic X-ray support it may be difficult to correctly understand in three-dimension the correct FB's position.

We obtained a 93.5% success rate within a 35-min procedural time. This high success rate was probably because of the fact that firstly we dislodged the FB from the right heart chamber with a normal diagnostic catheter and secondly that the adopted snare allowed a good vessel coverage also in the large cava veins and a better spatial maneuverability also in the beating heart. In this way, the patients had a rapid mobilization and could be discharged from the hospital mostly on the same day. To improve patients' outcomes and avoid the final surgical vein cut-down, necessary in 13.3% (2/15) of our venous approaches, a larger introducer sheath (e.g., 9 Fr) should have been used from the beginning of the procedure.

Because of the large use of central long-term intravenous catheters placement (e.g., port system, etc.), especially utilized for the chemotherapy treatment of active cancers, i.v. and right heart chambers FBs are more frequently observed than intramurally ones. However, because of the constant increase in the total number of worldwide performed peripheral interventions and especially due to an increase also in the technical difficulties of these vascular procedures (i.e., new devices + complex techniques), this kind of "new FB complication" will probably be more and more reported also in the arterial interventional literature.

In fact, in 7 of our 22 patients (31.8%), the last i.a. FB was the result of some kind of complication occurred during different types of peripheral endovascular interventions (Fig. 3). Interestingly, in three of these patients, the rupture of the 0.018" wire occurred in tortuous vessels during the utilization of a new percutaneous rotational thrombectomy device (Rotarex™, Straub Med., Wangen, Switzerland) specifically utilized in case of acute thrombotic peripheral vascular occlusion.

In the mid 90s, several series of patients presenting with lost stents in different vascular territories, have established that, a lost stent (especially the coronary ones), which has already migrated in the peripheral circulation, does not usually lead to clinically relevant complications, and thereby it has not to be...
REFERENCES


Recanalization of Chronic Occlusions of the Superficial Femoral Artery Using the Outback™ Re-Entry Catheter: A Single Centre Experience

Ulrich Beschormer,* MD, Sebastian Six, MD, Uwe Schwarzwälder, MD, Aljoscha Rastan, MD, Christian Mayer, Elias Noery, MD, Roland Machardina, MD, Karheinz Buergelin, MD, Robert Bonzini, MD, and Thomas Zeiller, MD

Purpose: To report our experience with a catheter system (The Outback™ catheter) designed to allow fluoroscopically controlled re-entry after subintimal passage during recanalization of chronically occluded femoro-popliteal arteries. Methods: Between March 2007 and August 2008, 55 legs in 51 patients (80% male, mean age 73 (48–90 years) with chronic occlusion of the SFA and proximal popliteal artery were treated. Clinical presentation was severe intermittent claudication (Rutherford category 3-5), rest pain (Rutherford category 4, 16%), and minor ulcerations (Rutherford category 5, 25%). In all cases, the true lumen could not be entered by using standard antegrade catheter and guide wire techniques. Results: Median lesion length was 200 ± 100 mm. Recanalization of the arterial occlusion was successful in 57 of 55 treated lesions (86%). One patient died of myocardial infarction after delayed femoral bleeding, which was possibly due to extensive recanalization attempts. There were no further procedure-related complications. Conclusion: Use of the Outback™™ re-entry catheter system is a valuable option for interventional therapy of chronically occluded femoro-popliteal arteries following failed standard antegrade recanalization attempt.© 2009 Wiley-Liss, Inc.

Key words: re-entry catheter; recanalization; superficial femoral artery; chronic total occlusion

INTRODUCTION

Therapy of chronic total occlusions of the superficial femoral artery (SFA) and proximal popliteal artery can be based on conservative, surgical, and interventional strategies. Best choice for the patient is not only determined by individual prognostic factors, but also by technical options and experience of the vascular specialist. One major challenge in endovascular treatment of long and heavily calcified lesions is the breakthrough into the true lumen after subintimal passage [1–3]. True lumen re-entry is attempted usually by antegrade guide wire and catheter maneuvers [3]. In case of failure, retrograde access by puncture of the popliteal artery remains an option [4,5]. However, this procedure is often time consuming and may lead to further complications at the puncture site [4]. An additional problem of the technical technique is that in some cases true lumen re-entry can be achieved only far distal the reperfusion point. This may lead to poor primary patency rates, loss of collaterals, and stenting of potential landing zones for future bypass-surgery [6,7].

