Peripheral Arterial Disease: An Overview of Endovascular Therapies and Contemporary Treatment Strategies

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Even in the absence of symptoms, peripheral arterial disease carries with it a significant risk of morbidity and mortality; thus, screening with the use of the ankle-brachial index is important in identifying patients at risk. Endovascular therapy in the lower extremities is continually evolving for treatment of patients with claudication symptoms or limb-threatening ischemia. Alternative treatments such as cryotherapy and the use of laser-assisted angioplasty hold much promise but need further investigation. In the case of renal artery stenosis and resulting hypertension, supportive clinical evidence is limited for renal revascularization despite the rationale for reducing cardiovascular risk. The current standard of care for significant carotid artery stenosis can include carotid stenting and carotid endarterectomy, but medical therapy may have a role also.
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Key words: Peripheral arterial disease • Endovascular therapy • Stenting • Renal artery stenosis • Carotid artery stenosis

Peripheral arterial disease (PAD) most commonly implies the development of systemic atherosclerosis with wide-ranging clinical manifestations, from asymptomatic status to extremity claudication, refractory hypertension, and stroke. Similar to coronary artery disease, PAD is highly prevalent in the general population, but recognition and treatment of this condition is often infrequent, contributing to a considerably high risk of adverse cardiovascular events, including mortality.[1-3] Accordingly, against the background of evolving pharmacologic and endovascular therapies intended to improve clinical outcomes, there remains a need to focus public health programs on the identification and treatment of patients with PAD. In particular, disease recognition with noninvasive imaging and catheter-based revascularization strategies may improve clinical outcomes as part of a comprehensive medical program for patients with systemic atherosclerosis. Here we review the indications for and endovascular treatment of PAD, summarize results of recent clinical trials evaluating percutaneous revascularization therapies, and describe future directions for therapeutic investigation.

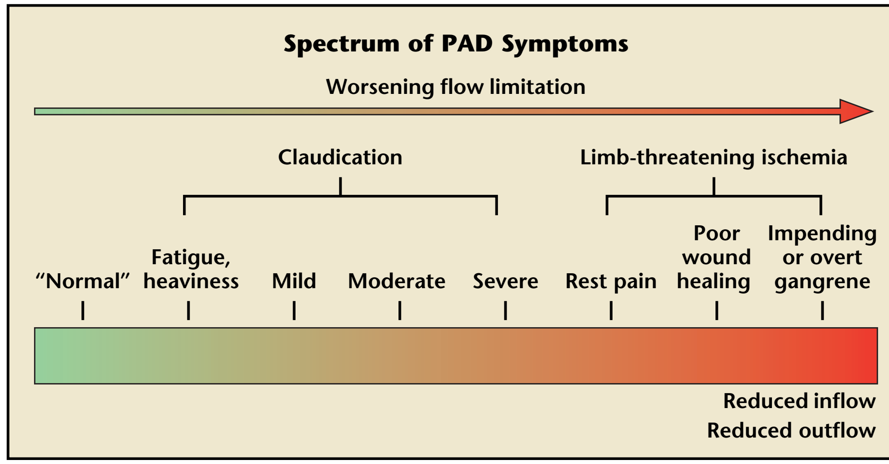


Figure 1. *The spectrum of symptoms of peripheral arterial disease (PAD).* www.medreviews.com

Peripheral Arterial Disease: Prevalence, Symptoms, and Disease Awareness

Estimating the true prevalence of PAD is difficult, since many affected persons may be asymptomatic or present with symptoms considered less typical of PAD. In most instances, however, symptoms associated with occlusive arterial disease vary relative to the corresponding vascular anatomy—for example, stroke or transient ischemic attacks associated with carotid artery disease, hypertension or renal impairment with renal artery stenosis (RAS), or leg claudication with lower extremity arterial disease. Further, symptoms may correlate with the extent of atherosclerotic disease (eg, ranging from lower extremity claudication to critical limb ischemia [CLI]; Figure 1), yet the predictive ability to identify which patients may progress to threatened limb loss is less certain.

Although the progression of systemic atherosclerosis evolves over the long term and the prevalence of PAD is expected to increase among an aging population, atherosclerotic disease begins in early adulthood, and complex abdominal aortic atherosclerotic plaques have been identified in persons younger than 20 years.[4-6] Nevertheless, the incidence of PAD expectedly increases with age, and the age-adjusted prevalence is approximately 12%.[7,8] Recently, the overall prevalence of PAD has been estimated to affect 27 million persons in North America and Europe.[9]

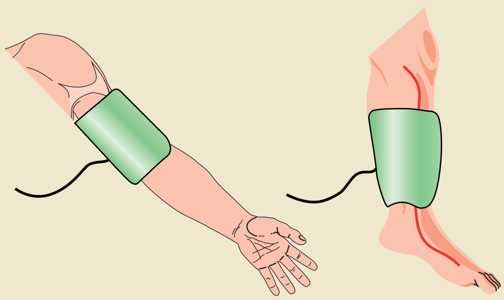
The Peripheral arterial disease Awareness, Risk, and Treatment: New Resources for Survival (PARTNERS) study provides the most contemporary perspective of peripheral atherosclerotic disease prevalence and clinical care.[10] This cross-sectional study evaluated 6979 patients older than 70 years or between 50 and 69 years with a smoking history or diabetes mellitus at 350 primary care practices. PAD, defined as an ankle-brachial index (ABI) less than or equal to 0.90 or a history of prior limb revascularization, was identified in 1865 (29%) of patients. Among them, 825 patients (44%) had a diagnosis of PAD but not coronary artery disease. Importantly, although 83% of patients with prior PAD were aware of their diagnosis, only 49% of physicians were aware. As a result, patients with PAD were less likely to receive treatment with risk factor–modifying therapies such as statins, antihypertensives, or antiplatelet agents.

Importantly, evaluation of symptoms should likely be considered complementary, rather than exclusionary, to hemodynamic assessment of occlusive arterial disease.[11] Typical claudication symptoms were present in only 11% of patients with diagnosed PAD in the PARTNERS study, emphasizing the need for additional screening measures to diagnose PAD. This issue is particularly relevant considering that the risk of cardiovascular mortality among patients with ischemic heart disease is similar to that in those with PAD, irrespective of symptom status.

