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Horizon Scan of Invasive Interventions for Lower Extremity Peripheral Artery Disease

and

Systematic Review of Studies Comparing Stent Placement to Other Interventions

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Horizon Scan of Invasive Interventions for Lower Extremity Peripheral Artery Disease and Systematic Review of Studies Comparing Stent Placement to Other Interventions

Technology Assessment Report

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Executive Summary

Background

About 12 million people in the United States have peripheral arterial disease (PAD) and it is increasing in frequency. In the lower extremities, PAD affects three major arterial segments: aorto-iliac arteries, femoral popliteal arteries, and infrapopliteal (primarily tibial) arteries. The disease is commonly classified clinically based on claudication, rest pain, or degree of tissue loss due to chronic ischemia. Treatment is based on lifestyle changes, including exercise, and medications to improve blood flow. Patients with more severe clinical disease often require invasive interventions aimed at reestablishing bloodflow to the affected limbs.

Invasive treatment options include open surgery of the lower extremity with either autogenous or synthetic grafts to bypass the arterial occlusion(s), endarterectomy, and catheter-based endovascular procedures. These latter procedures include percutaneous transluminal angioplasty (where the vessel lumen is expanded at the site of the occlusion with a balloon), balloon-expandable stents (which are left in place to support the opened lumen), and more recently self-expanding stents, in addition to other less commonly used interventions or cointerventions such as brachytherapy, cryotherapy, drug-eluting stents, and atherectomy.

In 2007, the Transatlantic Intersociety Consensus (TASC) Committee updated a consensus document on managing lower extremity PAD. TASC II updated a classification scheme for the disease based on anatomy of the disease and the extent of lesions. Treatment recommendations were established for the four classifications (A to D). The American College of Cardiology (ACC) and the American Heart Association (AHA) also published recommendations in 2006 based on clinical symptoms and anatomic level of disease.

The Centers for Medicare and Medicaid Services (CMS) has requested a technology assessment report from The Technology Assessment Program (TAP) at the Agency for Healthcare Research and Quality (AHRQ) on invasive interventions to treat occlusive lesions related to PAD, focusing primarily on peripheral artery angioplasty with stent placement. For this topic, CMS is primarily interested in clinical outcomes, in contradistinction to the most commonly researched outcome in the field of PAD, artery patency. AHRQ assigned this report to the following Evidence-based Practice Center: Tufts Evidence-based Practice Center (Contract No. HHSA-290-2007-10055-1-EPC3).

Key Questions

1. Perform horizon scan of published literature on invasive vascular procedures for the treatment of infrarenal PAD (surgical bypass grafting, angioplasty, angioplasty with stent placement, atherectomy). Categorize studies based on intervention; preoperative characteristics of PAD defined by clinical, anatomic, and hemodynamic features (based primarily on TASC II classification schemes); primary outcomes; study design; and sample size.

2. Review and describe the studies cited in the TASC II report that support the recommendations regarding choice of intervention. Judge whether the cited studies adequately support the recommendations.

3. Perform a systematic review across invasive vascular interventions for infrarenal PAD for the association between the TASC I or II classification schemes and rates of clinical outcomes (mortality, amputation, clinical stage, reinterventions, and quality of life) after the intervention, accounting for differences in anatomy and interventions.

4. Perform systematic review of the relative safety and effect of peripheral artery stenting with other invasive vascular procedures for occlusive PAD of infrarenal vessels. Also evaluate comparisons of different stents and/or different procedures with stents. Among comparative studies (stent versus other intervention; stent versus stent) evaluate the following questions and features:
   - Methodological quality of studies
   - Applicability of studies to patients aged ≥65 years with occlusive PAD (based on the CMS population)
   - Demographic and other preoperative (baseline) features of studied patients
   - Clinical, anatomic, and hemodynamic features of PAD lesions (based primarily on TASC II classification schemes)
   - Types of the stents used (specifically discussing steel, nitinol, drug eluting and other stents in this rapidly evolving field)
   - Concurrent and postoperative treatments, including but not limited to brachytherapy and antiplatelet therapy
   - Length of followup
   - Persistence of effects over time
   - Clinical outcomes (patient survival, limb salvage, primary patency, primary assisted patency, secondary patency, pain, quality of life)
   - Adverse events

Conclusions

Key Question 1: Horizon scan of invasive vascular procedures for PAD

The horizon scan evaluated the evidence on invasive vascular procedures for PAD at the level of study abstracts and titles. From a literature search conducted in MEDLINE and the Cochrane Clinical Trial Registry on July 19, 2007, we included citations of studies or systematic reviews of at least 10 patients with chronic lower extremity PAD with any invasive vascular procedure. The literature searches yielded 14,815 citations, of which 2,488 reported data on primary studies of invasive interventions for lower extremity PAD.

Single arm studies represented 79 percent of articles; only 5 percent were randomized controlled trials (RCTs) and 9 percent were nonrandomized comparative studies. Almost 570,000 patients have been evaluated in the literature to date; about 3 percent in RCTs. Among abstracts reporting the data, median followup time was 18 months in RCTs and 24 months in comparative studies and single arm studies. Fifteen percent of the studies have been published since 2000.

RCTs tended to be conducted in patients with femoral popliteal disease (67 percent) or combination artery disease (20 percent). In contrast nonrandomized studies included a greater variety of disease, with only one-third of patients with femoral popliteal disease. Only 3 percent of studies reported TASC classification in their abstracts; of these, the large majority included

patients with more severe disease (grade C or D); only 10 percent included only patients with grade A or B.

Almost half the articles pertained to surgical bypass, 40 percent to PTA, about one-sixth stent, and one-ninth atherectomy. About one-quarter of RCTs evaluated stent, one-half PTA, and one-half bypass. Only one-third compared different types of interventions (e.g., PTA versus stent). Among the 80 percent of abstracts that reported data on which outcomes were evaluated, imaging success (e.g., patency) was most commonly reported (69 percent), particularly among RCTs (84 percent). Complications, mortality, amputations, and hemodynamic success were reported in approximately one-third of abstracts, symptomatic relief and reinterventions were reported in about one-fifth, and quality of life and economic evaluations were rarely reported. Overall, 38 percent of studies reported clinical outcomes in their abstracts. Though, three-quarters of the comparative studies reported clinical outcomes. Only about a third of the studies reported complication rates in their abstracts, though it is likely that this underestimates the reporting of adverse events in the publications.

In summary, the study publications on invasive interventions for lower extremity PAD are heavily weighted toward single arm (noncomparative) studies of PTA and bypass surgery. Among the comparative studies, most evaluated comparisons between different bypass or different PTA interventions. Relatively few studies compared different categories of interventions. To inform clinicians, patients, and policymakers of the relative value of different techniques, the area that may be most fruitful for summarizing appears to be the comparison between PTA and stent. Reviews of comparative studies of atherectomy or of brachytherapy are likely to be premature, given the small number of publications. Most studies appear to have followed patients for a reasonable period of time (at least 18 months), but there has been a disproportionate use of imaging outcomes instead of clinically meaningful outcomes. Future systematic reviews of topics with multiple interventions, patient differences (such as anatomy of disease), and outcomes of interest could well benefit from preliminary horizon scans to help focus (or expand) topics and key questions for the subsequent systematic reviews.

Key Question 2: Review of TASC II report

Our review provides a brief synopsis of the studies that were cited as evidence and the strength of the evidence for each of the TASC recommendations, and a detailed examination of the anatomic descriptions of the atherosclerotic process in each of the studies. Our expectation was that the studies cited as evidence supporting the recommendations would have an anatomic description of the patients treated by a specific therapy. Preferably, the outcomes measured by the studies to assess the effect of the interventions should have been clinically based.

The cited aorto-iliac surgery studies did not describe the preoperative anatomy and no clinically relevant outcomes were reported. The majority of studies cited for the endovascular treatment of the aorto-iliac segment did have anatomic descriptions of the studied patients, but none used the TASC classification. Most studies did report on clinical outcomes. Similarly, studies cited for recommending endovascular treatment of femoral popliteal disease mostly did not provide sufficiently adequate anatomic descriptions of the involved segment to categorize by TASC classification. Clinically relevant outcomes, however, were employed in almost all of the studies. However, it was striking that only a minority of the relevant evidence for endovascular treatment of PAD was cited by the TASC II report.

Key Question 3: Systematic review of TASC classification and clinical outcomes

Thirty-one studies reported TASC classification and clinical outcomes after an invasive intervention for lower extremity PAD. The specific details of how the TASC classification of each patient was determined were generally not reported.

Eleven studies directly compared outcomes among TASC grades or between bypass and PTA for a specific TASC grade population. Only six of these, though, reported statistical analyses related to TASC classification. Three studies compared bypass to PTA with or without stenting, but did not find evidence that any procedure resulted in better clinical outcomes based on TASC classification. Across studies with direct comparisons of TASC classifications, there were trends suggesting that patients with higher levels of disease had worse clinical outcomes, though the studies were underpowered to detect differences. Indirect comparisons across studies were performed, but the studies were too heterogeneous to reach conclusions as to which treatment results in better clinical outcomes based on TASC classification.

Key Question 4: Systematic review of comparative stent studies

From the 14,815 citations, 82 articles potentially met eligibility criteria based on their abstracts and were retrieved for review; one additional RCT was added by domain experts. Among these, 27 studies (in 33 publications) met criteria, including 13 RCTs, 4 prospective comparative studies, and 10 retrospective comparative studies. The studies, in general, and the trials, specifically, were highly clinically heterogeneous regarding the type of stent used, the (selective) use of stent placement as a secondary intervention in the PTA arm (crossover), the severity and anatomy of PAD, the proportion of patients with cardiovascular risk factors, the dates of the interventions, the duration of followup, and the outcomes assessed.

Ten RCTs, 3 prospective and 8 retrospective comparative studies evaluated stent versus PTA. The studies primarily evaluated patients with femoral popliteal disease. The RCTs mostly used balloon expandable stents, though nonrandomized studies often evaluated self-expanding stents. One RCT and two retrospective studies compared bypass to stents. Two RCTs and one prospective comparative study compared different stents.

Individual studies did find statistically significantly better clinical outcomes with one intervention or the other, but overall, the trials and other comparative studies failed to provide adequate data to show that any one intervention is superior for any outcome over any other intervention in any group of patients. However, for the most part, the data cannot be said to convincingly show that stent and PTA (or the other comparisons) are equivalent. The studies are clinically too heterogeneous and both individually and collectively too small to accurately estimate relative differences in clinical event rates.

There is a dearth of trials of patients with either aorto-iliac or infrapopliteal disease. The newer nitinol stents were used by only three of the trials (plus one RCT of stent versus bypass and two RCTs comparing different stents). The predominant primary outcome of the trials remains patency (variously defined), which has not been adequately shown to be an excellent predictor of clinical outcomes. True clinical outcomes have frequently been inadequately or incompletely reported and analyzed.

To be able to assess the true relative value of stent placement compared to PTA, it is important that future trials analyze more clearly defined questions, use greater methodological rigor, and use appropriate clinical outcomes. This includes clearly defining what the population being analyzed is (by diseased artery, lesion morphology, and clinical severity) and what the intervention and comparator is (preferably analyzing stent to PTA, with minimal crossover, since

high rates of secondary stenting make the study results difficult to interpret). The primary outcomes should be important clinical outcomes, not surrogate outcomes such as patency (or even ABI). Researchers should choose the best standardized, clinically meaningful and useful measures of outcomes, particularly for potentially subjective outcomes such as "clinical status." Trials should be adequately powered to fully evaluate these clinical outcomes, with allowance made to capture long-term followup. And complications and other safety outcomes should be fully and actively solicited and analyzed. Until high quality trials are published that address these issues and study the patients for whom the interventions are actually being used, the value of stent placement compared to PTA for patients with PAD will remain unclear.

Chapter 1. Introduction

Note: The introduction is not based on a systematic review of the evidence. It is based on the best information available to us at the time of writing.

Rising prevalence of peripheral arterial disease (PAD)

About 12 million people in the United States have peripheral arterial disease (PAD) and this number is projected to increase to 16 million by 2030.[1,2] In an asymptomatic population, the National Health and Nutritional Survey found that the prevalence of PAD in the 50-59 age group was 2.5%, while it was 14.5% among those over age 70.[3] Several factors contribute to the projected rise in prevalence: 1) the aging of the population, 2) an increase in the incidence of diabetes, an important risk factor for PAD, and 3) improved surveillance for PAD. The rise in the prevalence of PAD is likely to occur despite efforts at modifying some risk factors (such as cessation of the use of tobacco products and various treatments of lipid abnormalities) in the face of worsening of other risk factors (such as rising rates of diabetes and obesity). Among people with PAD, lower extremity atherosclerosis was the most commonly treated anatomic area in 1980 with 111,560 procedures or 49 per 100,000 people.[4] Since then, there has been more than a 50 percent increase in the number of vascular procedures per capita from 182 per 100,000 in 1980 to 284 per 100,000 in 2000.[4]

Classification of PAD

The Society for Vascular Surgery (SVS) recognized the need for standardization of reporting methods to define the clinical severity of PAD and standards for reporting the results of treatment. Rutherford chaired a committee which produced a clinical classification system that is based on increasing severity of disease (Table 1).[5] Fontaine had earlier published an alternative classification system (Table 1), which is employed by many European physicians.[6] Both these clinical classifications allow investigators to compare the preoperative status of patients within various studies to other studies and to gauge the effect of therapy on an individual patient's clinical state.

Clinical classification categorizes patients by: 1) the degree of limitation in walking due to claudication; 2) rest pain; or 3) the amount of tissue loss associated with their PAD, irrespective of its anatomic site. These clinical symptoms are usually related to the degree of ischemia produced and therefore the extent of atherosclerotic blockage within the lower extremities, including the length, number and location of lesions, as well as the degree of stenosis.[7] The degree of clinical ischemia and the patient's symptoms influences the choice of interventions, when balanced against their risks. Rutherford and Becker developed reporting standards for endovascular therapy, which provided objective criteria to classify the severity of the disease and degree of improvement following this therapy.[8]

Diagnostic testing

Objective hemodynamic classification of the functional status of the limb has been in use for several decades. It has been incorporated into the clinical classifications and reporting standards for PAD (Table 1).[5] Several studies have correlated the clinical status of the limb with

Table 1. SVS (Rutherford) and Fontaine classifications and criteria for PAD.

Clinical	Fontaine Stage*	SVS (Rutherford) Grade	Category	Further Clinical Description	Objective Criteria
Asymptomatic	I	0	0	No hemodynamically significant occlusive disease	Normal treadmill or reactive hyperemia test
Mild Claudication	IIa	I	1		Completes treadmill exercise; Ankle pressure after exercise >50 mm Hg, but ≥20 mm Hg lower than resting value
Moderate Claudication	IIb	I	2		Between categories 1 and 3
Severe Claudication		I	3		Cannot complete treadmill exercise and ankle pressure after exercise <50 mm Hg
Ischemic Rest Pain	III	II†	4		Resting ankle pressure <40 mm Hg, flat or barely pulsatile ankle or metatarsal pulse volume recording; Toe pressure <30 mm Hg
Minor Tissue Loss	IV (ulceration or gangrene)	III†	5	Nonhealing ulcer, focal gangrene with diffuse pedal ischemia	Resting ankle pressure <60 mm Hg, flat or barely pulsatile ankle or metatarsal pulse volume recording; Toe pressure <40 mm Hg
Major Tissue Loss		III†	6	Extending beyond transmetatarsal level, functional foot no longer salvageable	

Inter-Society Consensus for the Management of PAD (TASC II). J Vasc Surg. 45(Suppl S): S29A. 2007

* The Fontaine stages defined by TASC II differ somewhat from Fontaine's original staging.[6]

† Critical limb ischemia

the degree of hemodynamic impairment, as measured by Doppler pressures.[9] Continuous wave Doppler measurements of the arterial pressure – the pressure at which the first pulse in the Doppler-scrutinized vessel is heard – has become the standard of care for establishing the hemodynamic status of a limb.

Ankle pressure or the ankle-brachial index (ABI, the ratio between ankle and brachial systolic blood pressures) has become the standard test used to estimate the severity of arterial disease. However, patients with claudication, but without flow- or pressure-reducing stenosis at rest, may have normal ABIs at rest. In this case, the patient usually undergoes a treadmill exercise test at a standardized incline (grade) and rate of speed for usually five minutes or until pain develops. The maximum walking time or maximal walking distance is recorded and may be further qualified as maximal pain-free time or distance. These values have good reproducibility and are clearly clinically relevant. In addition, ankle pressures are measured immediately after exercise.[10] The percent decrease in post-exercise pressure reflects a proximal stenosis as well as the degree of collateral vessel formation.[11]

The specific anatomic site of disease has been defined traditionally by catheter-based arteriography, but computerized tomographic angiography, magnetic resonance angiography and duplex ultrasonography are now used not only to determine the extent of disease across vessels, but also its luminal encroachment. Treatment choices (endovascular versus open surgery) can be made based on computerized tomographic angiography in the majority of patients.[12]

Anatomic Levels of Involvement

Lower extremity PAD spans three traditional anatomic areas of disease: 1) aorto-iliac segment 2) femoral popliteal segment and 3) infrapopliteal segment (also called the infrageniculate segment). When two or three anatomic segments are involved this condition is termed "combined segment disease", which commonly involves both the aorto-iliac and femoral popliteal segments. The patient's clinical status is usually more advanced in this latter situation.[13] The clinical relevance of the anatomic classification is based on the difference at each site in hemodynamic characteristics, vessel diameter, and the anatomic site's specific predilection for atherosclerosis.[7] The natural history without therapy appears to differ for each site.[14] For example, aorto-iliac stenosis with claudication has a relatively "benign" natural history, while occlusive tibial disease may not. Moreover, PAD is an important marker for the concomitant presence of coronary artery disease and carotid artery disease, which has a more morbid natural history. Indeed, the five year mortality of a typical patient with claudication is 30 percent, the major cause of deaths being due to cardiovascular disease.[15] An additional 5 to 10 percent will sustain a nonfatal cardiovascular event. Both the attitude toward intervention and the response to intervention have classically depended on the anatomic site as well as clinical symptoms. In the past these attitudes were influenced by natural history studies as well as case series on open surgical intervention. Clearly, the morbidity of an open surgical procedure and the possibility of death balanced against its benefits weighted intervention toward more limb threatening situations or severe claudication. Endovascular treatment with both its lower morbidity and chance of death has expanded the number of patients undergoing treatment for PAD. The question remains regarding how various treatment options compare for PAD in different anatomic areas of disease.

Treatment options

Open surgery in the lower extremity

Because of its historical relevance as the first intervention available, open surgery is discussed first. Earlier angiographic studies by Coran and Warren suggested that the femoral popliteal segment at the adductor canal (just above the popliteal artery) is the most common site for atherosclerosis in the lower extremity,[16] but the aorto-iliac bifurcation may be the earliest area of atheromatous involvement. In the past, treatment by open surgery for lesions in the femoral popliteal segment was reserved for patients with severe limiting claudication or chronic limb ischemia (as evidenced by rest pain or tissue loss). In patients with infrapopliteal PAD, surgery was reserved for patients with chronic limb ischemia. By contrast, surgery for aorto-iliac disease was used in patients with less severe claudication, despite the greater risks of open treatment of these arteries, because of the more durable long-term results with this approach compared to that with surgery in other segments.[17] The risk-benefit ratio of open surgery weighted the decision toward conservatism, because of the real mortality and morbidity of open vascular reconstruction. The current American College of Cardiology (ACC) and American Heart Association (AHA) consensus recommendations are to select surgery for patients with claudication only when "significant" vocational or lifestyle limitations are present and only after exercise or pharmacologic treatment has failed. These attitudes toward intervention, however, have been modified greatly by the availability of lower risk catheter-based techniques.

Surgical bypass is most commonly performed with an autogenous (the patient's own) saphenous vein and is the recommendation of both the Transatlantic Intersociety Consensus (TASC) II and ACC/AHA consensus documents. Synthetic grafts are reserved for absent or poor quality vein, particularly when employed to the below-knee popliteal or tibial arteries.[18] Successful infrainguinal bypass has been associated with resolution of symptoms, as well as a 5 year patency rate of 70 to 80 percent in the femoral popliteal segment[19] and a 60 to 70 percent patency rate in the tibial segment[20] in cohorts of patients. Open superficial femoral artery endarterectomy had been abandoned for the better durability of femoral popliteal autogenous vein bypass, but has enjoyed utility as a strategy to spare the saphenous vein for later use.[21] Endarterectomy in this segment has been revived by the development of a less invasive approach (remote superficial endarterectomy, which is still an open approach through the common/proximal femoral artery) where the intima and atherosclerotic disease of the entire superficial femoral popliteal segment is removed through a single femoral incision.[22,23] This technique, which is popular in Europe, has been employed in longer lesions, i.e., TASC C and D lesions. Recent reports emphasize the need for surveillance to detect restenosis due to neointimal hyperplasia, which may be treated by PTA.[23,24]. A recent systematic review of case series concluded that this approach had acceptable short and long term results, but emphasized the need for non-invasive surveillance and proper RCTs.[25]

The TASC II recommendations and usual clinical practice for selection of an open approach are apparently not based on any randomized controlled trials (RCTs) that compare surgical bypass to best medical treatment (or no treatment). The recommendations for surgical bypass are based on cohort studies, often retrospective.[26] On the other hand there are several RCTs that compare autogenous vein to synthetic grafts or synthetic to synthetic grafts.[18] However, as will be discussed further below, the majority of these studies, particularly the earlier studies, customarily focused on graft patency rather than clinical outcomes. Notably though, the standard length of followup for graft patency has been five years following the recommendation

of Szilagyi.[27] Shorter term followup was not felt to reflect the true durability of the surgical procedure. Indeed, one of the first multicenter RCTs, which compared autogenous vein to synthetic grafts for infrainguinal disease, showed comparability of patency at 2 years between vein and synthetic grafts, but a reduced patency rate for the synthetic graft arm at 5 years.[18] This longer followup period is related to the increased risk of death and higher morbidity with open techniques and the need to justify this risk. Shorter followup periods are reported in trials of catheter-based techniques, in part due to the procedures' lower morbidity and mortality.