To overcome these limitations, devices were developed to facilitate the re-entry procedure. In this report, we retrospectively describe our experience with a fluoroscopically controlled re-entry system (The Outback™ catheter, J & J Cordis, New Brunswick, NJ) in chronic total occlusions of the SFA and proximal popliteal artery.

PATIENTS AND METHODS

Between March 2007 and August 2008, 649 occlusions of femoro-popliteal arteries were treated in our Abteilung Angiologie, Herz-Zentrum Bad Kissingen, Germany.

Conflict of interest: The authors have no commercial, proprietary, or financial interest in any products or companies described in this article.

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TABLE I. Characteristics of 61 Patients Undergoing SFA Recanalization Supported by Outback™ Catheter

<table>
<thead>
<tr>
<th>Patient characteristic</th>
<th>N</th>
</tr>
</thead>
<tbody>
<tr>
<td>61</td>
<td></td>
</tr>
<tr>
<td>Age, y</td>
<td>73±3</td>
</tr>
<tr>
<td>Intermittent claudication</td>
<td>36</td>
</tr>
<tr>
<td>Critical limb ischemia</td>
<td>25</td>
</tr>
<tr>
<td>Rutherford category 2</td>
<td>39</td>
</tr>
<tr>
<td>Rutherford category 4</td>
<td>19</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>54</td>
</tr>
<tr>
<td>Diabetes</td>
<td>18</td>
</tr>
<tr>
<td>Coronary artery disease</td>
<td>27</td>
</tr>
<tr>
<td>Congestive heart failure</td>
<td>14</td>
</tr>
<tr>
<td>Stroke or cerebral vascular accident</td>
<td>7</td>
</tr>
</tbody>
</table>

Continuous data are presented as mean (range). Categorical data are given as counts (percentages).

center. Sixty-five lesions (10%) in 61 patients were treated using the Outback™ catheter system (Table I). There were 20 females and 41 males, mean age was 73 (range 49–98 years). All of them were referred because of chronic occlusion of the SFA and proximal popliteal artery. Thirty-six patients (59%) suffered from severe intermittent claudication (Rutherford category 4), 10 patients (16%) had rest pain (Rutherford category 3), and 15 patients (25%) had minor ulcerations (Rutherford category 5). Eighteen patients (30%) suffered from diabetes mellitus. All patients had recent femoral vessel imaging by duplex ultrasonography, CT angiography or MR angiography. Patients with suspected TASC C and D lesions were offered bypass-surgery as alternative treatment. Formal written informed consent was obtained from all patients prior to the procedure.

Technique of Endovascular Treatment

All procedures were performed under local anesthesia with 1% lidocaine and after systemic application of 5000 IE Heparin. All patients received a loading dose of 600 mg clopidogrel and 300 mg of aspirin if not already been under chronic antiplatelet therapy. Arterial access was achieved using either a retrograde transfemoral approach (64) or 7F Balken cross over sheath, William Cook Europe, Bjaeverskov, Denmark) or an antegrade access (n = 27). 6F or 7F Avanti™ sheath, J & J Cordis. After baseline angiography, intraluminal or subintimal passage of the lesion was attempted using a 0.035 inch hydrophilic coated J-carved guidewire (Guidewire™, Teleflex Corp., Leuven, Belgium). The Outback™ system was only used, if the true lumen could not be entered after sub-

Fig. 1. The Outback™ catheter with the cannula needle deployed and the 0.014-inch guide wire advanced through 5 mm minimal passage and multiple conventional re-entry maneuvers using SF diagnostic catheters with angled tip (Vertebrot or Jaffins configuration) remained unsuccessful after at least 15 mm. In that case, the 0.035-inch guide wire was exchanged for an 0.014-inch extra-support guide wire and the Outback™ catheter was delivered in the subintimal space distal to the occluded segment. If the catheter could not be advanced due to friction in heavily calcified segments, the subintimal space was predilated using 3- to 5-mm balloon catheters.

Device Description

The Outback™ catheter is a single lumen 7F catheter that can be tracked over a 0.014-inch extra-support guide wire. The catheter has an integral tube ending in a curved cannula needle. The needle can be either advanced or retracted from the end of the catheter using a control knob at the proximal end of the system (Fig. 1). The nose cone has a radiopaque orientation marker, that is “L”- and “T”-shaped, respectively and allows direction of the needle under fluoroscopy. Once the catheter is placed in the subintimal space immediately distal to the occluded segment, the “L” mark is orientated to point to the true lumen and the “T” mark is orientated in line with the target entry side in a 90° orthogonal projection. The guide wire is pulled back into the catheter and the curved cannula needle is advanced. Next, the guide wire can be advanced into the true lumen. The Outback™ system is retrieved and dilatation and optional stenting or atherectomy procedures can be accomplished (Fig. 2).