The ABI is a simple test that should be performed for evaluation of PAD. The ABI provides both diagnostic information (Figure 2) and risk stratification of patients for future events.[12-14] Even at modestly abnormal levels, the ABI correlates with both cardiovascular risk factors and clinical events, and with significantly abnormal indices, the ABI is independently associated with an increased mortality.[15,16]

In general, a decreasing ABI measurement corresponds linearly with reduced walking distance. For example, ABI values of < 0.50 and 0.50 to

Noninvasive Diagnosis of PAD



Interpretation of ABI

> 1.30	Noncompressible
0.91-1.30	Normal
0.41-0.90	Mild/moderate PAD
≤ 0.40	Severe PAD/critical limb ischemia

Figure 2. *The ankle-brachial index (ABI) provides diagnostic and risk-stratification information for patients with peripheral arterial disease (PAD).* www.medreviews.com

0.90 are associated with annual declines in walking distance of approximately 73 feet and 59 feet, respectively.[17] Additionally, the ABI has also been shown to provide diagnostic information in women and racially diverse populations.[18,19] Finally, ABI measurements may more accurately and objectively predict the decline in functional status than clinical history alone. Specifically, as disease severity progresses, patients may describe fewer symptoms related to PAD if they consciously or unconsciously avoid activities that precipitate symptoms.[17] Thus, patient-reported symptom improvement in functional status may instead herald disease progression and functional decline when patients also report decreased activities.

General Considerations for Endovascular Therapy in the Lower Extremities

Initially, endovascular therapies were most commonly applied to the treatment of patients with claudication symptoms or limb-threatening ischemia manifested as rest pain or ulceration. However, advances in catheter-based technologies and an improved understanding of clinical outcomes following percutaneous revascularization have broadened treatment to vascular territories aside from the lower extremities. We present an anatomy-based review of endovascular therapies for PAD, beginning with lower limb revascularization and followed by iliac, renal, and carotid interventional therapies.

Endovascular therapy for PAD is a practice in continual evolution; an already vast array of interventional device technologies is ever expanding, and physician expertise varies within a given institution and over time. As a result, for many patient settings and lesion subsets, treatment strategies vary considerably, and the preferred interventional technique for a certain lesion in a specific patient is wide-ranging. Given these treatment disparities, the 2000 statement from the TransAtlantic Inter-Society Consensus (TASC) Working Group devised a set of guidelines to standardize nomenclature and treatment for lesions recommended for percutaneous (Type A) and surgical (Type D) revascularization strategies.[20]

Between these groups, firm recommendations do not exist for Type B and Type C because of a paucity of evidence-based data. At the time of the publication of the guidelines, Type B lesions were most commonly treated with endovascular approaches, whereas Type C lesions were most commonly treated surgically. However, since the recent publication of these guidelines, an increasing number of Type C lesions have been successfully treated with percutaneous revascularization.

Iliac Arterial Disease

Interventional procedures in the iliac arteries are associated with favorable early and late clinical outcomes. The TASC recommendations for approaching the iliac arteries are summarized in Table 1 and Figure 3. Procedural success rates with angioplasty alone in iliac arteries exceed 90% in all major series and approach 100% with more discrete lesions.[20] Limitations of balloon angioplasty include abrupt vessel closure, spastic recoil, dissection, and residual translesion gradients, especially among initially occluded arteries—features that have largely been mitigated by the use of iliac stents.

Provisional stenting was performed in a case series of 118 patients with iliac disease reported by Vorwerk and coworkers.[21] In this observational study, the primary patency rates at 1, 2, and 4 years were 95%, 88%, and 82%, respectively. Primary stenting was studied in a series of 103 patients with chronic iliac occlusions. A procedural success rate of 98% was observed, with 2- and 4-year patency rates of 83% and 78%, respectively.[22] Meta-analysis of 6 angioplasty studies (N = 1300 patients) versus 8 stent studies (N = 816) in

Table 1
TransAtlantic Inter-Society Consensus (TASC) Morphologic Strata of Iliac Lesions

TASC type A iliac lesions:
1. Single stenosis < 3 cm of the CIA or EIA (unilateral/bilateral)
TASC type B iliac lesions:
2. Single stenosis 3-10 cm in length, not extending into the CFA
3. Total of 2 stenoses < 5 cm long in the CIA and/or EIA and not extending into the CFA
4. Unilateral CIA occlusion
TASC type C iliac lesions:
5. Bilateral stenosis 5-10 cm in length of the CIA and/or EIA, not extending into the CFA
6. Unilateral EIA occlusion not extending into the CFA
7. Unilateral EIA stenosis extending into the CFA
8. Bilateral CIA occlusion
TASC type D iliac lesions:
9. Diffuse, multiple unilateral stenoses involving the CIA, EIA, and CFA (usually > 10 cm)
10. Unilateral occlusion involving both the CIA and EIA
11. Bilateral EIA occlusions
12. Diffuse disease involving the aorta and both iliac arteries
13. Iliac stenoses in a patient with an abdominal aortic aneurysm or other lesion requiring aortic or iliac surgery

CIA, common iliac artery; EIA, external iliac artery; CFA, common femoral artery. Adapted with permission from the TransAtlantic Inter-society Consensus Working Group.[20]

aorto-iliac disease demonstrated that not only were immediate procedural success rates improved by stent utilization (96% vs 91%, stent vs angioplasty, $P < .05$), but mean postprocedural ABIs were also significantly higher (0.87 vs 0.76, $P = .03$), and 4-year follow-up showed a 39% relative risk reduction for failure of primary patency.[23] These findings were achieved despite a trend toward longer lesions among patients who received stents (mean lesion length, 41.0 mm vs 26.4 mm, $P = .1$). Importantly, complication and mortality rates were similar between treatment groups.

Recent procedural and technical advances include direct stenting and the use of self-expanding stents. Findings from a study by Thalhammer and associates[24] suggest that direct stent placement without balloon predilatation may decrease the risk of peripheral embolic complications, and therefore many operators practice this technique when lesions are morphologically favorable (low degrees of calcification, focal lesion, absence of angulation or vessel tortuosity).