For occlusive disease involving the aorta, a synthetic bypass (either polyester [Dacron] or polytetrafluoroethylene [PTFE]) is sewn in at the infrarenal aorta level (proximal anastomosis) and another at both femoral arteries (distal anastomosis) beyond the area of iliac stenosis, or more usually occlusion. Aorto-femoral bypass has been the surgical procedure of choice for this segment and had supplanted aorto-iliac endarterectomy (removal of the inner lining of the artery and atherosclerotic plaque), because of the propensity of the latter for the development of neointimal hyperplasia and occlusion. Aorto-femoral bypass has produced durable symptom relief and a patency rate at 5 years of 85 percent for patients with claudication and 80 percent for patients with chronic limb ischemia.[28] Again the data supporting this approach is derived from numerous and large case series rather than RCTs.

Endovascular procedures

It is projected that the number of patients undergoing arterial revascularizations will increase 19 percent from 2005 to 2010.[1] Overall catheter-based interventions for lower extremity PAD have risen from 0.1 per 100,000 population in 1980 to 58.3 per 100,000 in 2000.[2] An analysis of the National Inpatient Sample data found that while open lower extremity procedures decreased by 30 percent from 1996 to 2003, endovascular procedures in this segment rose by over 40 percent per capita.[4] Catheter-based techniques, thus, are one of the principal drivers of the increased volume of revascularizations. The key driver of this growth is the less invasive nature of endovascular treatments, which is associated with both lower mortality and morbidity. Vascular specialists have become quite comfortable in treating high-grade stenoses or short segmental occlusions of the iliac artery with an endovascular approach and techniques for longer occluded segments are being further refined. Percutaneous transluminal angioplasty (PTA) and stents are the two principle and primary techniques employed in endovascular therapy. Alternative treatments, such as subintimal angioplasty or covered stents, are modifications of PTA or stenting that expand applicability of the principle techniques. Drug-eluting stents, brachytherapy and cryoplasty have also been developed to reduce neointimal hyperplasia. Devices that remove plaque, such as the atherectomy catheter, may be used primarily or as an adjunct to the two basic techniques. Evidence supporting these alternative treatments is less robust than for PTA and stenting.

Over 40 years ago, Dotter and Judkins introduced the concept of "transluminal treatment of arterial sclerotic obstruction" as a catheter-based technique for relieving atherosclerotic stenosis, in order to reduce morbidity and mortality in patients with concomitant coronary artery disease.[29] Gruntzig subsequently developed a polyvinyl rigid sausage-shaped balloon on his kitchen table; not unlike De Bakey's sewing machine manufacture of the first aortic synthetic grafts.[30] Gruntzig successfully dilated a superficial femoral artery stenosis associated with claudication in 1974 and a patient with an iliac artery stenosis one year later with his double lumen catheter. Commercial availability of these devices with modifications has led to the rapid adoption of endovascular approaches. Since then, particularly over the past 10 years,

endovascular therapy has exploded in volume and created a tectonic shift in the way patients with PAD are managed.

Endovascular revascularization currently includes several techniques: 1) PTA, 2) arterial stenting, and 3) various adjunctive techniques such as atherectomy. The most recent major catheter-based development in the treatment of the PAD is peripheral stenting, which is a rapidly evolving technology. It has been used extensively in the past decade since publication of the first systematic review on the topic.[31] Stenting is generally performed to correct a suboptimal PTA, where there is a flow-limiting dissection or residual stenosis that reduces the lumen (usually by 30 percent), termed secondary stenting. Stenting allows avoidance of surgery and, in such cases, the stent is placed for residual stenosis or if there is a flow-limiting dissection. Stents are used primarily when an occlusion is being recanalized, particularly a lengthy one, or when performing a subintimal balloon angioplasty. PTA alone, however, may still be the first choice for segments involved by PAD of a relatively short length (TASC A), such as the superficial femoral artery segment. The TASC II recommended approach for aorto-iliac disease and, it appears, femoral popliteal disease is PTA with secondary stenting if needed for suboptimal results or acute occlusions. It should be emphasized that TASC II recommended PTA as "the procedure of choice" for limited disease stenoses or occlusions less than 10 cm in the femoral popliteal segment. However, primary stenting in all patients receiving angioplasty is more common for longer lesions, such as TASC C stenosis or occlusion of at least 15 cm length.

Although the mechanism of PTA was initially believed to be related to a controlled inflation of an intraluminal balloon to widen the arterial lumen by compressing the atherosclerotic plaque into the arterial wall, it is now clear that deep fractures in the intima with concomitant medial dissection and stretching is the actual mechanism leading to an increase in the lumen diameter.[32] In essence PTA involves a controlled stretch injury of the media without rupturing the adventitia. The complication of vessel rupture, which is unusual in experienced hands, is avoided by the correct matching of the balloon size to the lumen diameter. The major risks of angioplasty include bleeding due to arterial rupture, embolization due to fragmenting the plaque material, and arterial dissection. Remodeling of the vessel wall generally occurs, which allows the lumen to remain patent. However, early restenosis can occur due to intimal hyperplasia or vessel wall recoil as opposed to what is observed in surgical endarterectomies; whereas late restenosis is due to the same processes that caused the original stenosis.

Cryoplasty combines PTA with the application of cryothermal energy to the arterial wall, which induces aptosis of smooth muscle cells and programmed cell death. The primary aim of this method is to prevent or treat restenosis and has been employed as a primary endovascular technique. Mid-term evaluation of results as a primary therapy, which had been initially promising, have shown significant decrements in patency.[33] This technique had been advanced as a method to minimize the formation of neointimal hyperplasia, which occurs after PTA alone and had been considered to be an advantage in instances of restenosis, though a Cochrane review failed to show any advantages over conventional angioplasty.[34]

The long-term results of PTA in the superficial femoral artery have been affected by a restenosis rate of approximately 40 percent and do not match results achieved in other sites. The femoral popliteal segment places special demands on endovascular treatment due to the unique anatomy (its being a long artery without major collateral vessels), structural mechanics (subject to rotational and longitudinal compressive forces), and hemodynamic features (low flow with a high resistance run-off bed) of these arteries. The placement of a metallic stent may improve these results. Stents may have particular advantages in lengthy occlusions. There are two basic

types of stents, balloon- and self-expandable. Balloon-expandable stents employ an angioplasty balloon to expand and set the stent within the arterial segment. The Palmaz stent is an example of this type, though it has been supplanted by the next generation of self-expandable stents for arterial occlusive lesions. Self-expanding stents may have benefits in longer occlusive lesions as primary therapy, particularly in the femoral popliteal segment, where PTA and balloon expandable stents may be associated with higher rates of restenosis and failure. The self-expandable stent depends on the unique properties of a memory metal, such as nitinol, or alternatively the weave of the stent, to assume a preconfigured shape within the vessel lumen. Wallstents, an example of the latter are composed of elgaloy, a variant of stainless steel, and the radial force induced by the weave density determines expansion. Self-expandable stents may be post-dilated to ensure strut apposition to the arterial wall. The patency rates of these stents appear to be superior to the balloon expandable stent.

In addition, newer materials have been added to the stents with the goal of improving their clinical effect. The standard stent, whether balloon- or self-expandable, is bare metal, with no added materials. Covered stents employ a synthetic fabric, such as PTFE, that covers the metal component of the stent and acts as an exoskeleton. However, animal studies did not support the proposed advantage of the covered stent, that it lowers the incidence of neointimal hyperplasia, which can hasten restenosis.[35] While the incidence of neointimal hyperplasia was reduced in the midportion of the graft it was comparable to controls at the proximal and distal ends of the covered stent. One major advantage of a stent graft is that a longer infrainguinal lesion can be treated. In theory, the synthetic fabric of the covered stent excludes the atherosclerotic plaque from the lumen. In addition, there may be formation of a more stable layer from tissue ingrowth, which may be related to the specific "pore" size of the PTFE material may occur. Moreover, the combination of the nitinol exoskeleton and the fabric cover yields a flexible, but structurally stable device, which is particularly advantageous in the femoral popliteal segment.

However, fracture of the stent's metal struts may be an inherent problem to stent performance and some have suggested it has been associated with stent failure.[36] Device failure due to a stent fracture is a particular problem in the distal superficial femoral and proximal popliteal arteries, due to the unique mechanical forces (longitudinal bending and torquing) exerted on stents in this area. Scheinert and colleagues described a 37 percent incidence in their plain radiography survey of 121 treated legs.[37] They conclude that stent fracture risk increased with long segment stenting and that the primary patency was lower in those limbs with stent fractures (41% versus 84%; $P<.0001$). Schlager and associates compared the rates of in stent restenosis, stent fractures and clinical worsening in patients under going placement of either 116 Wall Stents or nitinol stents (45 SMART stents and 125 DYNALINK stents) in the superficial femoral artery.[38] The rate of stent fractures were 19 percent over 3 years; 28 percent for SMART stents and 2 percent for Dynalink/Absolute stents. The clinical deterioration paralleled the stent fracture findings. Irrespective of clear linkage to restenosis, Jaff et al, in 2007, have recommended that a standardized method of surveillance for stent fracture is required, which takes into account among many variables the types of radiographic equipment and imaging techniques.[39]

Drug-eluting stents, designed for the coronary circulation, have been applied to peripheral vascular lesions. This is an example of an "off label" use, as discussed below. These stents commonly contain sirolimus (rapamycin), an immunosuppressant drug used to prevent

neointimal hyperplasia. Other treated stents have been developed including the Carbostent, which has a thin coating of carbon meant to decrease its interaction with platelets.

"Off label" use of stents intended for the biliary tree (special weave configuration) or coronary vessels (drug coated) is common in peripheral arteries. Arguably, this is a problematic development because the device does not follow the usual FDA approval pathways. In the US, the safety of these devices is tracked through obligatory reporting in the Manufacturer and User Facility Device Experience (MAUDE) database. However, the self-reporting nature of the databases makes it difficult to validate actual incidence rates of problems with these devices. Additional RCTs are underway, one which compares PTA alone to PTA and a biliary stent in the superficial femoral and proximal popliteal arteries; another RCT has been performed, which examines a bare nitinol biliary stent in the same anatomic segment. Neither of these trials has yet been published in peer-reviewed journals at the time of our review.

An alternative approach to PTA or stenting is the atherectomy catheter, which removes the atherosclerotic plaque from the lumen, thereby remodeling a narrowed lumen to a nonstenotic flow stream. Frequently, this technique is used as an adjunct with arterial stenting

TASC and ACC/AHA Practice Guidelines

In 2000, the Transatlantic Intersociety Consensus (TASC) Committee was formed, representing 14 societies including vascular surgery, interventional radiology, angiology and cardiology. The original recommendations were published in that year.[15] In 2007, the working group was expanded to 16 societies from additional countries; it published an update of the consensus document.[26] These documents have had an important impact in the field as they represent a consensus among the various specialties that treat PAD. They also provide a clear standardization by anatomic description of the extent and degree of disease in both the aorto-iliac and femoral popliteal segments. Table 2 summarizes the TASC classification and treatment recommendations for aorto-iliac and femoral popliteal segments. The TASC committee used this anatomic classification system to make recommendations on the type of treatment (endovascular versus open surgical) based on the anatomic nature and extent of the lesions. However, as discussed in more detail below, the evidentiary basis for recommending treatment type based on TASC classification is unclear.

The American College of Cardiology (ACC) and The American Heart Association (AHA) convened a task force of cardiologists, vascular medicine specialists, interventional radiologists, and vascular surgeons to develop guidelines for PAD. Their important recommendations are published in Circulation 2006 and are available on line (www.acc.org or www.americanheart.org). These recommendations are based on "Level of Evidence": Level A, data from multiple RCTs or metaanalyses; Level B, data from single RCTs or nonrandomized studies; and Level C, consensus of experts, case studies, or standards of care. The Recommendations were also divided into descending grades: Class I, general agreement that the treatment is beneficial, useful and effective; Class II, conflicting evidence or divergence of opinions on the utility of the treatment; and Class III, evidence of no benefit or utility. The document recommends general methods for assessing PAD based on its severity, anatomy, as well as the type of intervention appropriate to clinical symptoms and anatomic involvement, or "morphological characteristics." Risk factor modification is emphasized.

Table 2. TASC classifications and treatment recommendations for aorto-iliac and femoral popliteal lesions[26]

Classification	Definition		Treatment Consensus
	Aorto-Iliac Lesions	Femoral Popliteal Lesions	
TASC A	• Unilateral or bilateral stenoses of CIA • Unilateral or bilateral single (≤3 cm) stenosis of EIA	• Single stenosis ≤10 cm in length • Single occlusion ≤5 cm in length	Endovascular therapy is the treatment of choice
TASC B	• 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	• Multiple lesions, each ≤5 cm (stenosis or occlusions) • 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 distal bypass • Heavily calcified occlusions ≤5 cm in length • Single popliteal stenosis	Endovascular is the preferred treatment. The patient's comorbidities, fully informed patient preference, and the local operator's long-term success rates must be considered when making treatment recommendations.
TASC C	• Bilateral CIA occlusions • Bilateral EIA stenoses 3-10 cm long not extending into the CFA • Unilateral EIA stenosis extending in 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	• Multiple stenoses or occlusions, totaling >15 cm, with or without heavy calcification • Recurrent stenosis or occlusions that need treatment after two endovascular interventions	Surgery is the preferred treatment for good-risk patients. The patient's comorbidities, fully informed patient preference, and the local operator's long-term success rates must be considered when making treatment recommendations.
TASC D	• Infrarenal aorto-iliac 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	• Chronic total occlusion of the SFA (>20 cm, involving the popliteal artery) • Chronic total occlusion of the popliteal artery and the proximal trifurcation vessels	Surgery is the treatment of choice

AAA, abdominal aortic aneurysm; CFA, common femoral artery; CIA, common iliac artery; EIA, external iliac artery; SFA, superficial femoral artery.

The TASC II document summarizes the principles that are employed by most vascular specialists: 1) balance the risks of the procedure to the benefits; and 2) assess the durability and amount of improvement that can be expected from that specific procedure.[26] The important classification of the morphology of the atherosclerotic involvement of the aorto-iliac and femoral popliteal segments depends on the location within the segment (e.g., common versus external iliac), stenosis versus occlusions, and the length of the lesion. The degree of calcification is not included. For both the aorto-iliac and femoral popliteal segments, endovascular intervention is the therapy of choice for TASC A lesions and is preferred for TASC B lesions or high risk patients with TASC C lesions, while surgery is recommended for TASC D lesions and "good" risk patients with TASC C lesions. Selection of the approach also depends on patient's preference and the individual treating physician's long term results.

In the ACC/AHA consensus document indications for endovascular treatment are based on the clinical symptoms and anatomic level. The level of evidence is provided as documented in the guidelines. PTA is indicated for patients with TASC A claudication and aorto-iliac disease. Stent placement is restricted to those patients who have either a suboptimal or failed result following PTA. Although the evidence for primary stenting of a common iliac and external iliac artery lesion is rated level B for common iliac lesions and C for external iliac artery disease, primary stenting is termed a Class I recommendation. For patients with femoral popliteal lesions PTA again is recommended as the initial endovascular treatment and the effectiveness of stents as well as other techniques is rated Class IIb with an A level of evidence. Similar to recommendations for the management of iliac disease, primary stent is not recommended as the primary treatment for femoral popliteal disease. Stents should be employed secondarily for a failed PTA. Chronic limb ischemia is discussed in brief and no apparent specific recommendations for endovascular treatment are given for these patients. The majority of the recommendations discuss surgery for chronic limb ischemia.

Outcomes evaluated in PAD intervention studies

Patency has been the standard method for assessing the efficacy of a vascular surgical intervention. Raw patency measures (e.g., number of patent grafts /number of grafts at risk) had been replaced by life table analysis of graft patency, which accounts for grafts lost to occlusion, subjects lost to followup or to death, and was modeled after survival data employed in oncology. Unfortunately with bilateral procedures investigators have employed the surgeon's perspective of limbs at risks rather than the patients' perspective of people at risk. This convention has continued into the assessment of catheter-based techniques. A further refinement was the concept of secondary patency to account for successful interventions on a failed or occluded graft.

Patency was originally defined by clinical means; i.e., recurrence of primary symptoms or loss of pulse. More recently, trials of catheter-based interventions have employed imaging criteria for patency and have further modified this outcome measure to include deterioration of morphologic status from a less than 10 percent stenosis at the treated site to a 50 percent or greater stenosis as determined by Duplex ultrasound peak systolic velocities 2 cm proximal to the suspected lesion (prestenotic), within the lesion (intrastenotic), and up to 4 cm distal to the lesion (poststenotic) to derive a ratio and percent stenosis. Binary restenosis has been customarily defined as a ratio greater than 2.4.[40] However, it is important to understand that patency is a surrogate outcome for a presumed accompanying change in clinical status. In the later form, restenosis or "loss of patency" is intended to provide earlier information on the

durability of the intervention and the eventual recurrence of symptoms. Reintervention may be chosen to prevent failure and the clinical status of the patient may not change. Patency is deep-rooted in the vascular literature as an outcome and many studies do not report more robust outcomes like improvement and maintenance of clinical status. As part of the reporting standards projects in vascular disease commissioned by SVS, Rutherford and associates developed outcome measures that do report clinical status as a criteria for efficacy of a vascular intervention.[5] Commenting the Schillinger 2006 trial, which compared PTA to nitinol stenting, Hirsch called for studies to include meaningful clinical endpoints, such as: 1) for patients with claudication, quality of life questionnaires and treadmill testing; and 2) for critical limb ischemia, complete wound healing, resolution of pain and limb salvage (absence of amputation).[41]

The TASC II document stresses that for the evaluation of treatment of claudication, a "patient-based outcome assessment…is the most important measure,"[26] based on the work of Dormandy and associates.[42] For chronic limb ischemia, a "primary outcome would be amputation-free survival."[26]

A recent international consensus document highlighted the problems of outcomes reporting in endovascular trials and focused on the drawbacks of using patency alone as an endpoint.[43] As the authors stated, "undoubtedly, clinical success has little correlation with patency of the treated vessel," The consensus committee ascribed some of the problem to applying a concept – patency, which is employed in describing the results of open surgery – to outcomes following endovascular interventions. In reports of open surgery, assisted primary patency (impending occlusion due to restenosis, which is prevented by a reintervention) or secondary patency (treatment of occlusion, which restores patency by a new intervention) are common outcome measures. By contrast, the results of endovascular procedures depend on defining restenosis within the treated segment. Commonly, the development of restenosis is monitored by duplex ultrasonography, but unfortunately different criteria for "restenosis" have been applied. The authors of the consensus document proposed essential patient characteristics that should be defined-1) baseline clinical, anatomic and demographics; 2) procedural outcomes and complications (harm); and 3) long- term outcomes (at least 12 months), including clinical, anatomic and hemodynamic outcomes. All three outcome measures appeared intertwined without priority given to clinical measures. These recommendations are an important step toward standardizing evaluations of endovascular interventions and as our document will demonstrate that the majority of RCTs fail to employ these reporting characteristics. The goal of this review is to describe "patient-important" outcomes rather than surrogate measures, which may have poor validity. Thus, patency outcomes are not systematically evaluated.

CMS request

The Centers for Medicare and Medicaid Services (CMS) has requested a technology assessment on invasive interventions to treat occlusive lesions related to PAD, focusing primarily on peripheral artery angioplasty with stent placement. The objective is to describe the types of published studies on invasive interventions for PAD and to address specific questions about the relative safety and effect of peripheral stenting compared to other interventions.

CMS had questions about whether there is evidence from clinical trials about clinical diversity and heterogeneity of lesions affecting different sections of peripheral arteries or, if the effectiveness of interventions varies depending on affected part of the arteries. Stent technology is also evolving rapidly and there are a number of comparative studies of different stents

(including drug eluting stents). It is important to appreciate that an earlier generation of stents may have been abandoned by clinicians in favor of newer technology with the promise of improved durability. CMS is specifically interested in clinically important patient outcomes. This includes outcomes that directly relate to patient health and well-being (e.g., death, amputation, quality of life) or that are accepted as adequate surrogates for assessing clinical severity of disease (e.g., ankle-brachial index, walking distance). CMS has requested that surrogate vascular measures that do not assess clinical status (e.g., asymptomatic restenosis found with ultrasonography) while frequently employed as an outcome measure, should not be the focus of this review.

Also of interest is clarification of which features of patients with PAD and of the PAD lesions themselves may differentiate which patients (or lesions) may best benefit from stenting. It is unclear whether categorizing patients or lesions by features other than anatomy (i.e., iliac, femoral, femoral popliteal, popliteal, tibial, etc) would be useful for estimating the balance between effect and safety of the intervention. Thus, determination of specific characteristics, which may include but are not necessarily limited to anatomy, lesion characteristics (stenosis, occlusion, and its length), age, comorbidities, physical status may be helpful in categorizing the different effects of stenting are also of interest to CMS.

Key questions

1. Perform horizon scan of published literature on invasive vascular procedures for the treatment of infrarenal PAD (surgical bypass grafting, angioplasty, angioplasty with stent placement, atherectomy). Categorize studies based on intervention; preoperative characteristics of PAD defined by clinical, anatomic, and hemodynamic features (based primarily on TASC II classification schemes[26]); primary outcomes; study design; and sample size.

2. Review and describe the studies cited in the TASC II report[26] that support the recommendations regarding choice of intervention. Judge whether the cited studies adequately support the recommendations.