Statistics

Continuous data are presented as means (range) ± standard deviation. Categorical data are given as counts (percentages).

RESULTS

According to the TASC II criteria [8] 56 TASC D lesions (55%), 19 TASC C lesions (20%), 9 TASC B lesions (14%), and 1 TASC A lesion (2%) were

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included (Table II). Median lesion length was 200 ± 102 mm (range 35-430 mm). Recanalization of the arterial occlusion was successful in 57 of 65 treated lesions (88%). In six cases, no re-entry could be established. Five of these patients were treated successfully by transseptal approach; one patient was treated with conservative medical therapy. In one case, the Outback™ catheter could not pass the cross-over sheath due to extreme kinking of the iliac vessels. This patient was also successfully treated by transseptal approach. In another case, re-entry could be established, but after placing the 14-inch wire the retraction mechanism of the cannula needle failed. Thus, the system had to be retrieved with the needle partially extended. Because of heavy friction, the wire had to be removed together with the Outback™ catheter and the subintimal channel was lost subsequently. This lesion was treated successfully 3 days after in a second procedure using the outback system again.

Table II: SFA Lesion Characteristics (66)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Outback™</th>
<th>Outback™</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lesion</td>
<td>37 (32%)</td>
<td>32 (33%)</td>
</tr>
<tr>
<td>Total lesion</td>
<td>100 (100%)</td>
<td>100 (100%)</td>
</tr>
<tr>
<td>Total lesion length</td>
<td>200 (35-430)</td>
<td>200 (35-430)</td>
</tr>
<tr>
<td>Total lesion length</td>
<td>171 (357-370)</td>
<td>171 (357-370)</td>
</tr>
<tr>
<td>TASC A</td>
<td>1 (25%)</td>
<td>1 (25%)</td>
</tr>
<tr>
<td>TASC B</td>
<td>1 (25%)</td>
<td>1 (25%)</td>
</tr>
<tr>
<td>TASC C</td>
<td>10 (25%)</td>
<td>3 (75%)</td>
</tr>
<tr>
<td>TASC D</td>
<td>75 (33%)</td>
<td>3 (75%)</td>
</tr>
<tr>
<td>Severe calcification</td>
<td>35 (35%)</td>
<td>30 (33%)</td>
</tr>
<tr>
<td>Endoluminal diameter</td>
<td>5 (8-3)</td>
<td>4.9 (8-3)</td>
</tr>
<tr>
<td>Patient risk factors</td>
<td>3 (17%)</td>
<td>3 (17%)</td>
</tr>
<tr>
<td>Patent risk factors</td>
<td>28 (45%)</td>
<td>28 (45%)</td>
</tr>
<tr>
<td>Patent risk factors</td>
<td>2 (25%)</td>
<td>2 (25%)</td>
</tr>
<tr>
<td>Patent risk factors</td>
<td>10 (10%)</td>
<td>10 (10%)</td>
</tr>
<tr>
<td>Patent risk factors</td>
<td>2 (25%)</td>
<td>2 (25%)</td>
</tr>
</tbody>
</table>

Continuous data are presented as means (range). Categorical data are given as counts (percentages).

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One patient died of myocardial infarction after delayed femoral bleeding 12 hr after the recanalization procedure. The bleeding occurred at the treated leg possibly due to earlier extensive puncture attempts with the Outback™ needle. There were no more procedure related complications such as peripheral embolization or vascular perforation with formation of pseudoaneurysms. Fifty-five of 57 (96.5%) successfully treated lesions underwent subsequent stenting. Median length of the stented segment was 231 ± 97 mm (range 40–476 mm). Median intervention time was 126 ± 53 min (range 28–266 min). In 35 (54.0%) recanalization procedures the subintimal space had to be predilated to deliver the Outback™ catheter to the re-entry side.

**DISCUSSION**

Interventional treatment of chronic total occlusions of the SFA is primarily limited by prognostic and technical restrictions. With the development of new nitinol stent design and drug coated balloons restenosis rates reached acceptable dimensions [9,10]. Thus, patients might be offered more frequently percutaneous transluminal therapy in future. Therefore, new ways to overcome acute procedural failures are needed, especially for long and heavily calcified lesions.