Self-expanding stents made of nickel-titanium alloy (nitinol) have a thermal memory property that allows them to be compressed into a low-profile housing sheath for delivery and "spring" to a predefined shape after release in the blood vessel. Nitinol achieves its optimal superelastic behavior at body temperature.[25] In the expanded state, they exert a constant radial pressure on the endothelial surface, and their longitudinal flexibility makes them ideally suited for implantation in areas subject to mechanical stresses. In a series of 172 patients with iliac disease treated with self-expanding nitinol stents with mean lesion length of 5.2 cm, 3-year patency rates exceeded 80%, similar to historical surgical patency rates.[26]

Femoropopliteal Arterial Disease

Unlike the iliac arteries, disease in the femoral and popliteal arteries is typically more complex and characterized by lengthy, diffuse disease and extensive calcification.[27] Multisegmental lesions are common, and patients with femoropopliteal (FP) disease are also more likely to have coexisting coronary artery disease than those with isolated aorto-iliac disease.[2,28] The TASC guidelines for FP disease are categorized in similar manner to treatment of the iliac arteries (Table 2, Figure 4). Procedural success rates for the treatment of FP disease from studies performed more than a decade ago were greater than 90% for nonocclusive stenoses and approximately 85% for total occlusions with angioplasty alone.[29]

High rates of restenosis and reocclusion have limited the enthusiasm for endovascular therapies for femoropopliteal disease.

High rates of restenosis and reocclusion have limited the enthusiasm for endovascular therapies for FP disease. Unlike treatment of iliac

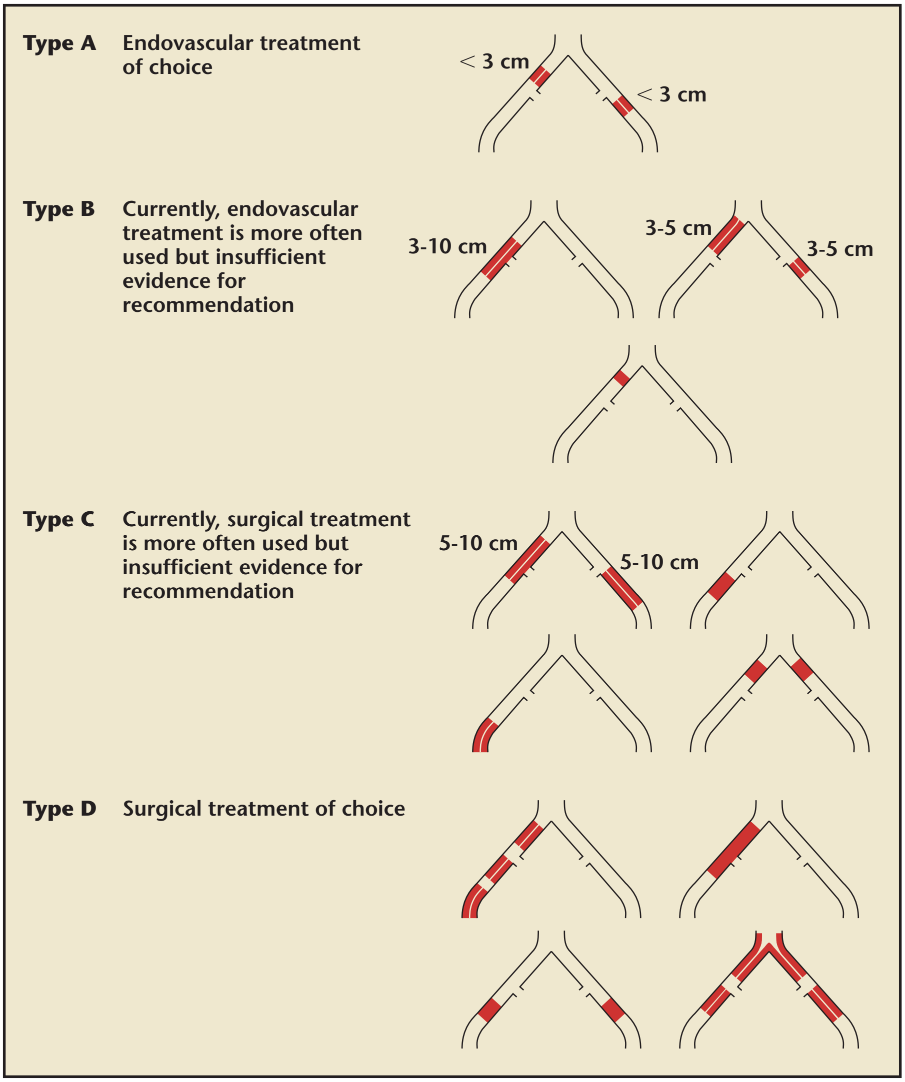


Figure 3. *Summary of TransAtlantic Inter-Society Consensus recommendations for iliac revascularization. Adapted with permission from the TransAtlantic Inter-society Consensus Working Group.*[20] www.medreviews.com

arteries, use of stents in FP revascularization has yielded inconsistent benefit compared with balloon angioplasty alone. In a study of 55 patients who underwent stenting of the superficial femoral artery (SFA), primary patency rates by Kaplan-Meier estimates at 1 month, 6 months, and 1 year were 88%, 47%, and 22%, respectively, and secondary patency rates were 94% at 1 month, 59% at 6 months, and 46% at 1 year.[30] In this study, stent placement was performed for suboptimal angioplasty including flow-limiting dissection, a residual pressure gradient (> 15 mm Hg) or stenosis (> 30%), or failure to establish initial patency. The low rates of primary patency were observed despite relatively short lesions (mean, 16.5 mm). Predictors of favorable outcomes included the absence of diabetes, claudication before therapy, proximal and shorter lesions, palpable distal pulses, and improvements of ABI by greater than 0.1.[31]

Nitinol stents may provide some promise for FP revascularization, with 1-year patency rates as high as 85% in several studies.[32,33] However, a cost analysis of a primary stenting trial has demonstrated that stent use is markedly more expensive compared with balloon angioplasty alone ($8435 vs $4980; $P < .001$) with uncertain added clinical benefit.[34] Furthermore, in a recent screening analysis, a high rate of stent fractures with nitinol stents in the SFA has been reported and associated with a significantly greater likelihood of reduced vessel patency.[35] Among 93 patients (121 treated limbs) followed for a mean duration of 10.7 months, stent fracture was observed in 45 (37.2%) of 121 (37.2%) treated legs (64 of 261 [24.5%]).

Of stent fractures, 48% were characterized as minor (involvement of only 1 strut), 27% were moderate (involvement of more than 1 strut), and 25% were severe (complete separation of stent segments). Stent length appeared to affect fracture rates, with fracture occurring in 13% of stents shorter than 8 cm, compared with 42% of stents 8 cm to 16 cm and 52% for stent lengths greater than 16 cm. Thirty-three percent of fractured stents had binary restenosis greater than 50%, and total occlusion occurred in 34% of the fractured stents.