3. Perform a systematic review across invasive vascular interventions for infrarenal PAD for the association between the TASC I or II classification schemes and rates of clinical outcomes (mortality, amputation, clinical stage, reinterventions, and quality of life) after the intervention, accounting for differences in anatomy and interventions.

4. Perform systematic review of the relative safety and effect of peripheral artery stenting with other invasive vascular procedures for occlusive PAD of infrarenal vessels. Also evaluate comparisons of different stents and/or different procedures with stents. Among comparative studies (stent versus other intervention; stent versus stent) evaluate the following questions and features:
   - Methodological quality of studies
   - Applicability of studies to patients aged ≥65 years with occlusive PAD (based on the CMS population)
   - Demographic and other preoperative (baseline) features of studied patients

- Clinical, anatomic, and hemodynamic features of PAD lesions (based primarily on TASC II classification schemes)
- Types of the stents used (specifically discussing steel, nitinol, drug eluting and other stents in this rapidly evolving field)
- Concurrent and postoperative treatments, including but not limited to brachytherapy and antiplatelet therapy
- Length of followup
- Persistence of effects over time
- Clinical outcomes (patient survival, limb salvage, primary patency, primary assisted patency, secondary patency, pain, quality of life)
- Adverse events

Chapter 2. Methods

This report on the use of peripheral stents in the treatment of peripheral artery disease is based on a systematic review of the literature.

For the background information on peripheral artery stents, we performed a horizon scan based on published abstracts on invasive vascular procedures for the treatment of peripheral artery disease (PAD), primarily surgical bypass grafting, angioplasty, angioplasty with stent placement, and atherectomy. We categorized the relevant studies based on intervention; preoperative characteristics of PAD defined by clinical, anatomic, and hemodynamic features (based primarily on TASC II classification schemes); primary outcomes; study design; and sample size.

We also performed a systematic review of the relative safety and effect of peripheral artery stenting with other invasive vascular procedures for occlusive PAD of infrarenal vessels. We included comparisons of different stents and of different procedures with stents. Among comparative studies (stent versus other intervention; stent versus stent), we evaluated the following questions and features:

- Methodological quality of studies
- Applicability of studies to patients aged ≥65 years with occlusive PAD
- Demographic and other preoperative (baseline) features of studied patients
- Clinical, anatomic, and hemodynamic features of PAD lesions (based primarily on TASC II classification schemes)
- Types of the stents used ,emphasizing balloon-expandable and self-expanding (e.g., nitinol), bare and drug-eluting or other treated or coated stents
- Concurrent and postoperative treatments, including but not limited to brachytherapy and antiplatelet therapy
- Length of followup
- Persistence of effects over time
- Clinical outcomes (patient survival, limb salvage, pain, quality of life)
- Adverse events (complications attributable to the intervention, as opposed to the underlying disease process)

The approach, methodology, and criteria used were agreed upon by consensus of the Evidence-based Practice Center (EPC) clinician-methodologists, an expert in cardiovascular surgery based at Tufts Medical Center, Centers for Medicare & Medicaid Services (CMS) staff, and staff at the Agency for Healthcare Research and Quality (AHRQ) with methodological expertise.

Search Strategy

A comprehensive search of the scientific literature was conducted to identify relevant studies addressing the key questions. The final search was conducted on July 19 2007. We searched MEDLINE (from 1950 to present) and the Cochrane Clinical Trial Registry to identify articles relevant to each key question. In electronic searches, we used various terms for PAD and specific interventions for PAD, limited to humans, and relevant research designs (see **Appendix**

A for complete search strategy). The same literature data set was used for the horizon scan and the systematic review. We did not systematically search for unpublished data.

Study Selection

We assessed titles and abstracts of citations identified from literature searches for inclusion, using the criteria described below. As described below, the horizon scan was based only on the titles and abstracts. For studies that potentially met criteria for the systematic reviews full text articles were retrieved and a second review for inclusion was performed, reapplying the inclusion criteria. A low threshold was used to retrieve articles for full rescreening.

Eligibility criteria for horizon scan

Population: Adults and children with infrarenal PAD (of the lower extremities); primary or recurrent (previously treated) disease. We limited the horizon scan to chronic PAD, as opposed to acute occlusion, where this determination was possible from the abstract data.

Intervention: Any invasive vascular procedure for the treatment of PAD. We excluded studies that used *only* medical or other noninvasive therapies (including brachytherapy). No comparator was necessary.

Outcomes: Studies were not excluded based on outcomes reported in the abstract.

Study design: At least 10 subjects receiving each intervention evaluated. Where sample size was not reported in the title or abstract, we retained the abstract. We also included systematic reviews. Narrative reviews were excluded. The abstract had to explicitly state or strongly suggest that it is a systematic review. There was no language restriction.

Eligibility criteria for TASC II report citations

The TASC II report was reviewed for recommendations regarding choice of intervention. All publications referenced in the text regarding the rationale for the recommendations were retrieved and reviewed. Any primary study was included, only excluding narrative reviews and opinion pieces.

Eligibility criteria for systematic review of TASC classification

Population: Adults with infrarenal PAD (of the lower extremities); primary or recurrent (previously treated) disease; excluding acute occlusion.

Intervention: Any invasive vascular procedure for the treatment of PAD. We excluded studies that used *only* medical or other noninvasive therapies (including brachytherapy). No comparator was necessary.

Outcomes: Long-term (≥6 months) clinical outcomes: mortality, amputation, reintervention of the treated vessel or lesion; clinical symptoms; quality of life. At least one of the clinical outcomes had to be mentioned in the title or abstract.

Study design: We included all comparative and noncomparative studies published since 2001, whether prospective or retrospective. Studies had to explicitly report the TASC classification of the patients; we did not attempt to infer the TASC classification from descriptions of the anatomy. Studies had to provide clinical outcome data for at least one group of patients at least 80 percent of whom were had either TASC A, B, A or B, C, D, or C or D disease. For analysis, each TASC group with reported clinical outcomes had to have at least 10 patients. Studies had to be peer reviewed and published in English. Studies were excluded if they did not provide separate data for different procedures (i.e., for bypass, for angioplasty, or for stent).

Eligibility criteria for systematic review of stent studies

Population: Adult humans with stenotic or occlusive infrarenal PAD. We excluded studies that included more than 20 percent of patients with previous failed procedures, studies with more than 20 percent of subjects had stenosis of a graft, and studies that evaluated patients with concomitant aortic or renal artery stenosis or aneurysms requiring treatment.

Intervention: At least one study arm used stent placement across PAD lesions.

Comparators: At least one study arm using an alternative invasive vascular intervention. These included angioplasty without stent, bypass surgery, atherectomy, or alternative stent interventions (either different stents or an added cointervention). Study arms that used primary angioplasty with secondary stent placement for immediate inadequate treatment were considered to be PTA interventions.

Outcomes: We limited our review to clinical and hemodynamic outcomes. These included mortality (survival), limb salvage (amputation), reintervention (a subsequent procedure), symptoms, change in clinical classification, ulcer healing, quality of life, ankle-brachial index (ABI) or equivalent, and standardized walking time tests or equivalent. In addition we included periprocedure complications attributable to the intervention and stent fractures. We relied on the studies to provide possible complications, but specifically extracted 30-day mortality, arterial bleeding, and emboli. The EPC, together with its domain expert and representatives from AHRQ and CMS agreed that patency rates, measures of residual stenosis, or other surrogate outcomes were not sufficiently clinically important and thus that they would not be reviewed. In general, only clinically relevant outcomes were of interest. Though ankle-brachial index is an outcome that does not directly measure patient events or well-being, we included this as a hemodynamic outcome of interest. We also included stent fractures (whether symptomatic or not) as a complication of interest.

Design: We included all comparative (stent versus comparator) designs, including RCTs, prospective comparative nonrandomized studies, and retrospective comparative analyses. Studies had to be peer reviewed. Studies had to analyze at least 10 subjects per intervention and follow patients for at least 1 month. English language only.

Data Extraction

Horizon scan

For the horizon scan, we extracted the following variables: year of publication, study design (single arm, case control, comparative nonrandomized study, RCT, systematic review), number of arms, total number of subjects, start and end year of procedures, average age of participants, followup duration (average or maximum), clinical classification (per SVS), anatomic site of PAD (aorto-iliac, femoral popliteal, tibial, or combination), TASC classification (if explicitly reported), reporting of occlusion rate, types of intervention (PTA, stent, bypass, atherectomy, medical without invasive intervention, and other), use of brachytherapy, types of outcomes reported (symptomatic relief, amputation, imaging test, hemodynamic test, subsequent intervention, quality of life, cost or cost-effectiveness, death, procedural adverse events), reporting of statistically significant difference between outcomes, and evaluation of predictors of outcomes.

After partial completion of the horizon scan data extraction, it became evident that there exist a large volume of older single arm studies that are of limited relevance today. To conserve available resources, it was agreed to focus our effort on those abstracts that are most likely to be of interest to CMS and to current clinicians. Therefore, for remaining single arm studies published before 2001 we extracted only study type, number of subjects, and interventions.

TASC II report citations

For each eligible study the following data were extracted: study design; sample size; whether the study was multi- or single center; whether an a priori power calculation was reported; whether adequate allocation concealment was reported; what the clinical classification (Fontaine or Rutherford) of the patients was; what the hemodynamic status of the patients was (primarily ABI); the anatomy (including TASC classification); whether the compared cohorts were comparable at baseline; whether intention-to-treat analyses were performed; whether dropouts were adequately described; whether blinding was performed; the followup time; the results (focusing primarily on whether one intervention performed better than another) for clinical improvement, hemodynamic status, imaging and patency, amputation, mortality, reintervention, and complications; and the study quality and applicability (see below).

Systematic review of TASC classification

For eligible studies, data were extracted separately for each relevant cohort of patients. Cohorts of patients were separated based on TASC classification (A, B, A or B – if separate data were not available for A and B, C, D, and C or D – if separate data were not available for C and D), intervention, and artery. For each cohort the following data were extracted: the study design, followup time, intervention (bypass, PTA alone, PTA with or without stent, stent (all), endarterectomy, medical, or other), whether results data were reported per patient or per limb, the artery (aorto-iliac,femoral popliteal, tibial, or combination), the TASC classification, the percent of patients in the cohort who had the given TASC classification, and the number of events and patients at risk for each outcome. If a study reported separate data for more than one TASC classification, but one or more groups of patients had fewer than 10 patients, that cohort was omitted. Where data were extracted from time-to-event (survival) curves, we assumed that all patients evaluated at time zero were also available at the time point of interest. We

preferentially extracted results at 12 months, since this was the most commonly reported time point.

Systematic review of stents

For the systematic review of the eligible full articles (comparative studies of stents), we extracted data on study year, country, setting, funding source, study design, dates of procedures, timing of endpoints, eligibility criteria, details of stent, comparator, and cointerventions, definitions of outcomes, subject characteristics, and baseline and final results for outcomes of interest. For RCTs, we evaluated whether the method of randomization and allocation concealment were adequate, whether patients and outcome assessors were blinded, whether results were analyzed on an intention-to-treat basis, whether groups were similar at baseline, and dropout rate. For nonrandomized studies, we extracted whether adjustments for severity of PAD were made and dropout rates. We extracted data for time points closest to 12 months, for the longest time point at which at least 10 subjects per arm were evaluated, and for procedural complications within 30 days. All complication (adverse event) data were extracted exactly as reported.

Quality Assessment

We assessed the methodological quality of each study in the systematic review of stents based on predefined criteria. We used a 3-category grading system (A, B, C) to denote the methodological quality of each study. This grading system has been used in most of the previous evidence reports from the Tufts EPC as well as in evidence-based clinical practice guidelines.[44,45] This system defines a generic grading system that is applicable to varying study designs including randomized and nonrandomized comparative trials, cohort, and case-control studies. For RCTs, we mainly considered the methods used for randomization, allocation concealment, and blinding as well as the use of intention-to-treat analysis, the report of dropout rate and the extent to which valid primary outcomes were described, as well as clearly reported. Studies were not rejected due to poor quality. Studies that are of overall good or fair quality, but poorly report or analyze specific outcomes, or have other problems with those outcomes (such as few patients analyzed), could be given different quality grades for different outcomes.

A (good)

Good quality studies are likely to have the least bias and results are considered valid. They include studies that adhere most closely to the commonly held concepts of high quality including the following: a formal randomized controlled study; clear description of the population, setting, interventions, and comparison groups; appropriate measurement of outcomes; appropriate statistical and analytic methods and reporting; no reporting errors; less than 20 percent dropout; clear reporting of dropouts; and no obvious bias.

B (fair)

Fair quality studies are susceptible to some bias, but not sufficient to invalidate the results. They do not meet all the criteria in category A because they have some deficiencies, but none likely to cause major bias. The study may be missing information, making it difficult to assess limitations and potential problems.

C (poor)

Poor quality studies have significant bias that may invalidate the results. These studies have serious problems in design, analysis, or reporting; have large amounts of missing information, large dropout rates, discrepancies in reporting, or other major sources of bias. All retrospective studies were graded C.

Applicability Assessment

Applicability addresses the relevance of a given study to a population of interest. Every study applies certain eligibility criteria when selecting study subjects. Most of these criteria are explicitly stated (e.g., disease status, age, comorbidities). Some may be implicit or due to unintentional biases, such as those related to location (e.g., multicenter versus single center, intensive care versus all inpatients), year of procedure, and other issues. The applicability of a study is dictated by the key questions, the populations, and the interventions that are of interest to this review, as opposed to those of interest to the original investigators.

For the systematic review of stents, we categorized studies within a target population into 1 of 3 levels of applicability that are defined as follows:

High Sample is representative of Medicare population in relevant settings. Patients' age (older adult), gender, spectrum of disease severity and type, etc. are representative of population of interest. No substantial exclusion criteria that would make the sample atypical of patients with PAD receiving invasive interventions.

Moderate Sample is an important subgroup of population of interest. Possibly limited by a narrow or young age range, type of disease, gender, restrictive eligibility criteria, etc.

Narrow Sample represents only a narrow, atypical subgroup of population of interest.

Data Synthesis

Horizon scan

We primarily evaluated frequencies of occurrence of variables of interest, with subgroup frequencies based on study design. For continuous variables, we calculated medians and interquartile ranges (25th and 75th percentiles). To summarize the data, we created tables by type of study design, type of vascular procedure and by other variables of interest. We also report in the tables, in addition to the number of studies in which we based the summary statistics, the total number of subjects included by type of intervention and type of study design. We noted when analyses included the limited data from single arm studies (due to partial data extraction of the older studies).

We explored graphically the changes in the number of studies of different research designs over time (single arm, RCT, nonrandomized comparative and systematic reviews) using frequency line plots. We constructed similar graphs for the number of published papers per intervention, and per type of artery over time. The graphs do not include 2007 publications

because the search does not include all papers published during 2007. For better visualization, time was split into 3-year intervals starting backwards from 2006 (inclusive).

TASC II report citations

Descriptive analyses were performed to evaluate the level and strength of evidence cited for each TASC II recommendation.

Systematic review of TASC classification

Graphical analyses were employed. The intent was to create a graph of the TASC data for each outcome, but there were insufficient data for quality of life, so this graph was omitted. For each outcome, the event rates were plotted against the TASC classification (A, B, A or B, C, D, C or D) with separate subcolumns for the intervention types bypass, PTA without stenting, PTA with primary or elective stenting, and other (endarterectomy, atherectomy, or cryoplasty). The different arteries treated were noted by different symbols. Data from cohorts of patients with the same treated arteries who were in the same studies were linked by connecting lines. When studies reported results at multiple followup times we preferentially used 12 month data. We excluded from the graphs event rates based on fewer than 10 patients (for each intervention-artery-TASC combination in each study), or when the followup length was less than 6 months.

We use these graphical analyses to summarize the observed event rates as reported in the literature. In addition, we summarized in details the relevant findings of studies that either directly compared interventions within a single TASC classification or directly compared TASC classifications.

Systematic review of stents

Summary tables and outcome metrics used

For each outcome reported by more than one study, we summarized data in summary tables which include data on study design characteristics, subject characteristics, category of stent type, crossover rates, number of subjects analyzed, results data, quality, and applicability. For continuous outcomes we included baseline values, final values, and net differences (change in stent arm minus change in control arm). Where necessary, confidence intervals (CI) of the net differences were estimated from the reported data. Because event rates were low for most outcomes we report risk differences (RD), calculated from the raw data, because odds ratios (OR) cannot be estimated when there are no events. For changes in clinical status, we report OR. For rates of reinterventions (repeat procedures) there was a wide range of event rates. We reported both OR and, because event rates were very low in some studies, RD.

Metaanalyses

Metaanalysis was performed to examine whether therapeutic management based on stent insertion led to improved patient outcomes compared to PTA, when there was sufficient clinical or statistical homogeneity to allow for a meaningful summary estimate. We restricted metaanalysis to RCTs to avoid performing analyses of mixed design types and because the inherent biases of nonrandomized studies suggest that they should be used only to support the randomized data or to suggest reasons for heterogeneity. Furthermore, the small number of nonrandomized studies that evaluated similar interventions and outcomes precluded meaningful metaanalysis.

Main Analyses

For the main analyses, we used DerSimonian and Laird's random effects model for syntheses.[46] The random effects model assigns a weight to each study based both on the individual study variance and the between-study heterogeneity. Compared with the fixed effect model, the random effects model is more conservative in that it generally results in broader confidence intervals when between-study heterogeneity is present. We tested for heterogeneity using Cochran's Q and assessed its extent with I^2, which evaluates the proportion of between study variability that is attributed to heterogeneity rather than chance.[47] In the case of sparse events (<5 percent), we instead used the Peto method to derive summary estimates for metaanalysis of odds ratios.[48]

Subgroup Analyses

To explore potential reasons for differences of results across studies, we performed subgroup analyses by overall methodological quality, and type of artery for all metaanalyses (as applicable). Because of the small number of trials per metaanalysis, extensive subgroup analyses were not feasible.

Sensitivity Analyses

Trials with no events in both arms pose (technical) difficulties in the calculation of effects sizes for binary outcomes, necessitating the addition of a "fudge factor" to the raw counts. Some methodologists suggest excluding such studies from metaanalyses [48,49]. Therefore, for all metaanalyses where at least one study had 0 events in both arms, we performed two sensitivity analyses, We repeated the main analyses excluding all studies with 0 events in both arms and we performed Mantel-Haenszel fixed effects metaanalyses, as suggested elsewhere [48,49].

Software

All analyses and graphs were performed in Intercooled Stata 8.2 (Stata Corp, College Station, TX).

Handling Multiple Publications of Studies

Some trials have multiple publications. As a result, data on some outcomes were reported in different publications for different study endpoints (times). Each study, regardless of the number of publications, was treated as a single entity. We thus had to pick and choose among the articles for those data that best conformed to the data of interest to this report. We attempted to use the descriptions of study design, interventions, outcomes, etc. that were most complete. For simplicity, we referenced all the publications related to the same trial once in the introductory section for each outcome but only referenced a single publication from the same trial in the subsequent sections for each outcome.

Chapter 3. Results

3.1 Horizon Scan

Key Question

Perform horizon scan of published literature on invasive vascular procedures for the treatment of PAD (surgical bypass grafting, angioplasty, angioplasty with stent placement, atherectomy). Categorize studies based on intervention; preoperative characteristics of PAD defined by clinical, anatomic, and hemodynamic features (based primarily on TASC II classification schemes); primary outcomes; study design; and sample size.

This horizon scan focuses on studies whose abstracts or titles indicate that they may have evaluated invasive interventions for treatment of PAD. Studies are categories and enumerated. Topics beyond this field are omitted, such that not all questions pertaining to management of PAD are addressed. We did not evaluate the findings of these studies, nor judge their quality. This horizon scan, thus, does not answer questions related to benefits or harms of any intervention, except to indicate the possible size of the literature base to answer those questions.

The literature searches yielded 14,815 citations, of which 2,488 reported data on primary studies of invasive interventions for lower extremity PAD. Of these, 89 percent had available abstracts.

All studies that compared interventions (including RCTs, nonrandomized comparative studies, and case control studies) had complete data extraction (these studies are listed in **Appendix C**). All single arm studies published since 2001 had complete data extraction. An arbitrary sample of 589 (40 percent) of earlier single arm studies had complete data extraction; the remainder had limited data extraction. Because we were usually unable to determine whether nonrandomized studies were prospectively or retrospectively designed, we grouped all nonrandomized comparative studies together (except case control studies) and all single arm (cohort) studies together.

An Excel database with the extracted data is available upon request from the report authors. This database can be queried to find specific articles that meet any given evaluated criteria.

Study characteristics and demographics (Tables 3-7)

Only 5 percent of the studies were RCTs and another 9 percent were nonrandomized comparative studies; 79 percent were single arm studies (Table 3). Six percent of the citations did not provide enough information to determine study design. Among the RCTs, case control, and nonrandomized comparative studies, 14 percent had more than 2 study arms.

Across publications, 11 percent did not have an electronic abstract available. All (seven) of the case-control studies and all systematic reviews had abstracts; 97 and 94 percent, respectively, of RCTs and comparative studies had abstracts. Similarly, 93 percent of single arm studies had abstracts. The study design of about half the publications without abstracts could not be determined; thus, 12 percent of studies without a known study design had abstracts.

RCTs and other comparative studies tended to have larger numbers of patients than single arm studies (Table 4). The relatively small sample size of the single arm studies is in part

explained by a large number of descriptions of small surgical cohorts. A total of 492,679 subjects were included in the (87 percent of) studies that reported sample sizes in their abstracts; extrapolating to those studies without sample size data, almost 570,000 patients have been evaluated (although this includes double counting of patients reported in multiple publications). About 3 percent of these subjects were enrolled in RCTs. The median followup time was 18 months in RCTs, 24 months in comparative studies and single arm studies, and 60 months in the small number of case control studies (Table 5). However, determining accurate followup durations from abstracts was problematic since only selected data are reported in abstracts. Notably, the large majority of RCTs (92 percent) reported study duration, but almost 30 percent of other studies did not report duration.