Subintimal guide wire passage during recanalization of chronic arterial occlusions occurs frequently and is often even sought deliberately [11,12]. The failure to re-enter the true lumen remains a major challenge especially in chronic total occlusions of the SFA. Recently, catheter systems had been developed that allow a directed approach into the true lumen guided by intravascular ultrasound (IVUS, Pioneer™, Medtronic, Danvers, MA) or fluoroscopy (Outback™) [6,13–15]. Because no additional IVUS console is needed, we routinely use the fluoroscopically guided Outback™ system due to its easier handling.

In our single center experience, we used the Outback™ system in 65 recanalization procedures of the SFA including the proximal segment of the popliteal artery, that could not be crossed by standard antegrade guidewire and catheter manipulation. To our knowledge, this is the largest series so far reported. The majority (58%) of the lesions were long and heavy calcified corresponding to TASC II classification D. As usual in TASC C and D lesions, in most cases extended subsequent stenting (96.5%) was necessary. The system was easy to use and visibility of the fluoroscopic guiding marks was excellent. Recanalization was successful in almost 90% of treated lesions. It is interesting that lesion lengths were longer in the successful procedures, suggesting that lesion length might not be determinant of success when using a reentry device. In one case we were not able to pass the crossover sheath due to extreme kinking of the iliac vessels. Placing a bigger sheath might have been a solution for this problem potentially reducing the friction between the sheath and the stiff metallic device tip.

In another case, the cannula-needle could not be retracted completely and the system and the wire had to be removed together with the needle partially extended. In August 2008, the Outback™ system was recalled because of this problem. The manufacturer notified our department in a letter that separation rate of the cannula to the deployment slide of the handle assembly might be higher than anticipated. So the cannula might be unable to be retracted into the device after deployment due to a separation of the inner key from the cannula. In February 2009, we were informed by Cordis that the Outback™ system is available again, so we assume that this technical problem has been corrected.

In spite of using the Outback™ system, six lesions could not be passed by antegrade approach. Five of those were treated successfully by retrograde access. We think that this method will still play its role as a bail-out procedure, even if reentry systems are used routinely.

We experienced only one severe complication. One patient died of myocardial infarction after delayed femoral bleeding possibly due to extensive recanalization attempts. We recommend that extensive puncture maneuvers with the cannula needle should be avoided and all patients should be carefully monitored for at least 24 hr after using the Outback™ system. We suggest that in future studies with this device the number of puncture attempts should be documented.

We conclude that use of the Outback™ system is a considerable option in interventional treatment of chronic occlusions of the SFA, if standard antegrade procedures fail. It might be even worth to prove if immediate use of the system is superior to standard approach regarding intervention time, length of stenting zones, and radiation exposure. We suggest a prospective randomized trial to answer these questions.

**REFERENCES**


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Endovascular Treatment of Common Femoral Artery Disease

Medium-Term Outcomes of 360 Consecutive Procedures

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Thomas Schwarz, MD,† Ulrich Frank, MD,‡ Marco Roß, MD,‡ Pierre André Dorée, PhD,‡
Uwe Schwarzwalder, MD,*, Karlheinz Bürglin, MD,*, Roland Michaltz, MD,*, Thomas Zeller, MD*
Bad Krozingen, Germany, and Geneva and Chur, Switzerland

Objectives
The purpose of this study was to evaluate the technical feasibility, safety, and 1-year efficacy of the endovascular treatment of atherosclerotic common femoral artery (CFA) obstructions.

Background
Atherosclerotic CFA obstruction is a known cause of symptomatic peripheral arterial disease. Although surgical endarterectomy is considered the primary choice for this condition, little is known about the percutaneous options.

Methods
Using a prospectively maintained single-center database, we retrospectively analyzed the outcomes of 360 consecutive percutaneous interventions of the CFA for atherosclerotic disease and assessed procedural success, in-hospital complications, and 1-year patency and target lesion revascularization rates.

Results
W不爱y seven procedures (26.9%) were isolated CFA interventions, whereas 167 (43.9%) and 152 (42.9%) also involved inflow and outflow vessels, respectively. Blunt dissection lesions were present in 140 cases (39.9%), and concomitant treatment of the profundus femoral artery was performed on 93 occasions (25.8%). Chronic total CFA occlusions were recognized in 60 cases (15.7%). balloon angioplasty was performed as the primary intervention in virtually all cases (98.9%), whereas stenting was needed in 6% and rotational atherectomy in 2.7% of cases. Angiographic success rates were achieved in 253 procedures (69.9%). Failure—defined as a final angiographic result with a >30% residual stenosis—were observed on 25 occasions (7.1%). In-hospital major i.e., requiring surgery and minor (i.e., treated percutaneously or conservatively) complications occurred in 5 (1.4%) and 18 (5.0%) procedures, respectively. One-year follow-up data were available for 281 patients (77.5%). Restenosis ≥50% by duplex scanning and target lesion revascularization were observed in 14 of 268 (5.3%) and 18 of 322 (5.6%) procedures, respectively.