To improve patency rates following stenting in FP disease, recent studies have evaluated the potential of antiproliferative therapies eluted from stents to reduce neointimal hyperplasia and the need for repeated revascularization. Compared with conventional bare metal stents, treatment with polymer-based, sirolimus-eluting stents has markedly reduced the occurrence of restenosis and the need for repeated target vessel revascularization in patients who are undergoing percutaneous coronary revascularization.[36,37]

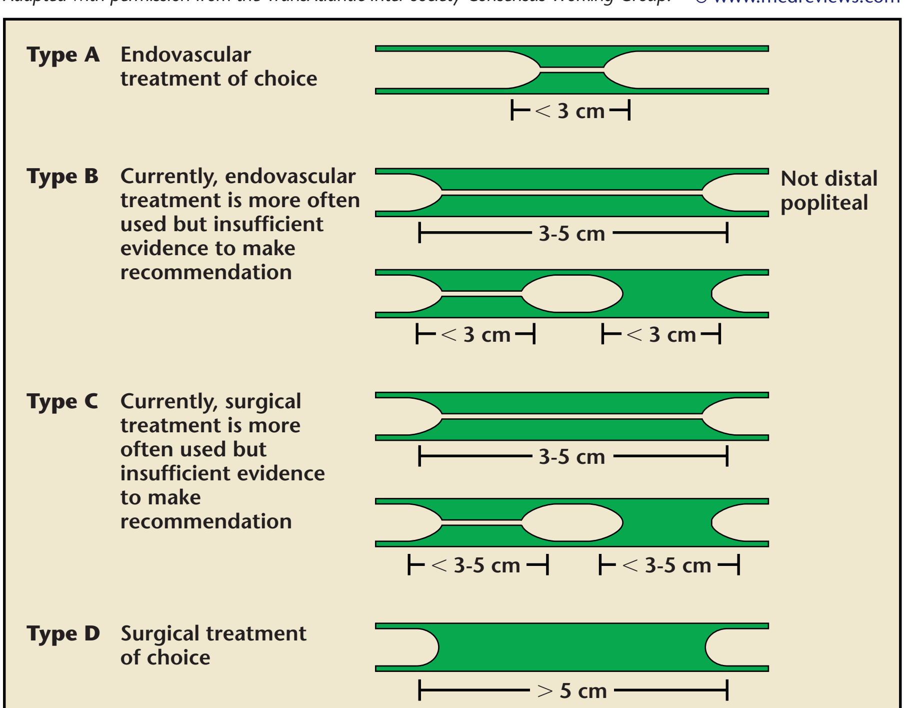
In a recent randomized double-blind study, 59 patients with FP

Table 2
TransAtlantic Inter-Society Consensus (TASC) Morphologic Strata of Femoropopliteal Lesions

TASC type A iliac lesions:
1. Single stenosis < 3 cm of the common iliac artery or external iliac artery (unilateral/bilateral)
TASC type B iliac lesions:
2. Single stenosis 3-10 cm in length, not involving the distal popliteal artery
3. Heavily calcified stenoses up to 3 cm in length
4. Multiple lesions, each less than 3 cm (stenoses or occlusions)
5. Single or multiple lesions in the absence of continuous tibial runoff to improve inflow for distal surgical bypass
TASC type C femoropopliteal lesions:
6. Single stenosis or occlusion longer than 5 cm
7. Multiple stenoses or occlusions, each 3-5 cm, with or without heavy calcification
TASC type D femoropopliteal lesions:
8. Complete common femoral artery or superficial femoral artery occlusions or complete popliteal and proximal trifurcation occlusions

Adapted with permission from the TransAtlantic Inter-society Consensus Working Group.[20]

Figure 4. *Summary of TransAtlantic Inter-Society Consensus recommendations for femoropopliteal revascularization. Adapted with permission from the TransAtlantic Inter-society Consensus Working Group.*[20] www.medreviews.com



disease were treated with either sirolimus-eluting stents or conventional bare metal nitinol stents. Approximately two thirds of patients enrolled had complete occlusion of the SFA, and the mean lesion length was 81.2 mm. The primary endpoint, in-stent minimal lumen diameter at 6 months determined by quantitative angiography, did not significantly differ between the 2 groups (4.94 mm ± 0.69 mm and 4.76 mm ± 0.54 mm for sirolimus-eluting and bare stent groups, respectively; $P = .31$).[38] Although the angiographic percent diameter stenosis tended to be lower in arteries treated with the sirolimus-eluting stent, there were no statistically significant differences in any of the angiographic variables between treatment groups. The mean late loss values were 0.38 mm ± 0.64 mm and 0.68 mm ± 0.97 mm for the sirolimus-eluting stent group and the bare stent group, respectively ($P = .20$). Angiographic binary restenosis (≥ 50% diameter stenosis at follow-up) rates at 6 months occurred in none of the patients treated with the sirolimus-eluting stent and in 7.7% of patients in the bare-stent group ($P = 0.49$).

Although sirolimus-eluting stents may have some efficacy in reducing neointimal hyperplasia in FP disease, the finding that angiographic outcomes do not replicate those in the coronary arteries indicates that further research is required. Possible explanations include the dose of antiproliferative agent, drug-delivery elution rates, and/or mechanical issues related to stent design (eg, strut fracture). A trial evaluating paclitaxel-eluting stents in FP disease is ongoing.

Based on disappointing long-term patency rates and additional cost, primary stenting is presently a Class III indication according to the 2006 American College of Cardiology/

American Heart Association (ACC/AHA) Guidelines for the management of PAD.[39] Instead, endovascular therapy of the FP segment is best approached with balloon angioplasty with provisional stent use for suboptimal results (a level IIa recommendation).

Infrapopliteal Arterial Disease

Endovascular therapy for infrapopliteal arterial disease has historically been even more disappointing than that for FP disease regarding short and long-term patency outcomes. However, the majority of endovascular therapy in infrapopliteal arteries has been performed in the context of limb-threatening ischemia that is characterized by tissue ischemia and/or gangrene (Rutherford-Becker classification 5 and 6). In these patients, the primary therapeutic concern is initial restoration of in-line lower extremity vessel patency rather than restenosis and late patency. Accordingly, percutaneous revascularization of infrapopliteal vascular disease may be an effective therapy for limb salvage, particularly in patients with comorbid illnesses that predispose to higher surgical risk.