Most studies did not report the years of the interventions in their abstracts (Table 6); this was particularly true among RCTs. Half of the studies that reported data began their interventions between the mid 1980s and the late 1990s. Across studies, 1 percent had interventions performed in the 1950s, 4 percent in the 1960s, 7 percent in the 1970s, 30 percent in the 1980s, 44 percent in the 1990s, and 15 percent since 2000.

The median age of participants in studies of different designs ranged from 67 to 70 years; however, we obtained age data from only about 15 percent of abstracts (Table 7).

Summary of study characteristics and demographics

- How many articles reported on direct comparisons of interventions (including invasive) for PAD?
  - 127 RCTs, 231 other studies
- How large were the studies of invasive interventions for PAD?
  - On average, between about 70 and 100 patients
  - ¾ of studies evaluate at least 30 patients per intervention
- How long were patients followed after their interventions?
  - Most studies followed patients for at least 18-24 months.
  - In general, fewer than ¼ of studies followed patients for less than 1 year.
- When were the invasive procedures performed?
  - Most data (¾) are from studies that began to perform the procedures more than a decade ago.
- How applicable are the studies to the Medicare population?
  - On the basis of age, most studies have fair to good applicability to the Medicare population.
  - Among studies that reported age in their abstracts, the average ages were 67 to 70 years. Fewer than ¼ of studies had mean ages below 65 years.

Table 3. Horizon scan: Study designs

Study Design	Number	Percent
Randomized controlled trial	127	5
Comparative	224	9
Case control	7	0.2
Single arm	1,955	79
Systematic review	26	1
No data (unable to determine)	151	6
Total	2,488	100

Table 4. Horizon scan: Number of subjects

Study Design	No. Studies with Data	Sample Size Median	Sample Size IQR	Total	% Studies No Data	Extrapolated Total*
RCT	120	100	56 – 199	16,788	6%	*17,767*
Comparative	198	120	62 – 240	83,239	12%	*94,169*
Case control	7	77	42 – 351	1,060	0%	*1,060*
Single arm	1,824	66	32 – 146	379,736	7%	*406,592*
Total across studies†	2154			492,679	13%	*566,968*

IQR, interquartile range. Details for studies with unknown study design (n=151) not included.
* Estimate of total number of subjects, including studies that did not report sample size in their abstracts.
† Including studies with unknown design.

Table 5. Horizon scan: Patient followup (months)

Study Design	No. Studies with Data	Followup* (months) Median	Followup* (months) IQR	% Studies No Data
RCT	115	18	9 – 36	8%
Comparative non RCT	158	24	12 – 40	29%
Case control	5	60	33 – 69	28%
Single arm†	787	24	12 – 41	60% (26%)‡

IQR, interquartile range; NA, not applicable. Studies with unknown study design (n=151) not analyzed
* Either average (mean or median) or maximum, as reported by authors
† Data from all studies published since 2001, but only arbitrary sample of earlier studies.
‡ Percent for which no data were available for analysis (percent of studies with full data extraction [n=1,056] with no data reported in title or abstract).

Table 6. Horizon scan: Year in which the interventions started

Study Design	No. Studies	Start Year Median	Start Year IQR	% Studies No Data
RCT	22	1994	1983 – 1997	83%
Comparative non RCT	74	1988	1985 – 1996	67%
Case control	2	1982, 1996		71%
Single arm*	335	1992	1986 – 1998	68%

Studies with unknown study design (n=151) not analyzed
* Data from all studies published since 2001, but only arbitrary sample of earlier studies.

Table 7. Horizon scan: Subject age (years)

Study Design	No. Studies with Data	Study Average Age Median	Study Average Age IQR	% Studies No Data
RCT	19	70	67 – 72	85%
Comparative non RCT	36	67	63 – 70	84%
Case control	1	69	--	86%
Single arm*	241	67	63 –70	88% (77%)†

IQR, interquartile range. Studies with unknown study design (n=151) not analyzed
* Data from all studies published since 2001, but only arbitrary sample of earlier studies.
† Percent for which no data were available for analysis (percent of studies with full data extraction [n=1,056] with no data reported in title or abstract).

PAD characteristics (Tables 8-10)

Across reviewed studies, 85 percent of the abstracts provided sufficient information to determine which arteries were treated (Table 8). RCTs tended to be conducted in patients with either femoral popliteal disease alone (67 percent) or combination artery disease (20 percent), which usually included the femoral popliteal artery. In contrast, nonrandomized comparative and single arm studies were more likely to be conducted in patients with mixed disease, with only about a third of studies evaluating femoral popliteal disease exclusively.

Our estimates of the maximum severity of PAD symptoms (Table 9) were necessarily limited. There was a great degree of heterogeneity in the ways that abstracts described the severity of disease. In many, if not most, cases we had to extrapolate the qualitative descriptions of patients into the SVS scale. Furthermore, our aim was to capture the most severe level of disease included in the studies, though this was not always clear. Ideally it would have been better to capture the average and range of disease severity in the studies, but this approach was not feasible from review of the abstracts. The distinction between minor and major tissue loss was particularly difficult to ascertain from the abstracts, so these categories have been merged. Furthermore, over half the studies did not report adequate data in their abstracts to assess disease severity. RCTs were more likely to include patients who had only claudication and correspondingly less likely to include patients with rest pain or tissue necrosis. Nonrandomized comparative studies were about equally likely to include patients with different levels of PAD severity as single arm studies. Overall, about 15 percent of studies were restricted to patients with claudication (but almost 40 percent of RCTs), about one-quarter included patients with rest pain or claudication, and almost two-thirds included patients with tissue loss (but only about 40 percent of RCTs). Only 41 studies (2.7 percent) reported the patients' TASC classification in the abstract (Table 10); the large majority of these included patients with TASC D disease. Note that studies that provided data on clinical outcomes for patients with specific TASC grades are analyzed in Question 2.

Summary of PAD characteristics

- Which arteries have been evaluated for invasive procedures?
    - About 1/3 of studies evaluated patients with femoral popliteal disease and ½ with disease in multiple arteries, usually including femoral popliteal arteries.
    - About 15 percent had aorto-iliac disease alone and only about 2 percent had tibial disease alone.
- What was the severity of PAD symptoms among patients in studies of invasive procedures?
    - A complete answer to this question is not possible without evaluating the full text of the articles.
    - Among those studies that reported some relevant data in their abstracts, about 60 percent included patients with tissue loss, about 25 percent included patients with rest pain but not tissue loss, and about 15 percent included patients with claudication only.
    - RCTs more commonly included patients with only claudication.

- What was the TASC classification of patients in studies of invasive procedures?
    - Only 3 percent of studies reported TASC classification in their abstracts.
    - Most of these studies included patients with more severe disease (grade C or D); only 10 percent included only patients with grade A or B.

Table 8. Horizon scan: Arteries evaluated, N (%, per study design)

Study Design	No. Studies with Data	Aorto-iliac	Femoral popliteal	Tibial	Combination	% Studies No Data
RCT	115	13 (11%)	77 (67%)	2 (2%)	23 (20%)	10%
Comparative non RCT	194	34 (18%)	67 (35%)	2 (1%)	91 (47%)	13%
Case control	4	1 (25%)	1 (25%)	0 (0%)	2 (50%)	43%
Single arm*	894	151 (17%)	262 (29%)	17 (2%)	464 (52%)	15%
Total†	1,207	199 (16%)	407 (34%)	21 (2%)	580 (48%)	15%

Details for studies with unknown study design (n=151) not included.
* Including only studies published since 2001 and an arbitrary sample of earlier studies
† Including studies with unknown design.

Table 9. Horizon scan: Maximum severity of PAD symptoms, N (%, per study design)

Study Design	No. Studies with Data	Mild	Moderate Claudication	Severe	Rest Pain	Tissue Loss	% Studies No Data
RCT	54	0 (0)	10 (19)	10 (19)	13 (24)	21 (39)	58%
Comparative non RCT	82	0 (0)	8 (10)	8 (10)	12 (15)	54 (66)	63%
Case control	1	0 (0)	0 (0)	0 (0)	1 (100)	0 (0)	86%
Single arm*	495	3 (0.6)	32 (6)	21 (4)	126 (25)	313 (63)	53%
Total†	640	3 (0.5)	51 (8)	40 (6)	154 (24)	392 (61)	58%

IQR, interquartile range. Details for studies with unknown study design (n=151) not included.
* Including only studies published since 2001 and an arbitrary sample of earlier studies
† Including studies with unknown design.

Table 10. Horizon scan: TASC classification

TASC classification	No. Studies*	Percent Studies	
		Total	With Data
A	1	0.1%	2%
B	3	0.2%	7%
C	10	0.7%	24%
D	27	2%	66%
No Data	1,466	97%	--

* Data from all studies published since 2001, but only arbitrary sample of earlier studies.

Characteristics of the interventions (Tables 11-15)

Overall (among all abstracts, including all single arm studies regardless of publication date), almost half the studies reported on surgical bypass, about 40 percent on PTA, about one-sixth on stent, and one-ninth on atherectomy (Table 11). About one-quarter of RCTs evaluated stent, one-half PTA, and one-half bypass. Among the RCTs, 67 percent compared the same type of intervention to itself (e.g., one surgery versus another surgery); only one-third compared

different types of interventions (e.g., PTA versus stent); two studies compared three different types of interventions. Similarly, among the nonrandomized comparative studies, 60 percent compared one type of intervention to itself, 32 percent compared two types of interventions, and 8 percent compared three types of interventions. Table 12 displays the number of RCTs and comparative studies (and the numbers of reported patients) that compared types of interventions (and the single arm studies evaluating each intervention). The most common comparison was between different types of bypass surgery (40 RCTs and 87 comparative studies). About 20 RCTs each compared different types of PTA or PTA and stent; between about 20 and 40 comparative studies compared PTA to itself, PTA to stent, or PTA to bypass. In addition about 20 comparative studies compared bypass and atherectomy. Other comparisons were relatively rare.

Notably, at the level of the horizon scan, 30 RCTs and 51 comparative studies compared stent to another intervention (or another stent). This is in contrast with the studies that met criteria for the systematic review (below), where 12 unique RCTs met criteria and 14 comparative studies met criteria. The difference in the numbers of eligible studies is due to duplicate publications, foreign language publications, lack of reporting of data comparing stent to an alternative intervention, lack of clinical outcomes, and other reasons.

Noninvasive (medical) therapy was compared to invasive interventions in 21 studies (Table 13). Single arm studies of noninvasive therapies were excluded from the horizon scan. Most of the abstracts did not describe the specific interventions used. Brachytherapy was described in 34 abstracts (Table 14). Interestingly, the majority of the studies reporting brachytherapy were RCTs, with only one comparative or case control study. Various other interventions were reported in abstracts that did not clearly fall into one of the intervention categories we evaluated (Table 15). We included laser angioplasty in this group, although these studies were also categorized as PTA studies. We also included abstracts that did not adequately describe the interventions used (e.g., "revascularization").

Summary of intervention characteristics

- What invasive interventions for PAD have been studied?
    - Almost ½ of studies evaluated surgical bypass; about 40 percent evaluated PTA.
    - We found 1,191 studies of bypass, 1,021 studies of PTA, 408 studies of stenting, and 271 studies of atherectomy.
    - Among comparative studies, almost 2/3 evaluated bypass and almost ½ evaluated PTA; 71 comparative studies evaluated stenting and 34 evaluated atherectomy.
- What interventions have been compared for the treatment of PAD (among studies that included an invasive intervention)?
    - The most common comparisons have been between different surgical bypasses (40 articles of RCTs and 87 other studies), followed by PTA versus stent (23 articles of RCTs and 34 other studies), PTA versus bypass (7 articles of RCTs and 39 other studies), and PTA versus PTA (19 articles of RCTs and 18 other studies).
    - Other comparisons appear in fewer than about 20 articles each.
- How many studies compared medical treatments to invasive interventions for PAD?
    - We found 21 studies that evaluated a range of interventions including usual care, anticoagulants, exercise, fibrinolysis, and others.

- How many studies have evaluated brachytherapy for PAD?
  - We found 34 articles that used brachytherapy in conjunction with invasive interventions for PAD.
  - 20 of these were comparative studies; there is 1 systematic review on the topic.
- What other interventions have been evaluated for PAD?
  - We found a wide range of interventions among the applicable articles (in addition to bypass, PTA, stenting, and atherectomy) including laser angioplasty, fibrinolysis or thrombolysis, endarterectomy, thrombectomy or embolectomy, amputation, cryoplasty, and others.

Table 11. Horizon scan: Interventions evaluated, N (%, per study design*)

Study Design	No. Studies	PTA	Stent	Bypass	Atherectomy
RCT	127	67 (53%)	30 (24%)	58 (46%)	7 (6%)
Comparative non RCT	224	89 (40%)	39 (17%)	163 (73%)	25 (11%)
Case control	7	4 (57%)	1 (14%)	3 (43%)	2 (29%)
Single arm	1,953	829 (42%)	322 (16%)	897 (46%)	213 (11%)
Systematic review	26	11 (42%)	5 (19%)	14 (54%)	1 (4%)
Total†	2462	1,021 (41%)	408 (17%)	1,191 (48%)	271 (11%)

Details for studies with unknown study design (n=151) not included.
* Add to more than 100% because studies with multiple interventions (used in different or the same individuals) are double-counted.
† Including studies with unknown design; not including systematic reviews.

Table 12. Horizon scan: Treatment comparisons by study design (Total number of subjects evaluated)*

Study Design		PTA	Stents	Bypass	Atherectomy	Medical	Single Arm Studies
PTA	RCT	19 (1312)	23 (3030)	7 (982)	6 (234)	7 (630)	828 (169,299)
	Comparative†	18 (2988)	34 (4379)	39 (40,097)	7 (1793)	9(1832)	
Stents	RCT		6 (467)	1 (86)	0	0	323 (89,109)
	Comparative†		4 (304)	9 (1222)	2 (320)	2 (475)	
Bypass	RCT			40 (7216)	2 (no data)	0	898 (211,521)
	Comparative†			87 (28,657)	19 (4634)	10 (1804)	
Atherectomy	RCT				0	0	213 (25,028)
	Comparative†				3 (403)	2 (174)	

* Ignores abstracts with no data on sample size. Double counting of articles and subjects occurs if 3 or more intervention types are evaluated.
† Comparative includes comparative nonrandomized studies and case control studies.

Table 13. Horizon scan: Medical treatments compared to invasive interventions

Medical Treatment	No. Studies
Angiography	3
Aspirin and advice on smoking and exercise	2
Best medical therapy and exercise	1
Conservative treatment	5
Fibrinolysis	2
Medical therapy	3
Physical training / Exercise	3
Probucol	1
Prostanoids and/or antibiotics	1
Total	21

Table 14. Horizon scan: Brachytherapy, N and %, per study design

Study Design	No. Studies	Percent of Studies
RCT	19	15%
Comparative non RCT	1	0.4%
Case control	0	0%
Single arm	16	0.8%
Systematic review	1	4%
Total*	34	1.4%

Details for studies with unknown study design (n=151) not included.
* Including studies with unknown design; not including systematic reviews.

Table 15. Horizon scan: Other interventions evaluated

Intervention	No. Studies
Laser angioplasty*	139
Fibrinolysis / Thrombolysis	27
Undefined revascularization procedures	13
Endarterectomy	10
Thrombectomy / Embolectomy	7
Amputation	7
Cryoplasty	6
Arteriovenous fistula	5
Laser recanalization	5
Extraluminal recanalization	4
Lumbar sympathectomy	3
Osteotrepanation	2
Gene therapy	1

* Also coded as PTA in horizon scan

Outcomes (Tables 16 & 17)

About 80 percent of the evaluated abstracts reported data on which outcomes were evaluated (Table 16). From our experience comparing full text articles to abstracts, we believe it is likely that the percentage of abstracts reporting specific outcomes underestimate the true number of articles that report the outcomes. It is common to report only statistically significant or "interesting" outcomes in the abstracts. That said, imaging success was the most frequently

reported outcome across study designs (69 percent) and was particularly common among RCTs (84 percent), but fewer than half the systematic reviews evaluated imaging success (our systematic review agrees with the majority and does not). The distribution of other reported outcomes was fairly similar across study designs. Complications, mortality, amputations, and hemodynamic success were reported in approximately one-third of abstracts, symptomatic relief and reinterventions were reported in about one-fifth, and quality of life and economic evaluations were rarely reported. Overall, 38 percent of studies reported clinical outcomes in their abstracts. However, three-quarters of the comparative studies reported clinical outcomes (Table 17).

In addition, 28 percent of abstracts (434 of 1510) reported an evaluation of risk factors or predictors of response to treatment, and 42 percent of RCTs (67 of 359) and 58 percent of comparative studies (93 of 359 studies) reported statistically significant differences between interventions.

Summary of outcomes

- What outcomes have been reported among (abstracts of) studies of invasive interventions for PAD?
    - Imaging success was the most commonly reported outcome, among almost 70 percent of studies. Imaging success was more commonly reported among RCTs (84 percent), but less commonly among systematic reviews (42 percent)
    - Clinical outcomes (and hemodynamic success) were reported less frequently. About 40 percent of studies, overall, reported clinical outcomes in their abstracts. About 75 percent of comparative studies, though, reported clinical outcomes.
    - Complications, mortality, amputations, and hemodynamic success were reported in about 1/3 of study abstracts each, across study designs, except that hemodynamic success was included in only 15 percent of systematic reviews.
    - Symptomatic relief and reinterventions were reported in about 20 percent of abstracts.
    - Quality of life and economic evaluations were reported in few studies (<5 percent).

Table 16. Horizon scan: Outcomes reported, excluding studies with no outcome data reported in abstracts, N (%, per study design*)

Outcome	All Studies†	RCT	Compar-ative	Case Control	Single Arm‡	Systematic Review
Imaging success	928 (69%)	103 (84%)	140 (68%)	5 (71%)	679 (69%)	11 (42%)
Complications	499 (37%)	38 (31%)	65 (31%)	2 (29%)	393 (40%)	6 (23%)
Mortality	462 (34%)	30 (24%)	81 (39%)	1 (14%)	348 (35%)	9 (35%)
Amputation	449 (33%)	28 (23%)	82 (40%)	1 (14%)	338 (34%)	9 (35%)
Hemodynamic success	386 (29%)	42 (34%)	44 (21%)	1 (14%)	299 (30%)	4 (15%)
Symptomatic relief	290 (22%)	28 (23%)	39 (19%)	1 (14%)	222 (22%)	3 (12%)
Reintervention	267 (20%)	22 (18%)	30 (14%)	1 (14%)	213 (22%)	3 (12%)
Quality of life	52 (4%)	6 (5%)	15 (7%)	0	31 (3%)	3 (12%)
Economic evaluation	26 (2%)	3 (2%)	11 (5%)	1 (14%)	10 (1%)	0
No. Studies	1,342	123	207	7	990	26

Details for studies with unknown study design (n=151) not included.
* Add to more than 100% because studies with multiple interventions double-counted.
† Including studies with unknown design, but not including systematic reviews)
‡ For single arm studies, data from all studies published since 2001, but only arbitrary sample of earlier studies.

Table 17. Horizon scan: Treatment comparisons of studies with clinical outcomes*

Study Design		PTA	Stents	Bypass	Atherectomy	Medical	Single Arm Studies‡
PTA	RCT	5	13	4	2	5	269
	Comparative†	10	17	21	3	4	
Stents	RCT		4	1	0	0	143
	Comparative†		3	5	0	0	
Bypass	RCT			31	0	0	278
	Comparative†			57	7	7	
Atherectomy	RCT				0	0	83
	Comparative†				0	2	

*Double counting of articles and subjects occurs if 3 or more intervention types are evaluated.
† Comparative includes comparative nonrandomized studies and case control studies.
‡ Since 2001.

Change in studies over time (Figures 1-3)

Figure 1 illustrates the number of studies published over time, according to research design. As commented above, the vast majority of the published studies are noncomparative. The increase in the number of publications around the late 1980s to early 1990s coincides with the introduction of widespread use of PTA for peripheral vascular disease (Figure 2). Studies on stents have increasingly been published since the early 1990s. Figure 3 shows the breakdown over time per type of artery. The analysis is restricted to only comparative studies because artery type was not extracted from all single arm studies before 2001. Similar increases in publications over time are seen for studies of interventions in all artery types.

Summary of time

- How have studies evaluating invasive interventions for PAD changed over time?
    - The exponential growth in single-arm studies stopped in about 1990, after which about 80 relevant articles have been published annually.
    - The growth of RCTs and other comparative studies continue to rise steadily since the 1970s. About 20-30 comparative studies a year are currently published.
    - Systematic reviews began to be published in the mid-1990s and are more common since about 2000.

    - Single arm studies of PTA peaked in about 1990 at about 50 articles; currently about 30 such articles are published annually. Single arm studies of bypass have steadily become more common; currently about 30 such articles are published annually. Single arm studies of stents have grown rapidly since the late 1980s; currently about 25 such articles are published annually.

    - The growth of comparative studies has generally matched those of single arm studies. Comparative studies of PTA or bypass are most common (about 10 per year currently). Comparative studies of stents are growing at a faster rate, but currently about 7 such articles are published annually.

    - Since about 1990, the proportion of studies evaluating the different arteries has remained fairly constant. Studies evaluating femoral popliteal arteries and studies evaluating a combination of arteries each are about twice as common as studies

evaluating aorto-iliac arteries. Studies exclusively of tibial arteries are relatively rare.