Conclusions
This large series suggests that the percutaneous approach may be a valid alternative to surgery for CFA atherosclerotic obstructions. (J Am Coll Cardiol 2011;58:792-8) © 2011 by the American College of Cardiology Foundation

Common femoral artery (CFA) disease may cause claudication and critical limb ischemia and is usually part of a broader atherosclerotic involvement including the carotid or femoropopliteal territories (1). Although percutaneous treatment has been accepted as the preferred initial revascularization strategy for the majority of atherosclerotic obstructions in the lower limb, CFA disease remains a mainly surgical domain because it is easily accessable and endarterectomy is associated with favorable long-term outcomes (2,3). In the last few years, the improvements in endovascular equipment and the technical skills of operators have led to an increasing number of percutaneous CFA interventions. Herein, we report a single tertiary center experience of consecutive percutaneous CFA interventions over an 11-year period.

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Methods
From a prospectively maintained database, we retrospectively selected all consecutive patients who underwent a percutaneous CFA intervention between September 1996
and December 2007 at the Angiology Division of the Heart Center in Bad Nauenberg, Germany. Patients with diseases of nonatherosclerotic nature or complicating another endovascular procedure were excluded from the analysis (Fig. 1). Concomitant inflow and outflow lesions requiring revascularization were described as supranigual (i.e., iliac) or infranigual (i.e., femoropopliteal, below the knee) or affecting a bypass territory. Bifurcation lesions of the CFA were classified according to the Medina classification. This classification was developed for the coronary arteries, and it is now applied for the first time also in the femoral bifurcation (4) (Fig. 2).

The aim of this analysis was to establish the feasibility defined as number of successful procedures/number of attempts), technical success rate (defined as a final angiographic residual stenosis ≤ 30%), safety (i.e., in-hospital major and minor complications), and medium-term outcomes of the endovascular CFA approach. Clinical follow-up, as well as duplex ultrasound (US), were per-

Total of 11,493 patients treated at our center (9,016 → 12,287) = mean 958 ± 679 patients/year

466 Patients presenting with a CFA lesion / 516 CFA interventions

Included Patients / Interventions:
- 321 Patients / 360 interventions, (= 2.8% of all patients treated at our center)

Excluded Patients / Interventions (= 4511/56):
- 31 CVA-related lesions
- 9 CFA stenosis
- 64 CFA thromboembolic lesions
- ≥ 2 stenosis < 70% (vascular estimation stage)
- 29 infranigual CFA dissection
- 4 other cases

CFA Lesions Characteristics:
- 64 (17.8%) CFA total occlusion
- 140 (38.9%) CFA bifurcation lesion
  - 67 (18.4%) 1:1 lesion
  - 27 (7.5%) 1:1 lesion
  - 36 (7.2%) 2:1 lesion
  - 30 (8.5%) 1:0 lesion
- 50 (13.9%) post-CFA stenosis
- 76 (21.9%) associated with an SFA occlusion
- 93 (25.8%) associated with a PFA lesion

Interventions:
- 97 (26.9%) isolated CFA intervention
- 157 (45.6%) CFA + iliac/infrainguinal Bypass intervention
- 123 (34.2%) CFA + iliac/infrainguinal Flow pap. intervention

Performed Interventions:
- 356 (99.4%) PTA
  - 133 (38.9%) PTA + stent
  - 122 (33.9%) bare stent
  - 111 (31.3%) two stents
- 36 (8.3%) special techniques:
  - 23 (6.8%) Silverhawk Atherectomy device
  - 3 (1.4%) Missing Balloon

The flow chart shows the included/excluded patients and interventions, common femoral artery (CFA) lesion characteristics, and interventions that were performed. Patients with nonatherosclerotic disease (e.g., thrombosis, Marfan syndrome, Wegener's granulomatosis, Kawasaki's disease, hemodynamic reasons) were excluded from the analysis. Angio = angiography; Fem pop = femoropopliteal; PFA = popliteal femoral artery; TGDS = transpulmonary transluminal guidewire; SFA = superficial femoral artery; TCE = transfemoral catheterization.
Figure 2  Common Femoral Bifurcation Schematics