The importance of medical attention for patients with CLI cannot be overstated, since up to 25% of patients die within 1 year of major limb amputation,[40] typically from cardiovascular comorbidity. In a recent study of tibioperoneal vessel angioplasty performed in patients with CLI, angioplasty was successful in 270 of 284 critically ischemic limbs (95%). Multi-segmental disease was prevalent, and 167 limbs (59%) required balloon dilatation of ipsilateral inflow disease to access and treat 486 of 529 (92%) tibioperoneal lesions.[41] Clinical success, defined as relief of rest pain or improvement in lower-extremity blood flow, was achieved in 270 limbs (95%). Five-year clinical follow-up in 215 patients (266 revascularized limbs) revealed that 91% of the limbs were salvaged from amputation, and only 8% had required subsequent surgical bypass. These data suggest that balloon angioplasty may be an effective primary treatment for CLI, even if treatment of inflow disease is required to access distal vessels.

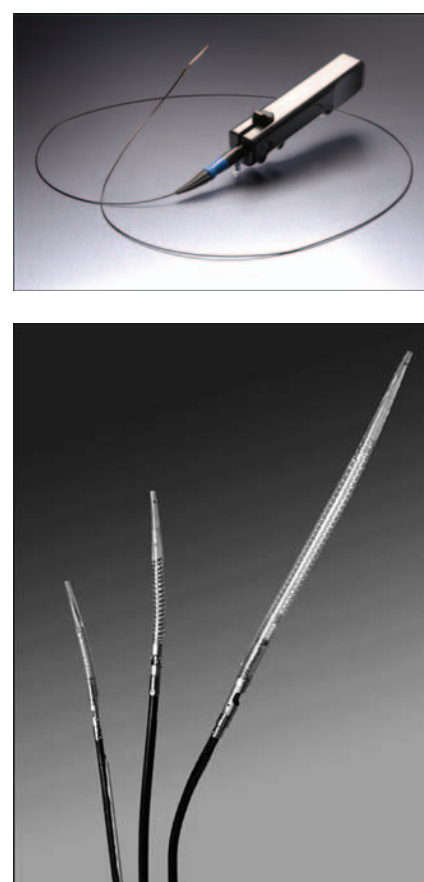
The use of stents in the infrapopliteal segment was recently investigated in patients with CLI and lifestyle-limiting claudication. Below-knee stenting was attempted in 82 patients with CLI (68%) or claudication (32%), with success achieved in 76 patients and 86 limbs. Peri-procedural antiplatelet therapy included indefinite aspirin and clopidogrel for 6 months. Technical success was 94% for de novo lesions, and there were no procedural or 30-day major adverse events (defined as the occurrence of death, myocardial infarction, major unplanned amputation, need for surgical revascularization, or major bleeding). ABIs improved in both the CLI group (0.32 ± 0.13 to 0.9 ± 0.14, $P < 0.0001$) and the claudicant group (0.65 ± 0.09 to 0.95 ± 0.12, $P < .0001$),[42] and relief of rest pain and healing of ulcerations and amputation stumps were observed in 96% of patients with CLI who underwent successful procedures. One-year follow-up of patients showed durable clinical benefits and a low rate of repeated percutaneous procedures with no major adverse events. This single-center study demonstrates promise for stent-supported balloon angioplasty and supports further investigation of this treatment strategy.

Alternatives to Balloon Angioplasty for Lower Extremity PAD

Atherectomy and Thrombectomy

A variety of devices have been tested for atherectomy and thrombectomy in peripheral arteries. The SilverHawk™ catheter (FoxHollow Technologies, Redwood City, CA) is a catheter compatible with 7F and 8F guiding sheaths that enables plaque excision, or atherectomy, of occlusive atherosclerotic tissue (Figure 5). Specifically, the monorail-design catheter is advanced over a 0.014-inch-diameter guidewire, and on device actuation, the catheter pivots against the lesion, exposing a cutting blade that rotates at 8000 rotations per minute. As the catheter is manually advanced across the lesion length, atherosclerotic tissue is excised and contained within a distal storage chamber. The catheter may then be retracted and rotated to treat

Figure 5. *The SilverHawk™ plaque excision catheter.* www.medreviews.com



additional diseased segments. On catheter removal, atherosclerotic tissue is removed from the device.

Unlike previous atherectomy devices, theoretical advantages to plaque excision using this catheter include the absence of barotrauma to the vessel wall, less Dotter effect, and the ability to remove significantly greater amounts of plaque. In the Treating PeripherALs with Silver-Hawk: Outcomes CollectioN (TALON) registry, procedural and clinical outcomes among 601 patients (760 limbs) were evaluated following plaque excision for lower extremity peripheral disease. Among 822 procedures, device and procedural success rates were 98% and 95%, respectively. Adjunctive treatment with stents was required in only 6.3% of lesions. The average lesion lengths (mean ± SD) for above- and below-the-knee disease were 62.5 mm ± 68.5 mm and 33.4 mm ± 42.7 mm, respectively. At 6- (N = 248) and 12-month (N = 87) clinical follow-up, rates of repeated target lesion revascularization were 10% and 20%, respectively.[43]

More recently, the efficacy of plaque excision has been examined in patients with CLI. Among 69 patients (76 limbs treated) with Rutherford-Becker disease classification 5 or 6, treatment with plaque excision was associated with a 6-month target lesion revascularization rate of 4%.[44] Amputation was less extensive than initially planned or avoided altogether in 62 (82%) of treated limbs. In addition to planned comparative trials with other catheter-based revascularization methods, future research directions for this technology are related to histologic, genomic, and metabolic assays on tissue removed with the plaque excision procedure.

Cryoplasty

Cryoplasty involves the use of a balloon angioplasty catheter that simultaneously dilates and cools a stenotic plaque. The mechanism is believed to promote intimal apoptosis and prevent neointimal proliferation and restenosis by transiently cooling the lesion to approximately −5°C with an angioplasty balloon that fills with nitrous oxide (Figure 6). A recently published, prospective series of 102 patients evaluated the utility of cryoplasty using the Polar Cath system (Boston Scientific, Boston, MA).[45] In this series, 84% of lesions were localized to the SFA and 15% were total occlusions. The technical success rate was 85.3%, with a mean residual stenosis rate of 11.2% ± 11.2% ($P < .05$ vs baseline) following cryoplasty. Clinical patency, defined as freedom from target lesion revascularization at 9 months, was 82.2% at 9 months. Further study with this device is warranted to determine the relative benefit of this technology compared with other revascularization therapies.