Figure 1. Evolution of the number of published studies over time per research design.

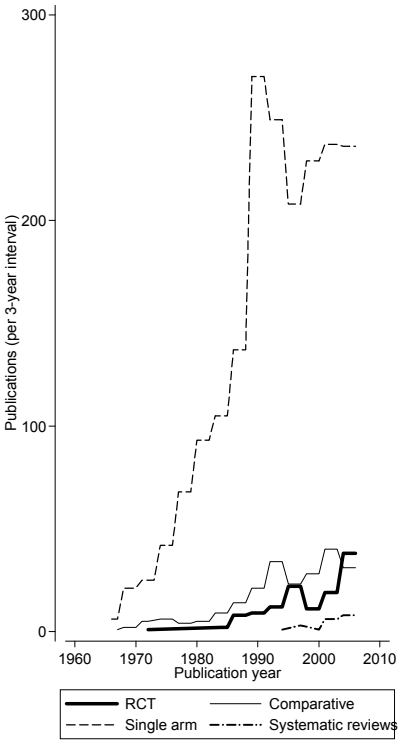


Figure 2. Evolution of the number of published studies over time per intervention.

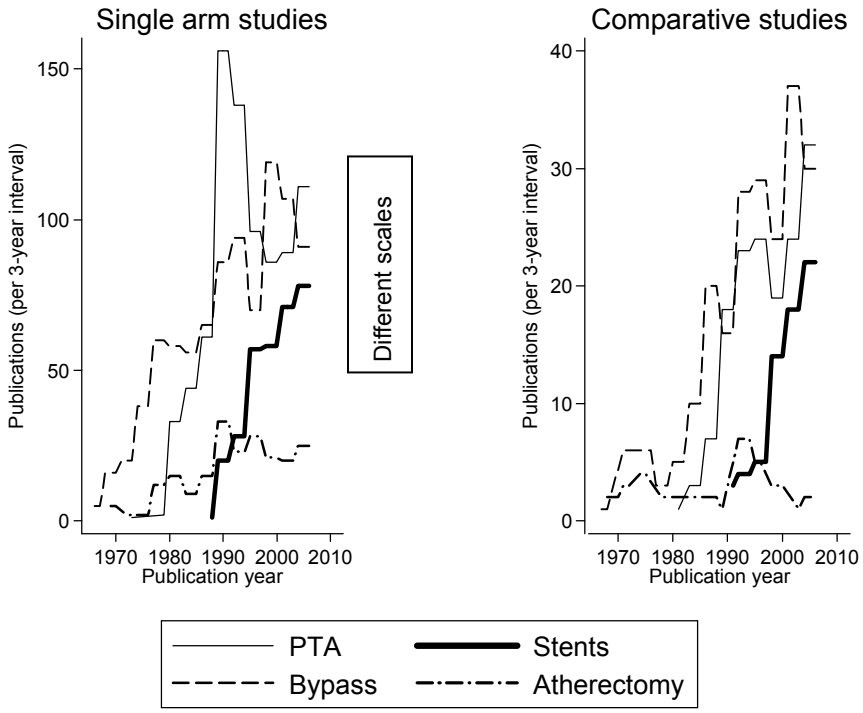
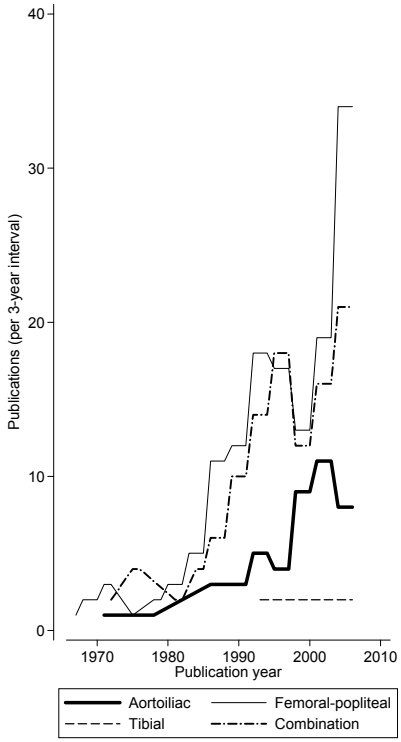


Figure 3. Evolution of the number of published studies over time per artery (comparative studies).



3.2 TASC II Citation Analysis

The TASC consensus document[26] was a result of collaboration by leading authorities in the area of PAD, which led to recommendations for both the surgical and endovascular management of PAD. These recommendations are based on the anatomic extent and severity of atherosclerosis, but the medical risk of the individual patient also influences the approach. Evidence from the literature is cited to support the management of each TASC Classification (A, B, C, D). Our review provides a brief synopsis of the studies that were cited as evidence for a specific approach, an analysis of the strength of the evidence for each of the TASC recommendations, and a detailed examination of the anatomic descriptions of the atherosclerotic process in each of the studies.

The studies cited in the TASC 2007 document upon which the recommendations for surgery or endovascular treatment of aorto-iliac disease, and for surgery or endovascular treatment of femoral popliteal disease were based are reviewed in that order. Since the studies for surgery of the femoral popliteal segment only compared the types of graft material used for femoral popliteal bypass, they are not included. Only studies that compared surgery to endovascular treatment of that anatomic segment are included.

Aorto-iliac disease

Comparison of surgery and endovascular treatment

TASC II did not cite any such comparative studies.

Surgery (Table 18)

The TASC II document relied on two studies as evidence for advocating aortofemoral surgery for "diffuse" disease or total occlusion. Reed 2003 summarizes the results of a retrospective review of 281 patients compiled in a vascular registry from 1980 to 1999.[50] This single institution case series provides no data on the patients' preoperative clinical state, other than a simple classification into claudication and limb salvage (59 percent had claudication). The major focus of this paper was to determine the effect of age on the results of aortobifemoral surgery as assessed by 5-year cumulative patency rates. No anatomic descriptions of the disease type and extent were given. The preponderance of patients received Dacron grafts. All distal anastomoses were at the femoral artery level. Overall, the 5-year primary patency rates averaged 85 percent and 5-year secondary patency rates 92.5 percent. The age of the patient influenced primary patency rates, such that younger patients had poorer patency rates. Other outcome measures, such as clinical improvement, hemodynamics, and the results of imaging were not reported. They had a mortality rate of 1 percent and major morbidity rate of 9 percent.

The TASC II document also cited a systematic review (de Vries 1997) of aorto-iliac/femoral bypasses published between 1970 and 1996.[51] The metaanalysis included 23 case series, with over 6,000 patients. The proportion of the patients in the limb salvage category was extremely variable across studies. The patency rate for people with claudication was 91 percent at 5 years, compared to 87.5 percent for patients with ischemia. The distal anastomosis was at the iliac level in several of the studies, which is a recognized factor that can potentially reduce patency. Postoperative improvement in clinical status, hemodynamics and imaging were not reported. Mortality decreased from 4.6 percent in the older studies to 3.3 percent in the more recent studies.

Notably, the two citations refer only to cohort studies, mostly retrospective in design. In both papers, important characteristics describing the disease were not reported, including clinical classification other than claudication versus limb salvage, hemodynamics, and anatomy to allow TASC classification. Neither specifically reported TASC classification (though the systematic review was performed prior to the original classification.

Clinical, hemodynamic and imaging data were not presented in these papers. Patency was the primary outcome. While complications and the mortality rates were cited, neither the incidence of amputation nor number of reinterventions was provided. Both studies were graded to be of poor quality.

Endovascular treatment (Table 19)

The evidence cited for the management of aorto-iliac disease by catheter-based techniques consists of two narrative reviews (Becker 1989, Rutherford 1992),[52,53] a single center cohort (Murphy-2004),[54] a metaanalysis (Bosch 1997),[31] and two RCTs (the Dutch Iliac Stent Trial[55-57] and Ponec 2004).[58] The two reviews provided summary overviews of previous studies, but no unique data or systematic reviews. Murphy 2004 was a retrospective analysis of a more than 9-year period (1992-2001) with aorto-iliac stents. At a mean followup of 33 months 80 percent of limbs improved at least two Rutherford grades (74 percent asymptomatic), while primary patency averaged 74 percent. The mortality rate was 0.5 percent and the major morbidity rate was 7 percent, which required corrective surgery in 2 percent overall. No postoperative clinical data were presented.

The Dutch Iliac Stent Trial, a multicenter RCT, compared primary PTA with selective stent placement versus primary stent placement.[55-57] This study is described in greater detail in the systematic review below (section 3.4) This well designed study included 213 patients from 1993 to 1996. The two groups were comparable at baseline and intention-to-treat analysis was employed, but no blinding was carried out. The clinical outcomes included: quality of life, improvement and maintenance of at least one Fontaine clinical classification, and improvement of the ABI of >0.10. The authors also reported patency of the treatment site, as determined by peak Duplex systolic flow velocities of <2.5. This trial concluded that PTA with selective stent placement leads to better clinical results as judged by symptomatic improvement. There was no difference between selective or primary stenting, however, with respect to quality of life, patency of the iliac artery and ABI.

The second RCT (Ponec 2004), also described in greater detail in section 3.4, compared two types of stents, the nitinol Smart stent, a memory shape alloy stent, to the Wallstent, a self expanding stainless steel stent, in an equivalency trial design trial at 20 sites.[58] In patients with a suboptimal iliac artery PTA 203 patients were recruited in this multicenter trial designed to show equivalency. Approximately 42 percent in the Wallstent group and 36 percent of the patients in the Smart Stent group had claudication preoperatively. At a mean followup of 9 months, post-treatment clinical outcomes correlated with improvement from severe to moderate claudication (3.5 to 1.9 on the Rutherford scale), while an increase in ABI from 0.6 to 0.9 was maintained at 12 months by both groups. The authors concluded that the self-expanding stainless steel stent (Wallstent) had comparable outcomes to the nitinol stent, a shape memory alloy.

Bosch 1997 was a metaanalysis of six PTA cohort studies (1300 patients) and eight stent placement cohort studies (816 patients).[31] The former was based on studies published from 1980, while the latter contained studies published from 1990 on. The authors encountered difficulty in applying a uniform definition of patency and used clinical angiographic and hemodynamic criteria. Thirty-three percent of the patients undergoing PTA met limb salvage criteria, in

contrast with 15 percent, on average, of patients in the stent studies. The mean length of lesions undergoing PTA averaged 2.6 cm, while the lesions undergoing stent placement averaged 4.1 cm. Occlusion was present in 20 and 28 percent of segments receiving PTA and stent, respectively. Clinical improvement measures were not reported, but hemodynamic improvement was greater in the stent group than the PTA group. The authors found variability in the rate of occlusions included in each study and concluded that the long-term patency rates were better with stenting.

Of the four papers cited for endovascular treatment of aorto-iliac disease two were RCTs, but one was a systematic review of cohort studies and the fourth was a retrospective single institution cohort. Only the Dutch trial provided clinical classification in a form recommended by TASC (Fontaine), while two studies merely provided the proportion of patients with claudication and limb salvage. All described the hemodynamic status of the study limbs. All provided some data on the anatomy of the lesion. The majority of the lesions were described as stenosis (average 80 percent). All four studies described the mean length of the lesion; the majority were less then 5 cm of stenosis/occlusion. None provided TASC classifications or adequate anatomic data to derive them.

The Rutherford or Fontaine classification was used to define clinical improvement in three of the studies, while the Dutch Trial also provided quality of life outcomes. All studies had hemodynamic outcomes by ABI or pulse-volume readings, as well as patency rates. Complications and mortality rates were detailed in three of the four studies, but amputation rates were not provided in any of the studies. Reintervention rates varied between 4 and 19 percent in the three studies where it was presented. The two trials were rated to be of either fair or good quality, the systematic review of fair quality, but the retrospective cohort study was of poor quality.

Femoral popliteal disease

Comparison of surgery to endovascular treatments (Table 20)

Two RCTs comparing surgery and PTA were cited by the TASC II document.[59,60] Wolf 1993 reported an RCT of whether PTA was as effective as surgery for atherosclerosis involving either the aorto-iliac or femoral popliteal segments.[60] Trial inclusion criteria were a greater than 80 percent diameter stenosis or a total occlusion less than 10 cm in length of the iliac or femoral popliteal segments. The patients spanned Rutherford clinical classification 2 to 5 and had an ABI less than 0.9 at rest. Thirty percent of the PTA patients required additional vascular procedures, approximately half due to treatment failure and half due to a technically successful PTA that failed to result in an adequate revascularization. Both groups evidenced a substantial and durable increase in the mean ABI. Survival and primary patency did not differ among the two treatment groups. Both groups of patients noted improvement in the Sickness Impact Profile Score following intervention.

Adam 2005 was a multicenter RCT, conducted in 27 hospitals;[59] the trial assigned 452 patients with severe chronic limb ischemia and involvement of the femoral popliteal segment to either surgery first or PTA first. The trial evaluated amputation-free survival and quality of life. Five percent of patients randomized to surgery and 3 percent to PTA died within 30 days of their intervention. The immediate failure rate was 3 percent in the surgical group. By one year 44 percent of the surgical patients had clinical failure (death, major amputation or return/persistence of symptoms). By contrast, 20 percent of the 224 patients undergoing PTA were technical failures. The 1-year amputation free survival was comparable between the PTA and surgical

groups, at approximately 50 percent; the 3-year rates were also comparable. However, after 2 years, surgery was associated with a statistically significant reduced risk of amputation, death or both. While morbidity was lower with PTA, immediate failure and re-intervention rate were higher than with surgery. The overall conclusion of this study was that there was no difference between the two strategies.

Surgery

TASC II did not cite any studies specific to surgery for femoral popliteal disease.

Endovascular treatment (Table 21)

One systematic review (Muradin 2001) of observational studies and one RCT was cited regarding the comparison of PTA and stent for femoral popliteal disease.[61] It included studies published from 1993 to 2000, including nine PTA studies and seven stent studies. Two studies included both PTA and stents and only one of the 19 was carried out in a randomized controlled fashion. The principal focus of the review was on patency, although clinical improvement by SVS criteria was reported in the 11 of 19 studies. The authors concluded that the results were equivalent for PTA and stent with claudication and stenosis, but PTA was inferior to stent for more severe disease.

Overall

In contrast with the studies cited for aorto-iliac disease, almost all the studies cited for femoral popliteal disease were RCTs. The majority of these trials gave a description of the pretreatment status of the patients with a version of the Rutherford classification, though two reported only the proportion of patients with claudication versus limb salvage. All the RCTs, but not the systematic review of cohort studies reported baseline ABIs. The two RCTs that compared surgery to PTA provided no anatomic data (including TASC classification). In the other studies, stenosis predominated over occlusion in 60 to 70 percent of patients. The lengths of the lesions were well described in these studies and the majority were around 2 cm. For most of the trials, sufficient anatomic data was available to retrospectively define the TASC anatomic category; though none explicitly provided this.

Postoperative clinical status, usually by the Rutherford classification, was available in the trials, while two studies described quality of life measures. Seven trials employed duplex scans to assess the long-term anatomic status of the intervention. Although morbidity was available in only a small number of the trials, mortality was provided in the majority. Amputation rates and reintervention was described in three of the trials. Among the trials, two were of good quality, four of fair quality, and two of poor quality; the systematic review was judged to be of poor quality.

Table 18. Characteristics of TASC II citations regarding surgery for aorto-iliac disease

Characteristic	Reed 2003[50]	de Vries 1997[51]
Study type	Retrospective cohort	Systematic review of cohort studies
No. subjects	281	6250 (23 studies)
Multicenter?	No	(Yes)
A priori sample size calculation?	No	NA
Allocation concealment?	NA	NA
Clinical classification by SVS?	No	(Claudication vs. limb salvage)
Hemodynamic classification?	No	No
TASC/Anatomic classification	No	No
Baseline comparability	NA	NA
Intention to treat analysis?	No (39% drop out)	NA
Reason for dropouts	nd	nd
Blinding	NA	NA
Length of followup	5 yr	Variable
Outcome: Clinical improvement	No	No
Outcome: Hemodynamics	No	No
Outcome: Imaging	No	No
Outcome: Patency	Yes	Yes
Outcome: Amputation	No	No
Outcome: Mortality	Yes	Yes
Outcome: Reinterventions	No	No
Outcome: Complications	Yes	Yes
Quality	C	C

Table 19. Characteristics of TASC II citations regarding endovascular treatments for aorto-iliac disease

Characteristic	Murphy 2004[54]	Dutch 2004[55-57]	Bosch 1997[31]	Ponec 2004[58]
Study type	Retrospective cohort	RCT	Systematic review of cohort studies	RCT
No. subjects	365	213	PTA: 1300 (6 studies) Stent: 816 (8 studies)	203
Multicenter?	No	Yes	(Yes)	Yes
A priori sample size calculation?	No	Yes	NA	Yes
Allocation concealment?	NA	Yes	NA	Unclear
Clinical classification by SVS?	No	(Fontaine)	(Claudication vs. limb salvage)	(Claudication vs. limb salvage)
Hemodynamic classification?	Yes	Yes	Yes	Yes
TASC/Anatomic classification	(Stenosis vs. occlusion)	(SCIVR)	(Percent occlusion)	(Length of stenosis)
Baseline comparability	NA	Yes	NA	Yes
Intention to treat analysis?	NA	Yes	NA	Yes
Reason for dropouts	NA	No	NA	Yes
Blinding	NA	No	NA	No
Length of followup	33 mo	6 yr	Variable	9 mo
Outcome: Clinical improvement	Yes	Yes	No	Yes
Outcome: Hemodynamics	Yes	Yes	Yes	Yes
Outcome: Imaging	Yes	Yes	Yes	Yes
Outcome: Patency	Yes	Yes	Yes	Yes
Outcome: Amputation	No	No	No	No
Outcome: Mortality	Yes	No	Yes	Yes
Outcome: Reinterventions	No	No	Yes	No
Outcome: Complications	Yes	No	Yes	Yes
Quality	C	A	B	B

SCIVR, Society for cardiovascular and interventional radiology.

Table 20. Characteristics of TASC II citations regarding PTA versus bypass for femoral popliteal disease

Characteristic	Wolf 1993[60]	Adam 2005[59]
Study type	RCT	RCT
No. subjects	263	452
Multicenter?	Yes	Yes
A priori sample size calculation?	nd	Yes
Allocation concealment?	Yes	Yes
Clinical classification by SVS?	(Claudication vs. limb salvage)	(Limb salvage)
Hemodynamic classification?	Yes	Yes
TASC/Anatomic classification	No	No
Baseline comparability	Yes	Yes
Intention to treat analysis?	Yes	Yes
Reason for dropouts	Yes	Yes
Blinding	No	No
Length of followup	4.1 yr	5.5 yr
Outcome: Clinical improvement	Yes	Yes
Outcome: Hemodynamics	Yes	No
Outcome: Imaging	Yes	No
Outcome: Patency	Yes	No
Outcome: Amputation	Yes	Yes
Outcome: Mortality	No	Yes
Outcome: Reinterventions	Yes	Yes
Outcome: Complications	No	Yes
Quality	B	A

Table 21. Characteristics of TASC II citation regarding endovascular treatments for femoral popliteal disease (not including RCTs of PTA versus stent or stent versus stent)

Characteristic	Muradin 2001[61]
Study type	Systematic review of cohort studies
No. subjects	1396 (19 studies)
Multicenter?	(Yes)
A priori sample size calculation?	NA
Allocation concealment?	NA
Clinical classification by SVS?	Yes
Hemodynamic classification?	No
TASC/Anatomic classification	No
Baseline comparability	NA
Intention to treat analysis?	NA
Reason for dropouts	NA
Blinding	NA
Length of followup	Variable
Outcome: Clinical improvement	No
Outcome: Hemodynamics	No
Outcome: Imaging	Yes
Outcome: Patency	Yes
Outcome: Amputation	No
Outcome: Mortality	No
Outcome: Reinterventions	No
Outcome: Complications	No
Quality	C

3.3 Systematic Review of TASC Classification

Overview (Table 22)

From the horizon scan, 399 articles met criteria for retrieval (published since 2001, evaluated an invasive vascular procedure, and mentioned a clinical outcome in the title or abstract. Of these, 31 studies met criteria and were analyzed.[62-92] Of the rejected studies, 339 did not report TASC classifications, 21 did not report clinical outcomes for patients within a specific TASC classification, 2 provided data for combined groups of patients receiving either stent or bypass, 1 reported results only at 3 months, and 5 were duplicate publications of included studies.

Only 16 of these studies reported outcomes by TASC classification. Only half of the eligible 31 studies reported TASC classification data in their abstracts or titles. The specific details about how the TASC classification of each patient was determined were generally not reported.

The distribution of outcomes data by artery, intervention, and TASC classification is shown in Table 22. The distribution of studies suggests that data are available to assess outcomes across TASC classifications for stenting (or PTA with or without stent placement) and to a more limited extent, for PTA alone or other interventions. Only for TASC classifications C and D combined (or in one instance TASC classification D) are there comparisons between surgical and endovascular procedures.

The percentage of studies that met eligibility criteria rose each year: 2001 0 percent; 2002 2 percent; 2003 5 percent; 2004 11 percent; 2005 15 percent; 2006 and 2007 16 percent. Thus, among studies of invasive interventions for PAD, reporting of data by TASC classification is becoming more common; though the percentage has stabilized over the past 2 to 3 years and remains low.

Table 22. Distribution of studies reporting TASC classification and clinical outcomes, by artery and intervention

Intervention	Femoral Popliteal						Aorto-iliac						Combination					
	A	A/B	B	C	C/D	D	A	A/B	B	C	C/D	D	A	A/B	B	C	C/D	D
Bypass					3						7							1
PTA±Stent	1	1	3	2	3	3	1	1	2	1	3	1	1		1	2		1
PTA			1	1	3	1					1		1*		1*	1*		
Other	1	1	1	3		2												

* Tibial artery disease

Direct comparisons

Eleven studies reported data providing direct comparisons among TASC grades[65,76,77,79,80,83,86-89] or between bypass and PTA for a specific TASC grade population.[75,76] Only six of these studies, though, reported statistical analyses related to TASC classification.