The schematics were adapted to the common femoral classification (6). The earlier location of the CCA were elucidated according to the Medin classification, a classification developed for coronary artery that was applied for the first time to femoral bifurcation. CCA = first number; SM = second number; PFA = third number. III = external iliac artery. I = presence of significant disease; O = absence of significant disease; other abbreviations as in Figure 1.

formed between 6 and 18 months following the procedure. Binary restenosis (>50%) was defined as a stenotic peak velocity ratio (PVR) >2.4 (PVR = stenotic peak systolic velocity [PSV/peak-to-peak PSV]. Restenoses >50% observed beyond 18 months were considered disease progression not related to the procedure and were excluded from the outcome analysis. Percutaneous CFA treatment was considered effective in the absence of restenosis (>50%) and target lesion restenosis (TLR)—either percutaneous or surgical—at follow-up. Because the majority of the CFA procedures were associated with an additional iliac or femoropopliteal procedure, the ankle-brachial index (ABI) and classification class were not considered reliable parameters to appreciate the hemodynamic impact of CFA revascularization and thus were not reported in the detailed patients’ analysis.

Statistical analysis. Continuous variables were expressed as means ± SD. Categorical data were presented as numbers and percentages, and comparisons among the groups were made with the chi-square test. p < 0.05 was considered statistically significant. Univariate analysis of clinical and procedural predictors of adverse events (i.e., procedural failure, periprocedural and in-hospital complications, restenosis, and 1-year TLR) were performed for approximately 20 parameters. Factors showing p < 0.1 were then included in a logistic regression model, and the odds ratios (ORs) and 95% confidence intervals (CIs) were computed.

Results

During 11 years, 466 consecutive patients underwent 516 percutaneous CFA interventions. A total of 145 patients (156 lesions) were excluded from the analysis because the procedure was performed for nonatherosclerotic disease or to treat an endovascular access complication (Fig. 1). Of the remaining 321 patients with a significant (>50%) CFA lesion, 35 (11.19%) presented with a bilateral CFA stenosis, for a total of 360 procedures. The baseline patient character...
limiting dissections or adopted results (i.e., >50% residual stenosis).

Table 3 reports clinical and procedural outcomes as well as re-stenosis and TLR rates at follow-up. Duplex US or clinical follow-up controls were available for 281 of 321 patients (87.5%) and 316 of 360 procedures (87.8%) for a mean of 10.3 ± 5.4 months. The re-stenosis rate was 27.6% (74 of 268 analyzable lesions), whereas the clinically driven TLR rate was 19.9% (64 of 322 analyzable interventions). The extent to which patients presenting with re-stenosis and those presenting with TLR were matched. Procedural-related complications were observed on 23 of 360 occasions (6.4%); 5 (1.4%) required surgery and the remaining 18 (5.0%) were treated percutaneously or conservatively.

The results of multivariate analyses addressing the predictors of adverse events are reported in Table 4. Probably related to the operators’ experience and the equipment used, the performance of CFA interventions in the second period of the study (i.e., 2002 to 2007) was independently associated with a decreased risk of procedural failure (OR: 0.35; 95% CI: 0.15 to 0.83; p = 0.013). The combination of a CFA intervention with another infragenual procedure was associated with an increased risk of 1-year TLR (OR: 1.97; 95% CI: 1.12 to 3.44; p = 0.015), whereas no significant outcome differences were observed for de novo lesions compared with post-endarterectomy lesions (Table 5). Procedures involving the CFA bifurcation were further associated with an increase in risk of procedural failure (OR: 2.71; 95% CI: 1.19 to 6.15; p = 0.013) and a trend toward more re-stenosis and TLR at 1 year. The use of stents was identified as the only independent protective factor against procedural failure (OR: 0.29; 95% CI: 0.16 to 0.69; p = 0.005), 1-year re-stenosis (OR: 0.52; 95% CI: 0.39 to 0.97; p = 0.046), and TLR (OR: 0.89; 95% CI: 0.26 to 0.91; p = 0.021), whereas the use of atherectomy devices was associated with only a trend toward a significant TLR reduction (Table 5).