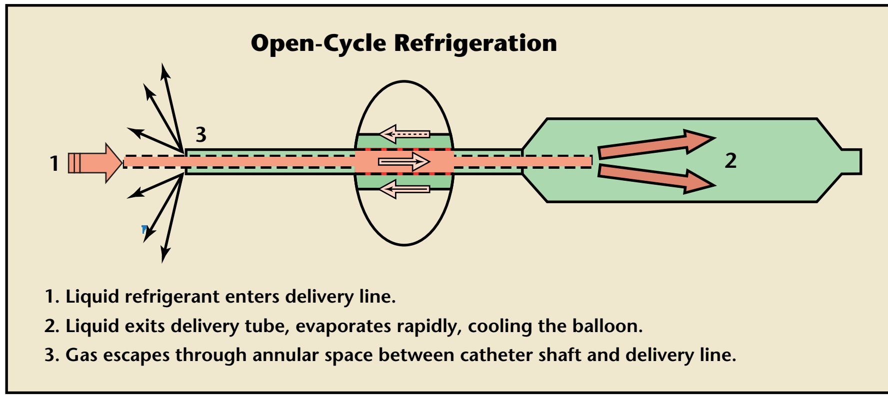


Figure 6. *Cryoplasty catheter mechanism of action.* www.medreviews.com

Excimer Laser

Laser-assisted percutaneous revascularization remains a common technique for the treatment of PAD. Results from the randomized PEripheral Laser Angioplasty (PELA) study showed that in 251 patients with occluded superficial femoral arteries, in comparison to balloon angioplasty, procedural success rates, complication rates, and 12-month restenosis rates are similar with excimer laser catheter, although the need for adjunctive stent therapy was lower with laser therapy.[46]

In the Laser Angioplasty for Chronic Limb Ischemia (LACI) trial, 145 patients with lower limb critical ischemia (423 lesions in 155 limbs) who were considered poor surgical candidates (eg, inadequate venous conduits, unsuitable distal anatomy, or perioperative high-risk comorbidity), were treated with laser-assisted angioplasty and provisional stenting. The primary endpoint, limb salvage among survivors at 6 months, was 92% (110/119).[47] Of patients who died, 2 required major amputations before death. Repeated endovascular procedures were performed in 23 patients at 6 months. This series suggests that laser-assisted percutaneous revascularization may have a role in complex PAD, and further study is warranted.

Brachytherapy

Prior to the widespread use of drug-eluting stents, intravascular brachytherapy was received with a great deal of enthusiasm in the area of coronary and saphenous vein graft lesions for the prevention of de novo and recurrent restenotic lesions, but it has been largely replaced by the use of drug-eluting stents. The limitations of the use of intravascular radiation are largely technical: longer procedural time, costs and logistical issues surrounding shielding, and training and certification requirements for therapeutic use and management of radioactive substances. However, given the frequency of in-stent restenosis in the FP segment, whether brachytherapy could be a promising modality to mitigate the need for repeated revascularization has been recently examined.

In a randomized, double-blinded trial of gamma brachytherapy, 88 patients with FP lesions (mean treatment length, 16.8 cm ± 7.3 cm) underwent angioplasty and stent implantation followed by treatment with either a 14-Gy gamma brachytherapy (iridium 192) source or treatment with nonradioactive seeds. The primary endpoint of the study, angiographic binary restenosis of more than 50% at 6-month follow-up, was similar in both arms. The 6-month restenosis rate was 35% in patients who underwent stent implantation and 33% in patients who underwent stent implantation with brachytherapy ($P = .89$).[48] Overall, early reocclusion in the segment treated with a stent developed in 9 patients (10%) (2 patients [4%] in the stent group and 7 [17%] in the stent and brachytherapy group). Of the latter, 3 patients experienced acute thrombotic occlusion within 24 hours, and another 3 patients experienced late thrombotic occlusion. Overall, brachytherapy did not improve 6-month patency after FP stent implantation because of a high incidence of early and late thrombotic occlusion. Additional antithrombotic or antiplatelet adjuvant medical therapy may make primary stenting with intravascular brachytherapy a feasible option, but this will also require further study.

Endovascular Therapy for Atherosclerotic Renal Artery Stenosis

RAS is perhaps the most common identifiable cause of hypertension, occurring in approximately 5% of all hypertensive patients and in up to 10% to 30% of hypertensive patients with evidence of atherosclerosis elsewhere or with renal dysfunction.[49,50] Although the method and role of routine screening for RAS remain debated, the identification of significant (≥ 50% stenosis) disease may occur in 10% to 20% of patients with abdominal aortography performed at the time of diagnostic cardiac catheterization.[51-53] The presence of RAS has been identified as an independent predictor of mortality, and long-term survival is particularly worse with increasing stenosis severity or the presence of bilateral disease.[54]

The clinical rationale for renal revascularization has been to improve control of hypertension, attenuate the progressive decline in renal dysfunction, and/or treat and stabilize cardiovascular syndromes (eg, acute pulmonary edema) associated with labile hypertension.[55] Considering the relatively higher rates of mortality, graft failure, and need for repeated revascularization with surgical bypass and endarterectomy,[56-58] percutaneous angioplasty and stent treatment is the preferred revascularization method.

The technical evaluation of endovascular therapy for atherosclerotic RAS has included studies comparing percutaneous balloon angioplasty with stent implantation.[59,60] In a randomized trial comparing angioplasty with stent placement,[61] both primary technical success rate (88% vs 57%, $P = .02$) and 6-month patency (75% vs 29%, $P = .01$) were improved with stenting. Among 208 patients treated with renal artery stenting following an inadequate angioplasty result (defined as 50% or more residual stenosis, translesional pressure gradient, or flow-limiting dissection), the 9-month restenosis rate assessed by angiography or duplex ultrasonography was 17.4%.[62] Similar to outcomes following coronary stenting, the probability of restenosis appears directly related to the target vessel diameter, with restenosis rates of less than 10% in arteries exceeding 6 mm in diameter.[63]

However, despite the pathophysiological rationale for renal revascularization, supportive clinical evidence is limited. Regarding treatment of hypertension, for example, results have varied widely, with improvement occurring in approximately two thirds of patients and no effect in one quarter to one third of patients.[59,64-66] Among 106 hypertensive patients randomized to angioplasty or medical therapy alone in the Dutch Renal Artery Stenosis Intervention Cooperative (DRASTIC) trial, angioplasty was not associated with a significant benefit in blood pressure compared with antihypertensive therapy.[67] Aside from the absence of stenting for inadequate angioplasty results, however, conclusions from this study were limited, as 44% of patients crossed over at 3 months from the medical management arm to the angioplasty arm yet were analyzed according to the intention-to-treat principle.