Different interventions

Bypass versus PTA

Kedora 2007 compared bypass and stent placement for femoral popliteal disease in an RCT of 100 limbs.[76] The study included patients with all TASC grades, but 83 percent of the

analyzed limbs had TASC C or D disease; therefore this study was evaluated as a TASC C/D population (68 percent TASC C). The study did not analyze their data based on TASC classification. Twelve-month amputation rates were statistically similar after both procedures (bypass 10 percent and stent 2 percent, P=.09). Mortality (9 and 11 percent) and reintervention (29 and 34 percent) rates were also similar after both procedures, though not analyzed by the authors.

Hynes 2004, in a retrospective analysis, compared bypass and PTA with or without stent placement in separate groups of patients with femoral popliteal and aorto-iliac disease.[75] Only patients with TASC C or D were included. For patients with femoral popliteal disease, 54 percent of 74 patients who received PTA had TASC C disease, while only 10 percent of 28 patients who received bypass had TASC C disease; similarly for patients with aorto-iliac disease, 40 percent of 14 patients who received PTA had TASC C disease, while only 10 percent of 21 patients who received bypass had TASC C disease. Despite these baseline differences, reintervention rates were not significantly different for either intervention, regardless of artery (7 to 14 percent). Amputation rates were not statistically analyzed, but were substantially higher after bypass (14 to 18 percent) than PTA (0 to 3 percent), in both arteries. The risk difference was not statistically significant for aorto-iliac disease (14, 95% CI -0.7 to 29 percent) but was for femoral popliteal disease (15, 0.5 to 30 percent). Because of the retrospective design of this analysis, the baseline differences, and the lack of adjustment, it is not possible to distinguish whether the different amputation rates are related to the intervention or the baseline severity of disease, as indicated by the differing TASC classifications.

PTA with primary stenting versus selective stenting

One study of 376 patients receiving PTA with or without stents for femoral popliteal disease reported that there was no difference between primary stenting and selective stenting, stratified by TASC lesion (A to D).[88] However, no data were reported.

Summary

Three studies compared either bypass to PTA or PTA with primary or selective stenting. The studies are limited by their design, generalizability, and incomplete reporting and analysis, but do not provide evidence that any procedure results in better clinical outcomes for patients based on TASC classification.

TASC classifications

Clinical status

Four studies reported data on symptomatic improvement based on TASC classification.[65,79,86,88] All evaluated PTA with or without stent; one evaluated patients with aorto-iliac disease, one with femoral popliteal disease, and two with combination disease; one restricted eligibility to patients with TASC C and D, the remaining included patients with all TASC classifications. Only one study reported statistically significant differences across TASC classifications. In a study of PTA with or without stent in 441 patients with femoral popliteal disease, patients with TASC A or B were significantly less likely to have no symptomatic improvement than those with TASC C or D disease (13 versus 23 percent; P=.047).[88] A second study of stents for 89 patients with TASC C or D combination artery disease found a substantial, but nonsignificant difference in likelihood of no symptomatic improvement (3 versus 12 percent); though the statistical analysis was not performed by the authors.[65] The two remaining studies found similar rates of no symptomatic improvement across TASC classifications for PTA

with or without stent in either aorto-iliac (151 patients) or combination artery (256 patients) disease (20 to 27 percent, except for 1/14 patients with TASC C disease in one study).[79,86]

Amputation

Six studies reported data on amputation rates across TASC classifications.[77,79,83,87-89] One study evaluated atherectomy; the others PTA with or without stent. Three included patients with femoral popliteal disease, two aorto-iliac disease, and one tibial disease. One excluded patients with TASC A disease, the remaining included patients with all TASC classifications. No study reported a statistically significant difference in amputation rate at the P=.05 level. One study of 52 patients receiving PTA for tibial disease found that TASC C lesions had higher rates of amputation than A or B (6/14 versus 1/17 and 0/16, P=.07).[87] One study of stent in 89 patients with aorto-iliac disease reported that patients with TASC B disease had lower amputation rates than TASC C or D, but this difference was not statistically significant (0 versus 3 or 5 percent, not analyzed by authors).[83] Another study found the same amputation rates among 70 patients having atherectomy for femoral popliteal disease in with TASC classifications A/B, C, and D.[77] Two other studies with a total of 452 patients also found higher amputation rates with TASC D disease after PTA for femoral popliteal disease (10 and 20 percent) than TASC A to C disease (0 percent in one study, about 12 percent in the second study).[88,89] A final study of PTA with or without stenting in 151 patients with aorto-iliac disease found no significant difference among TASC A, B, or C/D patients (5, 1, and 7 percent, respectively).[79]

Reintervention

Three studies reported data on reintervention rates across TASC classifications.[65,77,80] One study evaluated atherectomy in 70 patients with femoral popliteal disease found a significantly greater risk of reintervention with TASC D disease (32 percent) compared to TASC A or B (0 percent); patients with TASC C disease had an intermediate reintervention rate (9 percent); the statistical analyses were not reported by the authors.[77] The study of stents for combination disease in 89 patients with either TASC C or D disease and the study of cryoplasty for femoral popliteal disease in 102 patients with TASC A to C disease both found no statistically significant difference in reintervention rates; though rates were greater in patients with greater severity of disease (8 versus 3 percent [D versus C] and 20, 15, and 11 percent [C, B, and A]).[65,80]

Mortality and quality of life

No study compared mortality rates or quality of life across TASC classifications.

Summary

The studies tended to be underpowered to detect statistically significant differences across TASC classifications, largely because of small numbers of patients within specific TASC levels. Nevertheless, across interventions, arteries, and outcomes, but within studies, there was the common trend that patients with higher levels of disease had worse clinical outcomes.

Indirect comparisons (Figures 4-8)

We constructed graphs depicting the proportion of people with a clinical event (death, reintervention, amputation, no clinical improvement) for each combination of intervention, artery and TASC category. Overall, 31 different studies provided such information for the clinical

outcomes of interest (quality of life was reported in a single study[69] and is therefore not considered further).[62-92]

The majority of the data come from single cohorts of patients where no direct comparisons were reported between interventions or among TASC classifications. Therefore, the analyses from these studies should be used primarily to generate hypotheses to be tested by future research and, importantly, should not be used to draw definitive conclusions on the relative effectiveness of different interventions across arteries or TASC categories. Moreover, there are numerous confounding variables based on the differing study designs, baseline characteristics, eligibility criteria, and treatment thresholds across the studies. For this reason, estimates of prevalence of clinical outcomes in each patient subgroup must be interpreted with caution.

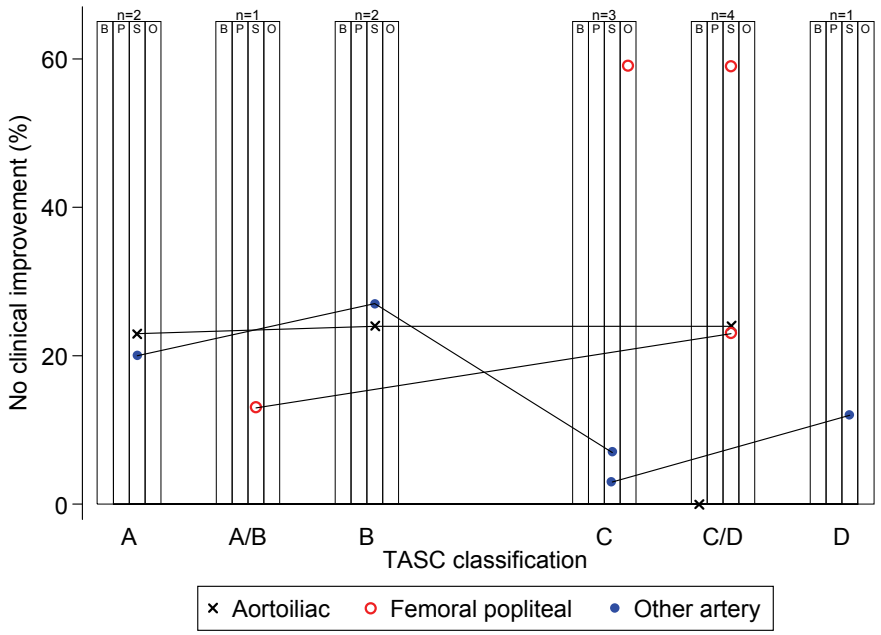
Allowing for the aforementioned caveats, we make general descriptive comments for each of the four analyzed clinical outcomes.

Clinical status (Figure 4)

Figure 4 illustrates the percentage of patients without clinical improvement across different TASC categories for each artery type and each intervention. Seven studies reported this outcome, most of which used PTA with (elective) stenting.[63,65,79,86,88,90,92]

In studies that allowed direct comparisons, outcomes tended to worsen with TASC category: most connecting lines in Figure 4 have a positive slope (see also the "Direct Comparisons" section above). Overall, across all studied subgroups, there is a general tendency for worse outcomes in higher TASC categories. There is insufficient evidence among these studies to discern which intervention results in the most clinical improvement within any TASC classification.

Figure 4. Proportion of patients with lack of clinical improvement per intervention, artery and TASC group.



B: Bypass, O: Other intervention (endarterectomy, atherectomy, or cryoplasty); P: PTA without stenting; S: PTA with primary or elective stenting. Other artery: tibial or combination of different arterial lesions.

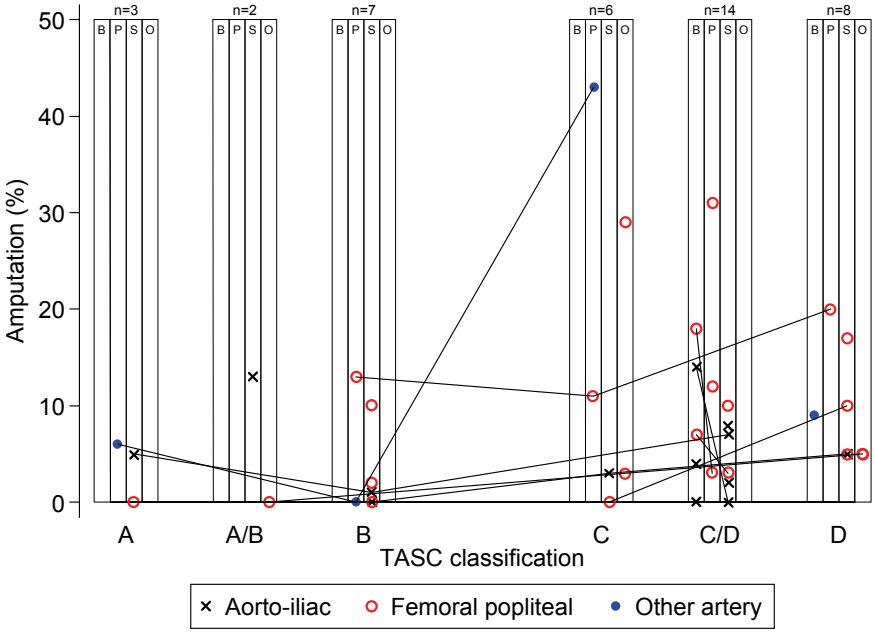
Each marker represents a subgroup of patients per study. Subgroups are defined according to intervention received (B, P, S, O), artery treated (aorto-iliac, femoral popliteal, other), and TASC category (A, A/B, B, C, C/D, D). The TASC categories are listed in the horizontal axis. Within each TASC category the 4 different intervention groups are represented by 4 thin frames (labeled empty boxes). Treated arteries are distinguished by different marker shape and color (see figure key). For each artery, subgroups of patients from the same study are connected with lines.

Of note, this graphical abstraction is subject to confounding by study and by indication for treatment, and is not a substitute for within-study adjusted statistical analyses.

Amputation (Figure 5)

Figure 5 illustrates the percentage of patients who had amputations from 23 studies.[62,63,67-69,73-79,81-85,87-92] In studies that allowed direct comparisons, outcomes tended to worsen with worsening TASC category: most connecting lines that span different TASC categories have a positive slope in Figure 5 (see also the "Direct Comparisons" section above). Overall, across all studied subgroups, there is general tendency for worsening outcomes in higher TASC categories. There is insufficient evidence among these studies to discern which intervention results in the most clinical improvement within any TASC classification.

Figure 5. Proportion of patients who had amputation per intervention, artery and TASC group.



B: Bypass, O: Other intervention (endarterectomy, atherectomy, or cryoplasty); P: PTA without stenting; S: PTA with primary or elective stenting. Other artery: tibial or combination of different arterial lesions.

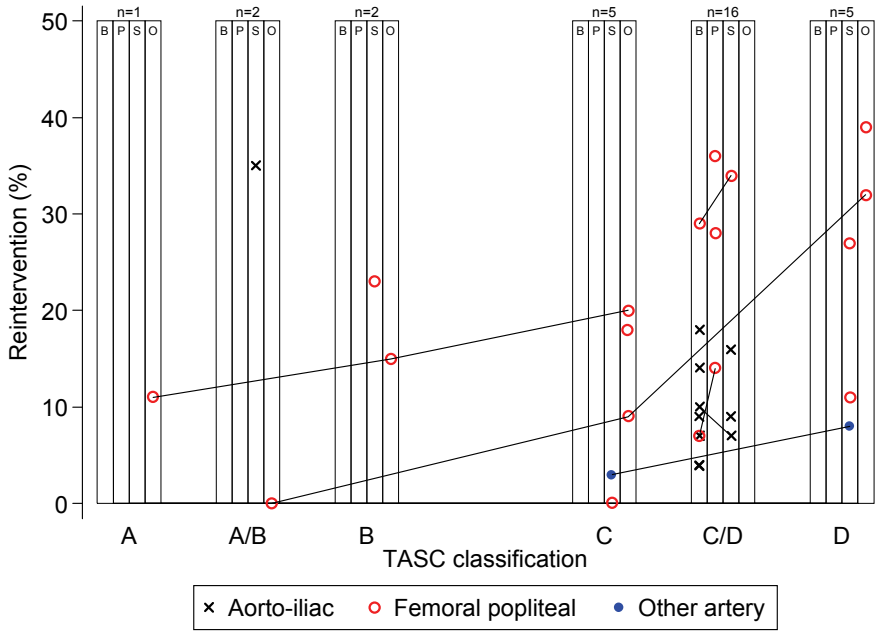
Each marker represents a subgroup of patients per study. Subgroups are defined according to intervention received (B, P, S, O), artery treated (aorto-iliac, femoral popliteal, other), and TASC category (A, A/B, B, C, C/D, D). The TASC categories are listed in the horizontal axis. Within each TASC category the 4 different intervention groups are represented by 4 thin frames (labeled empty boxes). Treated arteries are distinguished by different marker shape and color (see figure key). For each artery, subgroups of patients from the same study are connected with lines.

Of note, this graphical abstraction is subject to confounding by study and by indication for treatment, and is not a substitute for within-study adjusted statistical analyses.

Reintervention (Figure 6)

Figure 6 illustrates the percentage of patients who had reinterventions from 22 studies.[62-78,80,82,84,85,92] In studies that allowed direct comparisons, outcomes tended to worsen with worsening TASC category: most connecting lines that span different TASC categories have a positive slope in Figure 6 (see also the "Direct Comparisons" section above). Overall, across all studied subgroups, there is general tendency for worsening outcomes in higher TASC categories. There is insufficient evidence among these studies to discern which intervention results in the most clinical improvement within any TASC classification.

Figure 6. Proportion of patients receiving reinterventions per intervention, artery and TASC group.



B: Bypass, O: Other intervention (endarterectomy, atherectomy, or cryoplasty); P: PTA without stenting; S: PTA with primary or elective stenting. Other artery: tibial or combination of different arterial lesions.

Each marker represents a subgroup of patients per study. Subgroups are defined according to intervention received (B, P, S, O), artery treated (aorto-iliac, femoral popliteal, other), and TASC category (A, A/B, B, C, C/D, D). The TASC categories are listed in the horizontal axis. Within each TASC category the 4 different intervention groups are represented by 4 thin frames (labeled empty boxes). Treated arteries are distinguished by different marker shape and color (see figure key). For each artery, subgroups of patients from the same study are connected with lines.

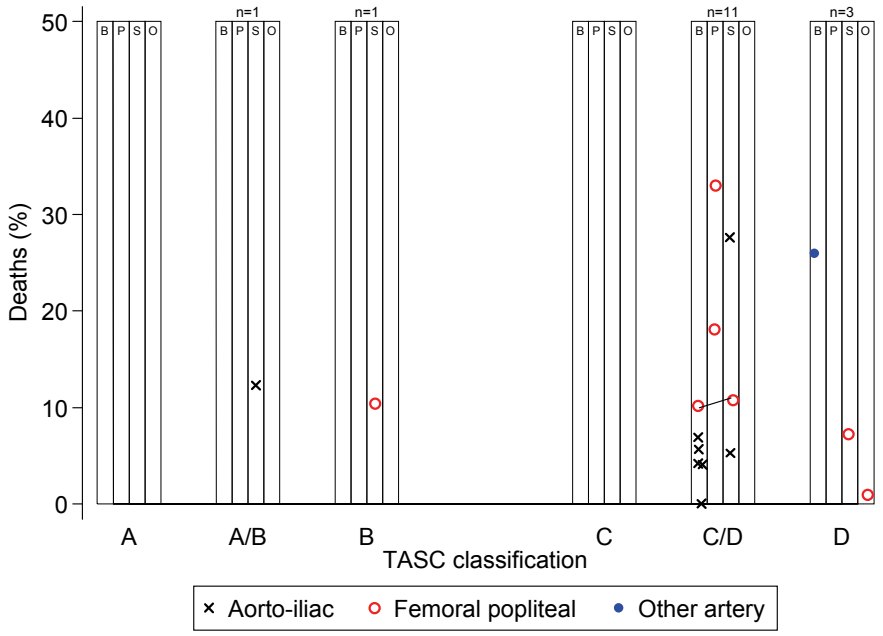
Of note, this graphical abstraction is subject to confounding by study and by indication for treatment, and is not a substitute for within-study adjusted statistical analyses.

Mortality (Figure 7)

Figure 7 illustrates the percentage of deaths across different TASC categories for each artery type and each intervention from 15 studies. [62,64,66,68,69,71-74,76,81,82,84,85,91] As shown, deaths

were reported mainly for patients with severe (TASC C or D and D) lesions. Bypass was performed mainly for aorto-iliac disease, whereas PTA with or without stenting was more commonly used among those with femoral popliteal or tibial disease. Overall, across all studied subgroups, there is general tendency for worsening outcomes in higher TASC categories. There is insufficient evidence among these studies to discern which intervention results in the most clinical improvement within any TASC classification.

Figure 7. Proportion of deaths per intervention, artery and TASC group.



B: Bypass, O: Other intervention (endarterectomy, atherectomy, or cryoplasty); P: PTA without stenting; S: PTA with primary or elective stenting. Other artery: tibial or combination of different arterial lesions.

Each marker represents a subgroup of patients per study. Subgroups are defined according to intervention received (B, P, S, O), artery treated (aorto-iliac, femoral popliteal, other), and TASC category (A, A/B, B, C, C/D, D). The TASC categories are listed in the horizontal axis. Within each TASC category the 4 different intervention groups are represented by 4 thin frames (labeled empty boxes). Treated arteries are distinguished by different marker shape and color (see figure key). For each artery, subgroups of patients from the same study are connected with lines.

Of note, this graphical abstraction is subject to confounding by study and by indication for treatment, and is not a substitute for within-study adjusted statistical analyses.

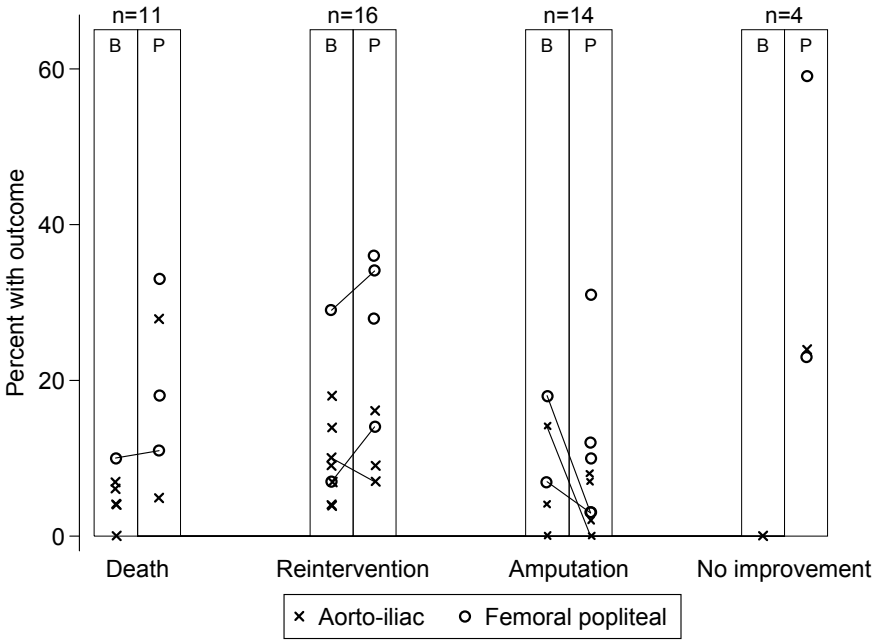
Visualization of outcome rates across different interventions (Figure 8)

Figure 8 juxtaposes the four clinical outcomes (lack of clinical improvement, amputation, reintervention and mortality) among patients with TASC C or D lesions. In this figure, PTA with or without stenting is compared to bypass surgery.