Table 4: Multivariate Analysis of Clinical and Procedural Predictors of Adverse Events for CFA Interventions

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Variable</th>
<th>% Present vs. Absent</th>
<th>OR</th>
<th>95% CI</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Procedure failure</td>
<td>IED</td>
<td>0 vs. 9.0</td>
<td>0.11</td>
<td>0.866-1.30</td>
<td>0.641</td>
</tr>
<tr>
<td></td>
<td>Diffusion</td>
<td>12.4 vs. 4.6</td>
<td>2.71</td>
<td>1.35-5.45</td>
<td>0.028</td>
</tr>
<tr>
<td></td>
<td>Semi use</td>
<td>2.27 vs. 10.1</td>
<td>0.29</td>
<td>0.064-0.89</td>
<td>0.036</td>
</tr>
<tr>
<td></td>
<td>&gt;2000 vs. ≤2000</td>
<td>5.5 vs. 24.4</td>
<td>0.36</td>
<td>0.16-0.83</td>
<td>0.024</td>
</tr>
<tr>
<td>Postprocedural complications</td>
<td>IED and DHRM</td>
<td>2.5 vs. 0.6</td>
<td>3.18</td>
<td>1.04-9.59</td>
<td>0.038</td>
</tr>
<tr>
<td></td>
<td>Chronic total occlusion</td>
<td>1.7 vs. 5.9</td>
<td>2.94</td>
<td>0.99-8.79</td>
<td>0.057</td>
</tr>
<tr>
<td>Re-stenosis &gt;50%</td>
<td>Semi use</td>
<td>26.9 vs. 5.0</td>
<td>5.03</td>
<td>2.05-12.97</td>
<td>0.041</td>
</tr>
<tr>
<td></td>
<td>Diffusion</td>
<td>34.0 vs. 24.7</td>
<td>3.51</td>
<td>1.91-6.78</td>
<td>0.001</td>
</tr>
<tr>
<td></td>
<td>MLA 1.0</td>
<td>8.5 vs. 27.0</td>
<td>0.65</td>
<td>0.22-1.80</td>
<td>0.442</td>
</tr>
<tr>
<td>TLR</td>
<td>CFA + infragenual</td>
<td>25.8 vs. 13.5</td>
<td>3.97</td>
<td>1.32-11.44</td>
<td>0.023</td>
</tr>
<tr>
<td></td>
<td>Diffusion</td>
<td>24.1 vs. 8.6</td>
<td>5.54</td>
<td>0.86-33.72</td>
<td>0.086</td>
</tr>
<tr>
<td></td>
<td>MLA 1.0</td>
<td>5.5 vs. 27.5</td>
<td>0.15</td>
<td>0.04-1.65</td>
<td>0.038</td>
</tr>
<tr>
<td></td>
<td>Semi use</td>
<td>15.1 vs. 28.5</td>
<td>0.49</td>
<td>0.26-0.91</td>
<td>0.021</td>
</tr>
</tbody>
</table>

*Procedural failure defined as total angiographic result with >50% residual stenosis, re-stenoses >50% at 12 months follow-up; IED, infragenual intervention; DHRM, DHRM intervention; MLA, main infragenual artery; CI, confidence interval; OR, odds ratio; other abbreviations as in Table 2.*
Table 5. Multivariate Analysis of Outcomes for 4 Different Patient Subgroups

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>Failure Rate</th>
<th>OR</th>
<th>95% CI</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Isolated CFA (n = 97)</td>
<td>1.2</td>
<td>1.2</td>
<td>1.0</td>
<td>0.02485</td>
</tr>
<tr>
<td>CTA (n = 106)</td>
<td>1.2</td>
<td>1.2</td>
<td>1.0</td>
<td>0.02485</td>
</tr>
<tr>
<td>Femoral vessel PTA (n = 283)</td>
<td>1.0</td>
<td>2.0</td>
<td>0.99</td>
<td>0.441-1.60</td>
</tr>
<tr>
<td>1-year TLR</td>
<td>1.0</td>
<td>1.0</td>
<td>1.0</td>
<td>0.074-1.05</td>
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</table>

**Discussion**

Finally, Figure 3 shows the Kaplan-Meier curves of patency (Fig. 3A) and freedom from TLR (Fig. 3B) over time.

Despite the good results shown in the stent subgroup analysis, several caveats should be considered before broadly applying stenting for the treatment of CFA lesions. Whenever possible, preservation of the CFA access should be targeted to allow subsequent percutaneous coronary and peripheral interventions, as well as surgical procedures. Therefore, if stenting is needed, a self-expanding stent as short as possible (e.g., 20 to 30 mm) should be chosen to allow the placement of the femoral bypass anastomosis or the CFA puncture—under fluoroscopic guidance—just above or below the implanted stent. Finally, in rare cases when another vascular access is available, direct puncture through the CFA stent may be carefully performed (9).