In a recent registry of hypertensive patients with RAS who were treated with stenting,[62] the systolic/diastolic blood pressure decreased from 168 ± 25/82 ± 13 mm Hg (mean ± standard deviation) to 149 ± 24/77 ± 12 mm Hg at 9 months ($P < .001$) and 149 ± 25/77 ± 12 mm Hg at

24-month follow-up ($P < .001$ compared with baseline). Mean serum creatinine level did not significantly change from baseline values at 9 and 24 months.

In addition to treatment of hypertension, percutaneous revascularization of RAS may also prevent deterioration of renal dysfunction and preserve kidney size.[60,64-66,68-70] In one study, patients with a serum creatinine level above 1.5 mg/dL and global renovascular obstruction, defined as bilateral obstruction or obstruction to a solitary kidney, underwent renal artery stenting.[70] Renal dysfunction was assessed by comparing the slope of the regression line of the reciprocal of serum creatinine (1/creatinine) over time before and after the stenting procedure, and renal size was measured with ultrasonography. Renal stenting led to a mean slope increase of 0.043 mg/mo ($P < .001$), and 18 of 23 patients had a complete reversal to a positive slope. Additionally, the kidney size remained the same before and after stenting, at 10.4 cm ± 1.1 cm.

Aside from renal artery revascularization, both medical and endovascular management of RAS must be evaluated against the background of contemporary therapies intended to improve blood pressure management and/or renal function. To examine the potential benefit of percutaneous renal artery revascularization on both blood pressure and renal function, the ongoing Cardiovascular Outcomes in Renal Atherosclerotic Lesions (CORAL) trial has been designed to randomize 1080 patients with significant RAS and hypertension to treatment with endovascular stenting and medical therapy or medical therapy alone. The trial will evaluate a composite endpoint of cardiovascular and renal outcomes over a median follow-up period of 3.5 to 5 years.

Additional advances in endovascular therapy for RAS include trials investigating the potential benefit of distal embolic protection[71] and drug-eluting stents. A study using a distal filter embolic protection device in 46 treated renal arteries (N = 37 patients) demonstrated a 95% procedural success rate, with 65% of the filter baskets containing embolic material, including fresh thrombus, chronic thrombus, atheromatous fragments, and cholesterol clefts. In addition, trials evaluating drug-eluting stents for percutaneous renal artery revascularization are currently under way.

Additional advances in endovascular therapy for RAS include trials investigating the potential benefit of distal embolic protection and drug-eluting stents.

The recent Palmaz Genesis Peripheral Stainless Steel Balloon Expandable Stent in Renal Artery Treatment (GREAT) trial evaluated the Palmaz Genesis Stent, a low-profile stent, for the treatment of obstructive RAS. Fifty-two consecutive patients with mean percentage diameter stenosis before percutaneous revascularization of 68.2% ± 12.0% underwent stenting using the 0.018-inch Slalom Delivery System, with a primary endpoint of angiographic binary restenosis (> 50%) at 6 months. There were no stent implantation failures, displacements, need for additional stent implantation, or other observed procedural complications during the index procedures. The primary endpoint occurred in 14.3% of the study group, which compares favorably with historical controls.[72]

Endovascular Therapy for Carotid Artery Stenosis

Irrespective of symptom status, significant atherosclerotic stenosis of the carotid arteries is associated with an increase in the incidence of stroke and death. Initial surgical studies evaluating carotid endarterectomy compared with medical therapy provide the background for evaluation of the current endovascular therapies. For example, the North American Symptomatic Carotid Endarterectomy Trial (NASCET) was a randomized study evaluating optimal medical therapy with surgical carotid endarterectomy. This study found that in patients with ipsilateral carotid stenosis from 70% to 99% leading to recent hemispheric and retinal transient ischemic attacks or non-disabling strokes, carotid endarterectomy was associated with a 17% absolute risk reduction at 2-year follow-up.[73]

The Asymptomatic Carotid Atherosclerosis Study (ACAS) evaluated the carotid endarterectomy compared with medical management in patients with stenosis greater than 60%.[74] This study found a statistically significant absolute 6% reduction in stroke or perioperative stroke or death in patients undergoing carotid endarterectomy in centers with less than a 3% rate of perioperative major complications. More recently, the Asymptomatic Carotid Surgery Trial (ASCT) randomized 3120 asymptomatic patients between 1993 and 2003 to carotid endarterectomy (88%) by 1 year versus deferred surgery (4% at 1 year). The 5-year risk of stroke or death, including the 30-day 3.1% perioperative stroke or death rate, was 3.8% in the endarterectomy group versus 11% in the deferred group ($P < .0001$).[75]

Therefore, the current standard of care includes carotid endarterectomy for symptomatic patients and possibly for asymptomatic patients at centers with low complication rates. An important limitation, however, is that these trials were generally conducted during a period before widespread treatment with conventional medical therapies, including statin and antiplatelet agents, and therefore the efficacy of revascularization (particularly in asymptomatic patients and those with high surgical risk) is less established.