In studies with direct comparisons (connecting lines in Figure 8) there are inconsistent indications as to which treatment results in better clinical outcomes. Looking at the individual cohort data, the highest rates of poor outcomes occurred in cohorts of patients receiving PTA or

stenting. However, this may equally be the result of confounding due to different characteristics and eligibility criteria across the studies or due to true superior results after bypass.

Figure 8. Proportion with a clinical outcome during study followup per intervention and artery among patients with TASC C or D lesions.



B: Bypass, P: PTA with or without stenting

Each marker represents a subgroup of patients per study. Subgroups are defined according to intervention received (B, P), artery treated (aorto-iliac, femoral popliteal). Different clinical outcomes are listed in the horizontal axis. For each clinical outcome the 2 different intervention groups are represented by 2 thin frames (labeled empty boxes). Treated arteries are distinguished by different marker shape (see figure key). For each artery, subgroups of patients from the same study are connected with lines.

Of note, this graphical abstraction is subject to confounding by study and by indication for treatment, and is not a substitute for within-study adjusted statistical analyses.

3.4 Systematic Review of Comparative Stent Studies

Key Question

Perform systematic review of the relative safety and effect of peripheral artery stenting with other invasive vascular procedures for occlusive PAD of infrarenal vessels. Also evaluate comparisons of different stents and/or different procedures with stents.

Organization of systematic review results section

This systematic review (section 3.4) covers comparisons of several interventions, clinical outcomes, and procedural complications. After a general description of the literature search and evaluated studies, the results are organized as follows:

- 3.4.1 Stent versus PTA
  - Individual descriptions of RCTs
  - Clinical outcomes
    - Clinical status
    - Amputation
    - Reintervention
    - Mortality
    - Walking distance
    - Ankle-brachial index (ABI)
    - Miscellaneous outcomes (other vascular, quality of life)
- 3.4.2 Stent versus bypass
  - Clinical outcomes
- 3.4.3 Stent versus stent
  - Bare versus drug-eluting stents
  - Stent+brachytherapy versus stent alone
    - Clinical outcomes
- 3.4.4 Procedural complications
  - Major and minor complications
  - Major and minor bleeding
  - Emboli
  - 30-day mortality

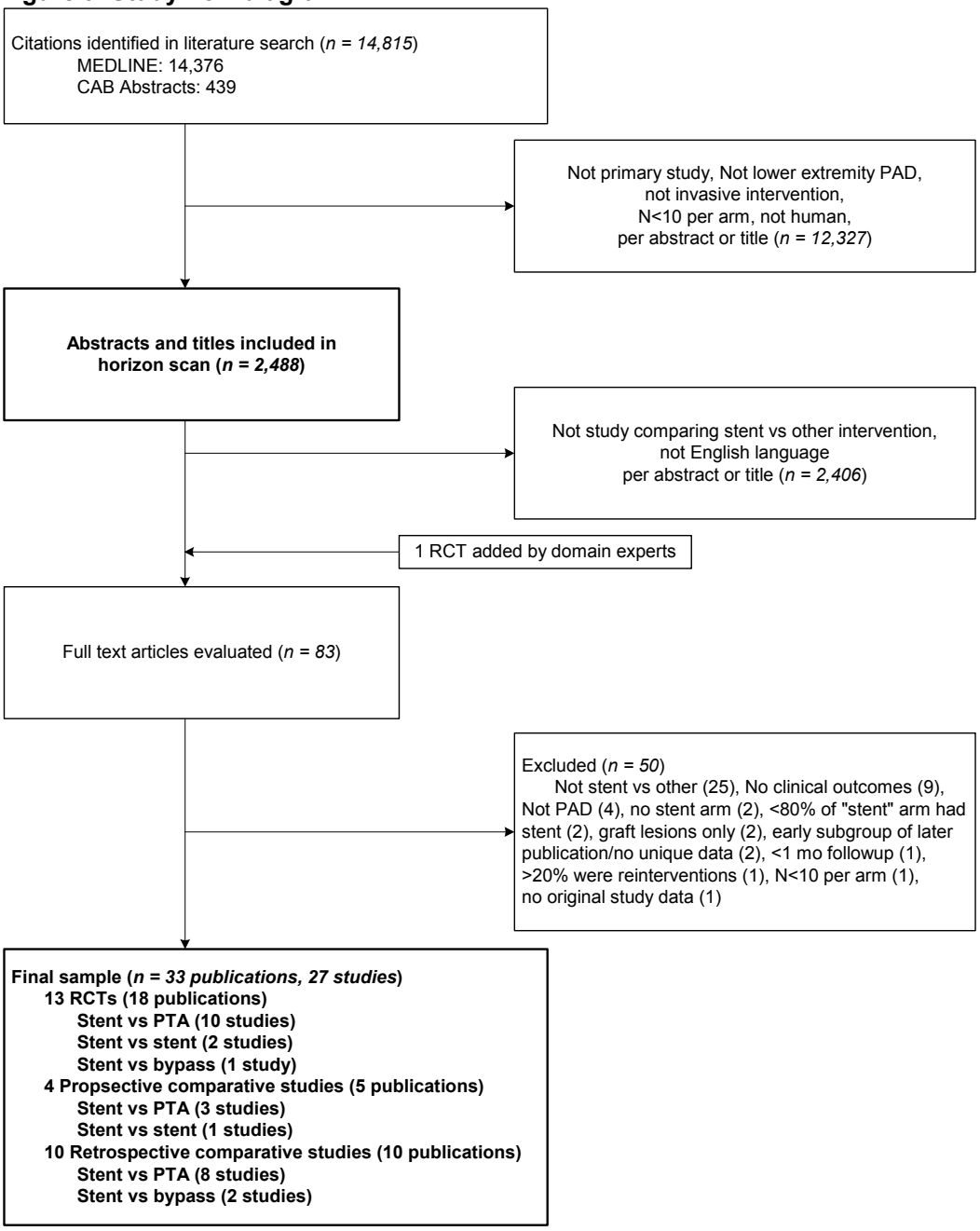
Within each outcome, the studies that evaluated aorto-iliac, femoral popliteal, and tibial disease are reviewed separately, where applicable.

Literature search and evaluated studies (Table 23, Figure 9)

From the 14,815 citations (see **Appendix A** for search strategy), of which 2,488 met criteria for the horizon scan, 82 full-text articles were retrieved for review. One RCT was added by domain experts for the systematic review. The remaining publications did not meet criteria based on their titles and abstracts. Among these, 27 studies (in 33 publications) met criteria and are included. Figure 9 details the flow of studies and reasons for exclusion. **Appendix B** lists the reviewed but rejected publications, including the reasons for rejection.

The studies included 13 RCTs, 4 prospective comparative studies, and 10 retrospective comparative studies. The studies, in general, and the trials, specifically, were highly clinically

Figure 9. Study flow diagram



heterogeneous regarding the type of stent used, the use of stent placement as a secondary intervention in the PTA arm (crossover), the severity and anatomy of PAD, the proportion of patients with cardiovascular risk factors, the dates of the interventions, the duration of followup, and the outcomes assessed.

Table 23 displays which clinical outcomes and procedure complications each study reported. The RCTs were more likely to report the long-term clinical outcomes than the prospective or retrospective nonrandomized studies. However, as is evident from the table, there was little uniformity in the reporting times, though data were more likely to be reported at 1 year

Table 23. Outcomes evaluated and time of assessment in included studies

Study Year	Clinical Outcomes (Times outcomes evaluated)							Complications				
	Clinical Status	Amputation	Reinter-vention	Mortality	Walking distance	ABI	QoL	Overall Complications, 30 day	Bleeding, 30 day	Embolic Events, 30 day	30-day mortality	Stent Fracture
RCTs												
Krankenberg 2007[40]	1 yr	1 yr	1 yr	1 yr	1 yr	1 yr		X	X	X		1 yr
Becquemin 2003[93]	4 yr	4 yr	4 yr	4 yr		1 yr		X	X	X	X	
Cejna 2001[94]	1 yr		1 yr	1 yr				X	X	X	X	
Dutch Iliac Stent Trial 1998[55-57,95,96]	1, 2, 6-8 yr	6-8 yr	6-8 yr	5.6 yr	1, 2 yr	1, 2, 6-8 yr	1, 2, 5 yr	X				
Duda 2006[97]	1.5, 2 yr	2 yr	1, 2 yr	2 yr		2 yr						18 mo
Grimm 2001[98]			~11 mo	nd	nd	nd		X	X			
Kedora 2007[76]	nd	1 yr		nd		1 yr		X	X			
Rand 2006[99]		5.5 mo	5.5 mo									
Saxon 2003[100]	0.5, 2 yr					0.5, 2 yr			X	X		
Schillinger 2006[101,102]	1, 2 yr	1, 2 yr	2 yr	1 yr	1, 2 yr	1, 2 yr		X		X		1 yr
Vroegindeweij 1997[103]	1 yr					1 yr			X	X		
Wolfram 2005[104]	1, 2 yr				1 yr	0.5, 1 yr		X	X	X		
Zdanowski 1999[105]	1 yr					1 yr		X	X		X	
Prospective												
Bosiers 2006[106]		0.5 yr										
Do 1992[107]			1 yr									
Schillinger 2002[108]						0.5 yr						
Siablis 2005[109,110]	0.5 yr	0.5, 1 yr	0.5, 1 yr	0.5, 1 yr		0.5 yr		X	X		X	30 d
Retrospective												
Ballard 1998[111]				22 mo		"Early"					X	
Burns 2000[112]								X	X			
Cho 2003[113]						nd		X				
Kudo 2005[79]	10 mo	10 mo	10 mo					X	X		X	
Laxdal 2007[114]								X	X		X	
Pozzi Mucelli 2003[115]						nd		X	X	X	X	
Schillinger 2003[116]								X				
Westcott 1998[117]	1 yr					1 yr			X			

than other times. ABI and clinical status were the most commonly reported clinical outcomes. However, as described below, a wide range of definitions of clinical status were used by the various studies. Amputation rates, reinterventions (subsequent vascular procedures for the treated artery), and mortality were reported by most RCTs. Walking distance was reported only by four RCTs. Only one trial has evaluated quality of life. Most studies reported overall complications and bleeding (major and to a lesser extent minor for both outcomes) within 30 days of the procedures, however, varying definitions of these outcomes were used. Embolic events related to the procedures were reported in half the RCTs but only one other study. Thirty-day mortality was more commonly reported in the observational studies. Only four studies reported stent fracture rates.

3.4.1 Stent versus Angioplasty (PTA)

Description of RCTs

Ten trials evaluated stent versus PTA. The trials analyzed a total of 1190 patients (range 28 to 279, median 78 patients per trial). By anatomic segment, one addressed the aorto-iliac segment, eight the femoral popliteal segment, and one the infrapopliteal (tibial) segment. Overall, seven used balloon-expandable stents and three self-expandable. One trial used treated balloon-expandable stents and one trial used covered self-expandable stents; the remaining used bare stents. Four of the trials were of good quality, one fair quality, and five of poor quality. The poor quality studies suffered from inadequate reporting of design, definitions, or data, inadequate analyses, poorly reported or inadequate randomization and allocation concealment, very small sample size, high dropout rates, or combinations of these problems. Two studies had high applicability to the Medicare population of patients requiring PAD interventions; eight were of medium applicability, generally due to restrictive eligibility criteria; and one of narrow applicability, due to its analysis of fewer than 30 patients. All but one trial included patients with a mean age over 65 years, though all included patients in their 40s and 50s.

Aorto-Iliac Segment

Dutch Iliac Stent Trial[55-57,95,96]

The trial compared Palmaz (bare, balloon-expanded) stent to PTA in 279 patients. Included patients had at least 50 percent stenosis or elevated pressure gradient in the iliac arteries. Stenoses over 10 cm and occlusions over 5 cm were excluded. The procedures were performed between 1993 and 1996. The results were reported in 5 articles published over 7 years. The longest mean followup was 6.3 years (up to 8.6 years). Aspirin or other anticoagulants were used per local guidelines or per the referring physicians' preferences.

Patients had a mean age of 58 years; 72 percent were male, 10 percent had diabetes, 90 percent had a smoking history, 28 percent had hypertension, and 25 percent hyperlipidemia. Most patients (90 percent) had claudication, while 3 percent were asymptomatic, and 7 percent had tissue necrosis; 10 percent had occlusions.

Outcome assessors were blinded, but not patients. Randomization and allocation concealment were adequate. Up to 10 percent of patients did not have followup for various outcomes. Notably, as per protocol, 43 percent of patients assigned to primary PTA had secondary stent placement because hemodynamically significant gradients remained after PTA. Intention-to-treat analyses were performed.

The trial was rated good quality with medium applicability.

Femoral Popliteal Segment

Vroegindeweij 1997[103]

Palmaz (bare steel, balloon-expandable) stents were compared to PTA in 51 patients. Patients had mild to severe claudication due to femoral popliteal lesions that were less than 5 cm. Patients with lesions below the knee, multisegmental disease, or with no runoff were excluded. Patients had no previous intervention on the affected femoral artery. The procedures were performed between 1993 and 1995, and patients were followed for a median of 14 months (between 0 and 31 months). Patients who received stents were anticoagulated for 3 months.

Patients had a mean age of 65 years (range 41 to 82 years). Seventy-one percent were male; 12 percent had diabetes, 63 percent had a smoking history, 18 percent had hypertension, 31 percent had hyperlipidemia, and 29 percent had concomitant cardiac disease. Few patients (18 percent) had severe claudication. Apparently none had critical limb ischemia, though 18 percent had occlusions.

Patients and outcome assessors were not blinded to intervention. No description of an adequate randomization method or allocation concealment was reported. All enrolled patients were analyzed and the patients receiving each intervention were similar at baseline. Four (17 percent) of the patients randomized to receive stent had angioplasty alone because of technical failure to deploy the stents; an intention-to-treat analysis was performed.

The study was rated to be of fair quality and medium applicability.

Zdanowski 1999[105]

Strecker (flexible bare tantalum, balloon-expandable) stents were compared to PTA in 32 patients. Patients had claudication or more severe symptoms due to femoral popliteal lesions. Eligibility criteria were not well described. The dates of the procedures were not reported. Patients were followed for 1 year after the interventions.

Patients had a median age of 71 years (range 41 to 86 years). Two-thirds of those who received stent were male, but only 24 percent of those receiving PTA alone were male; 31 percent had diabetes, 34 percent had had a smoking history, 25 percent had hypertension. Two-thirds of patients had ulcerations; 19 percent had rest pain; 14 percent had claudication. All were reported to have occlusions.

No data on blinding were reported. The authors reported an adequate randomization method and allocation concealment. Between 9 and 22 percent of patients were not analyzed for various outcomes; intention-to-treat analyses were not conducted. All patients received the intervention to which they were assigned.

The study was rated to be of poor quality with medium applicability.

Cejna 2001[94]

Palmaz (bare steel, balloon-expandable) stents were compared to PTA in 141 patients (154 limbs). All results were reported per limb, not per patient. Patients with intermittent claudication or chronic critical limb ischemia due to femoral popliteal disease that was less than 5 cm were enrolled. Patients with previous vascular surgery in the treated segments were excluded. The procedures were performed between 1994 and 1997. Patients were followed for a mean of 1 year (range 1 day to 3.4 years). All patients received aspirin as a continuous, life-long medication. Intravenous heparin was used for 2 days.

Patients had a mean age of 67 years (range 39 to 87 years). Most (62 percent) were male; 40 percent had diabetes, 62 percent had a smoking history, 41 percent had hyperlipidemia. By

the SVS-ISCVS classification, 16 percent had mild or moderate claudication, 55 percent severe claudication, 12 percent rest pain, and 18 percent minor tissue loss; 39 percent had occlusions.

Patients and outcome assessors were not blinded. The randomization method was not reported, but an adequate system for allocation concealment was used. Between 10 and 20 percent of limbs were not analyzed for various outcomes. Stents were placed in 13 percent of limbs assigned to PTA for secondary reasons. One patient had a stent that failed to deploy; this patient had bypass surgery. Intention-to-treat analyses were employed.

The study was rated to be of fair quality and high applicability.

Grimm 2001[98]

Palmaz (bare steel, balloon-expandable) stents were compared to PTA in 53 patients. Included patients had occlusion or severe stenosis (≥70 percent) in the superficial femoral artery or proximal popliteal artery that was less than 5 cm, with sufficient runoff. Patients with more distal disease or thrombus within the femoral artery were excluded. The dates of the procedures were not reported. Patients were followed for an average of 29 and 34 months after stent or PTA, respectively; the primary endpoint was at 12 months. Heparin and aspirin were used at the time of the procedures and patients were given aspirin 100 mg/day to take life-long.

Patients had a mean age of 70 years; 60 percent were male. No data were provided on rates of cardiovascular risk factors or concomitant disease, but it was reported that there were no statistically significant differences between the trial arms. The mean SVS score was 2.3 and the mean Fontaine classification was 2.7; 19 percent had claudication, 36 percent had rest pain, and 43 percent had tissue loss; 30 percent had occlusions. Notably, there were large differences at baseline for several variables, though none of the differences was statistically significant (male: stent 73 versus PTA 43 percent; occlusion: stent 43 versus PTA 13 percent; mean ABI: stent 0.47 versus PTA 0.62).

No data were reported about blinding. The randomization method was adequate, but the method of allocation concealment was unclear. It was unclear whether intention-to-treat analyses were performed. All patients had the intervention to which they were assigned and there were no dropouts reported. The timing of outcomes was poorly reported and the analyses did not directly compare the interventions.

The trial was rated to be of poor quality with medium applicability.

Becquemin 2003[93]

Palmaz (bare steel, balloon-expandable) stents were compared to PTA in 227 patients. Patients with stage IIb to IV stenosis or occlusion of the superficial femoral artery between 1 and 7 cm in length and sufficient outflow were included. Only a single lesion in the artery was allowed. Patients with acute ischemia, distal disease, and previous revascularization of the artery to be treated were excluded. The procedures were performed between 1995 and 1997. Patients were followed for a median of 2.4 years (up to 4 years); the primary endpoint was 12 months. Heparin was used periprocedure.

Patients had a mean age of 67 years; 63 percent were male, 12 percent had diabetes, 59 percent had a smoking history, 52 percent had hypertension, 41 percent had hyperlipidemia, and 26 percent had concomitant cardiac disease. Most patients had claudication (79 percent), 6 percent had rest pain, and 15 percent had focal tissue necrosis; 20 percent had occlusions.

No data were reported about blinding. Adequate methods were reported for randomization and allocation concealment. Loss to followup was unclearly reported; 13 percent of patients assigned to PTA had a stent placed for suboptimal angioplasty; it was implied that all

patients assigned to stent had the procedure. Intention-to-treat analyses were used. Independent reviewers were used for clinical outcomes.

The trial was rated to be of good quality (except for ABI outcomes, which was poor quality, because only 20 patients had followup at 1 year) and medium applicability.

Saxon 2003[100]

A nitinol (self-expanding) stent with a thin wall ePTFE lining was compared to PTA in 28 patients. Patients had claudication or ischemia due to superficial femoral artery or proximal popliteal artery lesions less than 13 cm in length. Patients with small vessels, extensive disease, or insufficient runoff were excluded. The procedures were performed in 1998 and 1999. Patients were followed for an average of 38 months (range 28 to 48 months) with a primary endpoint at 24 months. Aspirin 325 mg/day was prescribed to all patients; most also took either ticlopidine or clopidogrel.

Patients had a mean age of 70 years; the percent male was not reported; 39 percent had diabetes, 39 percent had a smoking history, 71 percent had hypertension, 64 percent had hyperlipidemia, and 49 percent had concomitant cardiac disease. The mean SVS category was 2.3; 78 percent had TASC classification B, 3 percent A, and 19 percent C; 10 percent had occlusions.

Neither patients nor outcome assessors were blinded. Randomization and allocation concealment were not adequate; 2 of 15 patients assigned to stent were assigned as training cases, not through randomization. Intention-to-treat analyses were used; 6 percent of patients assigned to PTA had stents placed; all stents successfully deployed.

The trial was rated to be of poor quality and narrow applicability.

Schillinger 2006[101,102]

Nitinol (self-expanding) stents were compared to PTA in 104 patients. Patients had severe claudication or more severe disease (SVS 3 to 5) from stenoses of at least 50 percent in the superficial femoral artery; lesions were at least 3 cm long. Patients were excluded if they had acute ischemia, previous surgery or stenting of the femoral artery, inflow disease or no runoff. The procedures were performed in 2003 and 2004. The primary endpoint was 6 months, with followup up to 24 months. Aspirin and clopidogrel were used after both procedures.

Patients had a mean age of 67 years; 53 percent were men, 37 percent had diabetes, 44 percent had a smoking history, 91 percent had hypertension, 89 percent had hyperlipidemia, and 71 percent had concomitant cardiac disease. Notably, these patients had substantially higher rates of elevated cardiovascular risk factors and cardiac disease than other trials. Most (88 percent) had severe claudication, 3 percent had rest pain, and 9 percent had tissue loss; 36 percent had occlusions.

Outcome assessors were blinded, but not patients. The trial used adequate methods for randomization and allocation concealment. All enrolled patients were analyzed by intention-to-treat methods. As per protocol, 33 percent of patients assigned to PTA had secondary stenting for suboptimal results after two prolonged dilations. All stents successfully deployed.

The trial was rated as being of good quality and high applicability.

Krankenberg 2007[40]

In the Femoral Artery Stenting Trial (FAST), a self-expanding nitinol stent was compared to PTA in 224 patients. The trial included only patients with de novo isolated SFA lesions with at least moderate claudication (Rutherford category 2) and stenosis over 70 percent.