Recently, at our institution, the Silverhawk atherectomy device (Cook Endovascular, Inc., North Plymouth, Minnesota) became one of the preferred revascularization strategies for CFA intervention, with the exception of severe calcified lesions. This is because with the Silverhawk or similar atherectomy devices, it is possible to obtain a good angiographic result, avoiding balloon-induced dissections, thus finally minimizing the need for stent implantation (10). However, this approach was mainly used in the last 2 years of the series, only once operators' confidence with the device became sufficient; allowing the safe and effective treatment also of complex CFA lesions (i.e., bifurcations). Interestingly, the use of this device was associated with a positive trend toward less TLR at 1 year (OR: 0.18; 95% CI: 0.02 to 1.42; p = 0.090). The lack of statistical significance, despite the impressive OR, is likely due to the limited sample size of patients treated with this technology (n = 25).
Clinical implications: endovascular versus surgical approach for CFA lesions. Surgery is considered the gold standard treatment for CFA lesions. It may be associated with a technical success rate close to 100% and a 1-year primary patency rate approaching 93%. Long-term outcomes after surgical endarterectomy are also favorable, with cumulative patency rates—including primary, primary assisted, and secondary patency—up to 90% at 5 years (2,3). However, the morbidity associated with the surgery is not negligible (3,11). Accordingly, major hemorrhage, wound infection, nerve damage with persistent sensory disturbances, and the need for surgical revision may occur in up to 5% of cases (11), and the incidence of minor complications such as seromas and hematomas may be as high as 20% (3).

The Transatlantic Inter-Society Consensus (TASC) II guidelines, published in 2007, recommend a surgical approach for CFA stenosis, and no alternative treatment is mentioned in this document, fostering the assumption that surgery is the only available approach for CFA lesions (1). However, it should be stressed that data for surgical CFA endarterectomy are rare. Indeed, the largest series published so far included 101 patients, with a complication rate of 22.6% (3% mortality, 3.6% complications requiring a second operation, and 18.8% minor complications) (3).

Concerning the percutaneous approaches to endovascular choice, data are even scarcer, with only a few retrospective series—the largest series published so far (7,8). However, thanks to modern endovascular equipment and techniques, the successful treatment of a growing number of TASC II-D lesions is now possible (12), and this trend is associated with our favorable results suggesting that CFA stenosis may reasonably be treated with an endovascular approach first.

Study limitations. The major limitations of the present study are the retrospective nature of the analysis and the lack of a control group during the same period. An important issue is that 70.7% of the patients (227 of 321) had a combined revascularization procedure, thus not allowing isolation of the CFA revascularization effect. For this reason, this paper, similar to most of the published CFA series, does not include any clinical efficacy parameters (e.g., ASLR classification) and is focused only on the technical feasibility, safety, and 1-year patency and revascularization rates (3,7,8).

Another limitation of the present study is that because of the constant and rapid evolution of the endovascular field in recent years, our results, obtained from an 11-year time period, might be considered relatively out of date, especially in Europe, where modern techniques and equipment are readily available. However, we believe that reporting the satisfactory results with standard techniques serves as a foundation for further testing of newer technology.

Finally, the follow-up CTA imaging (mainly duplex US) was not standardized and was performed at different time points in nearly 75% of the patients, resulting in an analyzable reocclusion rate of 268 of 360 CFA lesions. However, our standard practice is to conduct clinical follow-up examinations and determine ASLR in the first year after the procedure, and only mandatory duplex US if symptoms have recurred. With this routine follow-up program, we have obtained sufficient data concerning reocclusion and most importantly concerning clinically driven TLR for the majority of the patients (281 of 321 [87.5%]), and this for the most important period concerning reocclusion occurrence (i.e., from the sixth to 18th months after the intervention).
Conclusions

This retrospective analysis of 360 consecutive CFA interventions performed in 321 patients showed that the endovascular approach with balloon angioplasty and provisional stenting is associated with a high success rate, low rate of in-hospital complications, and acceptable restenosis rate at midterm-term follow-up. Our data suggest that the endovascular approach of CFA, even for complex lesions, may be a valid alternative to surgery. Randomized trials are needed to define the optimal revascularization strategy for patients with CFA atherosclerotic lesions.

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REFERENCES