The introduction of endovascular techniques for carotid artery stenosis began against the background of these surgical clinical trials with the intent that with percutaneous revascularization, major morbidity and mortality would be less than the 6% and 3% surgical rates observed for symptomatic and asymptomatic patients, respectively.[76] An initial randomized trial of percutaneous balloon angioplasty for carotid stenosis compared to surgical endarterectomy demonstrated similar clinical outcomes.[77] In addition, early stent studies were limited to observational analyses of cohorts of patients undergoing carotid stenting.[78] In this early experience, patients treated by experienced operators had outcomes comparable to those with endarterectomy. Patient groups such as those with prior neck irradiation, restenosis following surgical carotid endarterectomy, and high-risk clinical features such as advanced age with concomitant requirement for bypass surgery, emerged as likely candidates for initial percutaneous carotid stenting.[79,80]

Distal embolization of atherothrombotic debris following carotid revascularization is believed to be the most frequent cause of early post-procedural stroke,[81] leading to the rapid development of embolic protection devices.[82,83] The Stenting and Angioplasty with Protection in Patients at High Risk for Endarterectomy (SAPPHIRE) trial was the first randomized trial evaluating distal protection with carotid stenting compared to carotid endarterectomy in patients with coexisting medical conditions that placed them at high perioperative risk for adverse events. The primary composite endpoint of stroke, myocardial infarction, or death within 30 days and death and ipsilateral stroke at 1 year was 12.2% in the carotid stenting arm compared with 20.1% in the surgical group (P = .004 for noninferiority and P = .053 for superiority).[84] A systematic review of randomized trials comparing endovascular therapy (including balloon angioplasty, stenting, and stenting with distal protection) to surgical endarterectomy showed no difference at 1 year in the rate of stroke or death between the 2 groups (odds ratio, 1.01; 95% confidence interval, 0.77-1.44) but reported a lower rate of minor complications for endovascular therapy including less cranial nerve damage (odds ratio, 0.13; 95% confidence interval, 0.06-0.25).[85]

Continued interest in distal embolic protection devices has led to randomized evaluations of different devices. The randomized Carotid Revascularization Endarterectomy vs Stenting Trial (CREST) is ongoing among patients with high-risk clinical characteristics, and several nonrandomized studies in a population with high surgical risk have also been performed. In addition, the Asymptomatic Carotid Stenosis, Stenting Versus Endarterectomy Trial (ACT 1) is ongoing to clarify the potential role of carotid artery stenting with distal embolic protection in asymptomatic patients without increased surgical risk. Specifically, 1658 patients with a lead-in enrollment of 200 patients to ensure investigator experience are planned to be randomized in a 3:1 fashion to treatment with stenting or surgery to evaluate the primary noninferiority endpoint of any stroke, myocardial infarction, and death during a 30-day post-procedural period, and ipsilateral stroke between 31 and 365 days post-procedure.

In October 2005, the Centers for Medicare and Medicaid Services approved reimbursement for carotid angioplasty and stenting in patients with symptomatic carotid stenosis and high perioperative surgical risk under a Food and Drug Administration–approved post-approval program.[86] The current clinical approach for carotid stenting outside of clinical trials should first involve appropriate patient selection and adequate operator experience. Specifically, patients with high-risk features that include age, prior carotid endarterectomy, previous radiation, high surgical risk from coronary disease, or anatomical reasons such as distal stenosis requiring jaw disarticulation, should be considered. In addition, distal protection with carotid stenting is the current standard of care. However, in some instances, the carotid artery anatomy may not be suitable for distal embolic protection. Finally, a skilled team that includes a neurologist, vascular surgeon, and interventionalist with significant experience should be involved in the selection and treatment of these patients.

Conclusions

PAD is an under-recognized and important manifestation of atherosclerotic disease. In addition to a careful history and physical examination, the care of patients with suspected PAD should include measurement of the ABI, which can be easily performed in routine practice.[87] For patients with significant reductions in

ABI (< 0.90), intense risk factor modification should be undertaken in addition to evaluation of the vascular compromise. The increasing use of noninvasive imaging (eg, magnetic resonance angiography, computed tomographic angiography), in addition to invasive angiography, allows for a more definitive anatomic diagnosis and for many potential endovascular therapies. Although symptom-directed imaging may be performed in many patients, increasing attention should also be directed to asymptomatic patients with risk of peripheral vascular disease.

In an effort to increase the skill of peripheral vascular specialists, clinical competency recommendations have been made by the relevant professional societies.[88] These recommendations serve to ensure that the training of peripheral vascular specialists will continue to include both the incorporation of current noninvasive and invasive procedures and involve a comprehensive approach in caring for patients with peripheral vascular disease. Additionally, the ACC/AHA recently published guidelines for the management of PAD.[39] These guidelines focus on infradiaphragmatic PAD and serve as an exceptional reference for clinicians caring for patients through all stages of peripheral vascular disease.

Significant advances have occurred with regard to endovascular therapies for PAD involving limb, renal, and carotid arteries. Patients may now begin to benefit from the percutaneous therapy in many arterial vascular beds. These advances will allow for less invasive methods for limb salvage, resolution of claudication symptoms, and prevention of stroke and renal failure. However, as with many advances in cardiovascular disease, innovation must be supported with rigorous scientific method. Specifically, systematic clinical trials of novel endovascular technologies and treatment methods must be performed before their routine adoption in clinical practice. At present, many areas of PAD still require significant scientific research. These studies must be carried out with a concerted effort by researchers and clinicians to ensure that our current and future patients receive the benefits of these advances. ■

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Main Points

- Typical claudication symptoms may be present in few patients with peripheral arterial disaese (PAD), but the risk of cardiovascular mortality with PAD is similar to that with ischemic heart disease. Thus, additional screening measures are needed, and the ankle-brachial index should be obtained for diagnosis and risk stratification of patients with PAD.
- Interventional procedures in the iliac arteries are associated with favorable early and late clinical outcomes, whereas disease in the femoral and popliteal arteries is typically more complex: unlike with iliac arteries, use of stents in femoropopliteal (FP) revascularization has yielded inconsistent benefit compared with balloon angioplasty alone. To improve patency rates following stenting in FP disease, polymer-based, sirolimus-eluting stents can be used.
- Percutaneous revascularization of infrapopliteal vascular disease may be an effective therapy for limb salvage in the setting of critical limb ischemia.
- A promising piece of technology for lower limb PAD, the SilverHawk™ catheter enables plaque excision of occlusive atherosclerotic tissue without barotrauma to the vessel wall.
- Cryoplasty and laser-assisted percutaneous revascularization may have a role in PAD, and further study of these techniques is warranted.
- Percutaneous angioplasty and stent treatment is the preferred revascularization method for renal artery stenosis (RAS), and although its effect on hypertension is not completely clear, percutaneous revascularization of RAS may also prevent deterioration of renal dysfunction and preserve kidney size.
- The current standard of care for carotid artery stenosis includes carotid endarterectomy for symptomatic patients (and possibly for asymptomatic patients at centers with low complication rates). However, current widespread treatment with medical therapies such as statin and antiplatelet agents renders the efficacy of revascularization (particularly in asymptomatic persons) less certain.

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