Patients with long lesions (more than 10 cm in individual lesion or total length across lesions), whose disease extended into the popliteal artery, or had lack of runoff were excluded. The patients were randomized in 2004 and 2005. Aspirin and clopidogrel were used in patients who received PTA and stent, respectively. The endpoints were reported at 12 months.

The mean age was 66 years; 69 percent were male; 34 percent had diabetes; 65 percent had a smoking history, 36 percent had concomitant cardiac disease (42 percent in stent arm, 31 percent in PTA arm; implied nonsignificant difference); two-thirds had severe claudication (Rutherford 3), 3 percent had more severe symptoms; 37 percent of patients assigned to stent had occlusions as opposed to 25 percent assigned to PTA (P=.053).

It was implied that outcome assessors who measured patency were blinded to intervention, but blinding of clinical outcomes was not reported. Intention-to-treat analyses were reported. For selected outcomes, on-treatment analyses were also reported. As per protocol, 13 of 121 (11 percent) of patients assigned to PTA had a stent placed after two technically unsuccessful angioplasties (residual stenosis greater than 50 percent). Target lesion revascularization and overall mortality were analyzed in 90 percent of subjects; however, treadmill distance, ABI, and improvement in Rutherford classification were reported in only 136 patients (56 percent).

Overall, the study was rated to be of good quality, though poor quality for most outcomes due to very high dropout rate, with medium applicability to the Medicare population.

Infrapopliteal Segment

Rand 2006[99]

Carbostents (treated balloon-expandable) stents were compared to PTA in 51 patients. The trial included patients with critical chronic limb ischemia (Fontaine 3 or 4) with isolated stenosis of at least 70 percent in tibial arteries. Patients with multiple (>3) or long (>3 cm individually or 9 cm cumulatively) lesions were excluded, as were those with inflow obstruction, previous stent placement at the target lesions, or lack of runoff. In addition people with gastrointestinal bleeds or ulcers in the previous 6 months were excluded. The dates of the procedures were not reported. Patients were followed for an average of only 5.5 months, though the primary endpoint was at 6 months; patients were followed up to about 15 months. Heparin was used during the procedures, enoxaparin for 3 days after the procedures, and aspirin indefinitely. In addition, patients having a stent received clopidogrel for 4 weeks.

The mean age was 72 years (range 47 to 80 years); the sex distribution was not reported; 59 percent had diabetes (stent 46 percent, PTA 70 percent); 61 percent had a smoking history, 40 percent had concomitant cardiac disease; 76 percent had focal tissue necrosis, the remaining 24 percent had rest pain; 12 percent had occlusions.

Outcome assessors were blinded to intervention, though patients could not be. The randomization and allocation concealment methods were unclear. Intention-to-treat analyses were not performed. One patient assigned to PTA received a stent; one stent failed to deploy. There were several instances where the number of patients described and analyzed varied. Mortality was evaluated in all 51 patients, though the procedures were described in only 45 patients; 8 patients were reported to be lost to followup, but 14 patients were not included in most outcome analyses.

The study was rated to be of poor quality with narrow applicability.

Overall

Ten RCTs have compared stents to either PTA or PTA with selective stenting; one additional study compared stent to surgery.[76] Balloon expandable stents were employed in six earlier studies, covered stents (PTFE on nitinol exoskeleton) in two, and nitinol in three, one of which compared bare nitinol to drug-eluting nitinol. The length of the atherosclerotic lesion and runoff were employed as exclusion criteria in the majority of studies. In earlier studies, which employed Palmaz stents, the extent of atherosclerotic plaque undergoing treatment generally was limited to lesions less than 5 cm in length. Treatment crossover, usually from PTA to stent when a limb in the PTA arm had a less than desirable response to PTA, was common. The incidence of conversion varied from 0 percent in two balloon expandable stent trials (Zdanowski 1999 and Grimm 2001) through 13 percent in two other trials that also employed Palmaz stents (Cejna 2001 and Becquemin 2003). Schillinger 2006 allowed optional secondary stenting for PTAs that were suboptimal, which accounted for 36 percent of patients assigned to PTA, while Krankenberg 2007 had a lower 13 percent incidence of converting from PTA to stent placement. Vroegneder 1997 was the only study with more than 1 percent of patients converting from stent to PTA, accounting for 8 percent of subjects. While intention-to-treat analysis accounts for these crossovers from one study arm to the other, the high rates of crossover in some study make interpretation of the comparisons difficult. In theory the crossover may have improved the results in the PTA arms because limbs with potentially bad outcomes with PTA alone were treated more aggressively with stents. These studies with high crossover rates must be interpreted as comparisons between the initial plans of performing PTA alone, with the option of stent placement if deemed necessary, and of placing a stent in all patients.

Clinical Status (Table 24)

Studies

Eight RCTs[40,57,93,94,100,102,103,105] and two retrospective studies[79,117] reported on changes in clinical status comparing stent versus PTA. Three RCTs were of good quality, one fair quality, and four poor quality for this outcome; the two retrospective studies were, by definition, rated to be of poor quality. Three RCTs had high applicability to the Medicare population of patients requiring PAD interventions, four had medium applicability, and one narrow applicability. The retrospective studies were of high and narrow applicability.

Five of the RCTs and one retrospective study evaluated bare, balloon-expanded stents, two RCTs used a bare, self-expanding stent, and one RCT used covered, self-expanding stents. One retrospective study included both balloon- and self-expanding stents. All but one of the RCTs included patients with femoral popliteal disease, the remaining studies included patients with iliac or infrarenal aortic disease. Patients were followed for a wide range of time, from 6 months to 8 years. Eight of the studies reported results at about 1 year.

Outcome definitions

One study reported changes in Fontaine classification.[57] Seven studies reported changes in SVS classification (otherwise known as the Rutherford stages).[40,79,93,94,100,102,117] Two studies created their own systems for assessing clinical improvement.[103,105] Vroegindeweij 1997 created a scoring system based on changes in SVS classification and ABI; Zdanowski 1999 defined clinical improvement by "an improvement in claudication distance by at least 50 percent, resolution of rest pain, or healing of ulcers."

Results

Randomized Controlled Trials

Between 28 and 227 patients were analyzed in the trials. In the two largest trials, 80 to 90 percent of the patients had intermittent claudication prior to intervention.[57,93]

Iliac. The Dutch Iliac Stent Trial study found no significant difference in clinical status, as measured by the Fontaine score, at multiple time points up to 6 to 8 years.

Femoral popliteal. The three studies that evaluated self-expanding stents (Krankenberg 2007, Schillinger 2007, and Saxon 2003) all found no statistically significant difference in clinical status at 6 or 12 months between patients randomized to stent or PTA. Only Saxon 2003 reported data indicating a statistically significant difference by odds ratio, in one of its measures of clinical status, "clinical success" at 24 months, strongly favoring stent over PTA.[100] However, importantly, the authors did not perform this analysis or report this as a significant finding. While the high crossover rate from PTA to stent in Schillinger 2007 may partially explain the lack of a difference in clinical status after 1 or 2 years, the low rate of poor status in this small RCT makes it unlikely that a statistically significant difference could have been achieved.

Among the four studies of balloon expandable stents (Becquemin 2003, Cejna 2001, Vroegindeweij 1997, and Zdanowski 1999), only Becquemin 2003 found a statistically significant difference in clinical status, measured as worsened SVS stage at 4 years, favoring PTA over balloon stent, with an odds ratio of 2.0 (95% CI 1.2-3.4).

Retrospective Studies

Two retrospective studies compared stent with PTA. Westcott 1998[117] evaluated 12 patients who had abdominal infrarenal artery stent versus 13 who had PTA; Kudo 2005[79] evaluated 34 patients with iliac artery stents versus 117 with PTA.

Infrarenal aorta. In Westcott 1998, 77 percent of patients had moderate claudication; while in Kudo 2005, most patients had either severe claudication or ischemic rest pain. Mean followup in these studies ranged from 9 to 21 months. Improvements in SVS grading were comparable between stent and PTA (11/12 versus 11/13 patients, respectively).

Iliac. Continued clinical improvement rates were not significantly different between the two groups in Kudo 2005 in univariate analysis, but it was significantly different in multivariate analysis; the group without the iliac stenting failed to have continued clinical improvement compared with the group that received the stenting (HR 3.7, $P<0.02$).

Summary

The studies were generally small and there was considerable clinical heterogeneity in the different study populations. Six of the eight trials did not find any significant difference in followup clinical status comparing stent with PTA. The one study on iliac artery intervention found no significant difference in followup clinical status comparing primary balloon-expandable stent with selective stent placement (or PTA). None of the studies of self-expanding stents in the femoral popliteal artery reported a statistically significant difference compared to PTA; though one very small study reported data indicating possibly better clinical status at 2 years after stent placement. The only statistically significant finding among the balloon-expandable stent studies in the femoral popliteal artery found that patients who received stent had worsening of the clinical stages comparing to patients who received PTA. It is plausible that the small sample sizes in these studies lacked the statistical power to detect such a difference. However, the clinical heterogeneity of the studies – different eligibility criteria and stents –

together with the varying crossover rates, primarily from PTA to stent, and the wide variety of measures of clinical status used, make interpretation of the body of evidence difficult.

In summary, a weak body of evidence – due to study heterogeneity, heterogeneity of outcomes, small study size, varying crossover rates, and generally small study size – do not indicate that either stent placement or PTA alone (or planned PTA with conversion to stent placement) is superior in achieving long-term clinical success.

Amputation (Table 25, Figure 10)

Studies

Five RCTs,[40,93,96,99,102] one prospective study[106] and one retrospective study[79] reported on amputation rates comparing stent versus PTA. Followup time in these studies ranged from a mean of 5.5 months up to 8 years. There was little consistency in reporting times. Methodological quality was rated good in three RCTs and poor in two RCTs for this outcome, the prospective study, and the retrospective study. Three of the studies were judged to have high applicability and four medium applicability.

Three of the RCTs used bare balloon-expandable stents, one of which used carbofilm treated stents, and two used bare self-expanding stents. The nonrandomized studies used a variety of stents. Three of the RCTs included patients with femoral popliteal lesions, one iliac and one tibial lesions. One each of the nonrandomized studies evaluated patients with tibial or iliac lesions.

An important limitation of these studies regarding the clinical outcome of amputation is that only Rand 2006 (with Fontaine III or IV patients) and Kudo 2005 (a retrospective study with 50 percent of patients with chronic limb ischemia) had substantial numbers of patients at substantial risk of amputation prior to vascular interventions. Across studies there was a range in severity of disease, with critical limb ischemia in only 3 percent of patients in Krankenberg 2007[40] and 50 percent in Kudo 2005[79]; though some studies did not report this information.

Outcome definitions

Both major and minor amputations were evaluated. The studies generally did not explicitly define the terms, but minor amputations are understood to mean those of the foot involving the metatarsal or digital level and major amputation are above the metatarsal, generally requiring a prosthesis.

Results

Major amputations

Seven studies on stents versus PTA (5 RCTs, a prospective and a retrospective study) evaluated major amputations. The rate of major amputations across stent arms ranged from 0 percent (1 study) to 1 out of 24 (4 percent). The corresponding range in the PTA arms was 0 percent (3 studies) to 8 out of 136 (6 percent). Figure 10 shows the results of the metaanalysis across the five RCTs (791 patients total); the Peto method was used for the metaanalysis due to rare events.[48] The summary OR for stents versus PTA was 0.76 with very broad 95 percent confidence intervals (CI) (0.28, 2.05) and no evidence for heterogeneity of the results, despite the clinical heterogeneity, including the different diseased arteries and the different types of stents used. Though the range of followup times was wide, the rates of major amputations across all study arms were similar, so the summary risk difference is meaningful to calculate (–0.5 percent, 95% CI -2.8, 1.6 percent). Sensitivity analyses yielded very similar estimates. Subgroup analyses

Table 24. Clinical Status: Stent versus PTA

Study Year UI	Intervention Years (Mean Age)	Artery (CLI, % [A])	Stent Type	Xover [B], % (ITT?)	Time	No. Analyzed Stent (Control)	Outcome	Events	OR (Significance)	Quality Applicability
RCTs										
		Iliac	**Balloon**							
Dutch Iliac Stent Trial 1998[96] 15286319 [C]	1993-1996 (58 yr)	Iliac (7%)	Balloon	43%/nd (ITT)	12 mo	80 (77)	Improvement Fontaine	64 (62)	0.97 (NS)	A Medium
					24 mo	37 (34)		29 (26)	1.12 (NS)	
					6-8 yr	90 (78)		31 (38)	0.55 (NS)	
					12 mo	112 (107)	Fontaine 3-4	0 (0)	--	
					24 mo	92 (91)		0 (1)	--	
					6-8 yr	90 (78)		14 (13)	0.92 (NS)	
		Fem-Pop	**Self-expand**							
Krankenberg 2007[40] 17592075	2004-2005 (66 yr)	SFA (3%)	Self-expanding	11%/nd (both)	12 mo	ITT: 61 (75)	Improve ≥1 Rutherford classification	54 (69)	0.67 (NS)	C Medium
						On treatment: 68 (68)		61 (62)	0.84 (NS)	
Schillinger 2007[102] 17502568[E]	2003-2004 (66 yr)	SFA (13%)	Self-expanding	32%/nd (ITT)	12 mo	49 (52)	Worsen 2 SVS stages	1 (1)	1.06 (NS)	A High
					24 mo	46 (52)	SVS 4-5	4.4% (4.2%)	~1.05 (NS)	
Saxon 2003[100] 12631634	1998-1999 (70 yr)	SFA (SVS 2.3, mean)	Self-expanding, covered	6%/0% (ITT)	6 mo	15 (13)	Mean SVS (Final)	2.6 (1.3)	Net: +0.7 (NS [F])	C Narrow
					24 mo			2.8 (1.9)	+0.3 (NS)	
							Clinical success	14 (6)	16 (1.6-163)	
			Balloon							
Becquemin 2003[93] 12618680	1995-1997 (67 yr)	SFA (21%)	Balloon	13%/1% (ITT)	4 yr	115 (112)	Worsened SVS stage	57 (37)	1.99 [D] (1.16-3.4)	A Medium
Cejna 2001[94] 11200349	1994-1997 (67 yr)	Fem-Pop (86%)	Balloon	13%/1% (ITT)	12 mo	71 (63)	Final SVS ≥3	6.8% (7.5%)	~0.90 (NS)	B High
Vroegindeweij 1997[103] 9354709	1993-1995 (65 yr)	Fem-Pop (18%)	Balloon	0%/8% (ITT)	12 mo	24 (27)	Clinical improvement	74% (85%)	~0.50 (NS)	C Medium
							Worsening	9 (8)	1.43 (NS)	
Zdanowski 1999[105] 10811511	nd (73 yr)	SFA (85%)	Balloon	0%/0% (no)	12 mo	14 (15)	Clinical improvement	10 (14)	0.18 (NS)	C Medium
Retrospective										
		Ao-iliac	**Mixed**							
Kudo 2005[79] 16171589	1993-2004 (67 yr)	Iliac (50%)	Balloon or self-expanding	29%/NA (NA)	10 mo (median)	34 (117)	Worsened SVS stage	nd	HR=3.7 [B] (P=0.02)	C High
			Balloon							
Westcott 1998[117] 9540904	nd (56 yr)	Infrarenal aorta (12%)	Balloon	NA	12 mo	12 (13)	Improvement SVS	11 (11)	2.00 (NS)	C Narrow

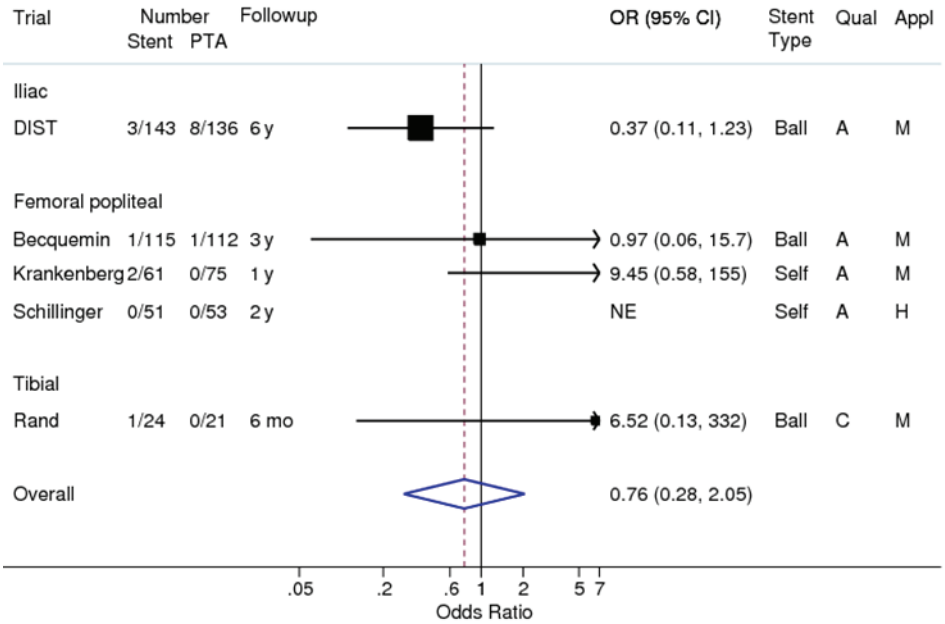
[A] Ischemic rest pain or greater severity.
[B] Percent assigned to PTA who received stent / Percent assigned to stent who received only PTA.
[C] Also 8994707[57], 9643685[95], 10377079[55], 15286319[96].
[D] Stent outcome worse than PTA.
[E] Also 16672699[101].
[F] Estimated, Comparison of final values P=.02, but baseline dissimilar (Stent 2.6, PTA 2.0).

did not offer additional insights. Similar to the RCTs, the nonrandomized studies (one prospective and one retrospective) did not reveal any significant differences.

Minor amputations

Three RCTs on bare metal stents versus PTA (428 patients) reported relevant data. Results were reported over followup periods that ranged from about 6 months up to 8 years. The rates of minor amputations ranged from 0 to 4 percent in the stents arm and from 2 to 7 percent in the PTA arms. The summary OR for the minor amputations was 0.44 (95% CI 0.16, 1.26) favoring stenting, without evidence for between study heterogeneity. Subgroup analyses did not provide further insights. Sensitivity analyses resulted in very similar estimates.

Figure 10. Metaanalysis (Peto method) of odds ratio of major amputation for stents versus PTA



Appl: applicability (H, high; M, moderate; N, narrow); Ball: balloon expandable; CI: confidence interval; DIST: Dutch Iliac Stent Trial; mo: months; NE: not estimable; OR: odds ratio; PTA, percutaneous transluminal angioplasty; Qual: quality (A, good; B, fair; C, poor); Self: self-expanding; y: years

Summary

The comparative studies provide no evidence for statistically significant differences in the rates of major or minor amputations between stent placement versus PTA, regardless of diseased artery or stent type. The small number of studied patients and the rarity of major (and minor) amputations result in uncertain estimates regarding the relative likelihood of major and minor amputations across different interventions; even large effects in either direction cannot be excluded. The major caveat though, is that, on the whole, the studies did not evaluate patients at high risk of amputation prior to their vascular interventions.

Reinterventions (Table 26, Figure 11)

Studies

Seven RCTs,[40,56,93,94,98,99,102] one prospective study,[107] and one retrospective study[79] reported on reinterventions comparing stent versus PTA. Followup time in these studies ranged from 1 to 96 months. Methodological quality was rated good in four RCTs, fair in one RCT, and poor in two RCTs, the prospective study, and the retrospective study.

Outcome definitions

We initially defined as reintervention any repeated intervention on the initially treated *lesion* or *vessel*, irrespective of type (PTA, stent or bypass). However, all studies reported collectively all reinterventions on the treated leg rather than the treated lesion or vessel, with the exception of Schillinger 2007, where target vessel revascularizations were recorded. Studies did not stipulate explicit criteria on when to reintervene. Reinterventions were clinically driven (reported or implied).

Results

Iliac

One good quality RCT[56] and a poor quality retrospective cohort study[79] evaluated reintervention rates in patients with iliac disease. The two studies found similar results with nonsignificant risk differences of 4 or 5 percent, favoring PTA, and odds ratio of 1.3 with wide confidence intervals for reintervention with stent compared to PTA. The RCT used balloon stent; the retrospective study used either balloon or self-expanding stents.

Femoral popliteal

Across the six studies (five RCTs, one prospective study) reintervention rates among patients who received stents varied between 12 and 38 percent. The corresponding range among patients who received PTA (as a first treatment) was 0 to 54 percent. Risk differences ranged from 5 percent favoring stents to 38 percent favoring PTA (in a prospective nonrandomized study), but the differences were not statistically significant in any study.

Two good quality studies evaluated self-expanding stents and did not find a statistically significant difference in reintervention rate at 12[40] and 24[102] months. In metaanalysis, their summary OR was 0.72 (95% CI 0.37 - 1.40; Figure 11). One prospective nonrandomized study found a statistically significant increase in the risk of reintervention in the self-expanding stent group compared to PTA.[107]

Balloon stenting was compared to PTA in three RCTs, all of which found no significant difference in reintervention rates, with no consistency in direction of trends across the three trials. As shown in Figure 11, among the 3 trials using balloon expandable stents the summary

Table 25. Amputations: Stent versus PTA

Study Year UI	Intervention Years (Mean Age)	Artery (CLI, % [A])	Stent Type	Xover [B], % (ITT?)	Time	No. Analyzed Stent (Control)	No. Events Stent (Control)	RD, % (95% CI)	Quality Applicability
							Bold=Major Amputation *Italic=Minor Amputation*		
RCTs									
		Iliac	**Balloon**						
Dutch Iliac Stent Trial 1998[96] 15286319 [C]	1993-1996 (58 yr)	Iliac (7%)	Balloon	43%/nd (ITT)	6-8 yr	143 (136)	**3 (8)**	**-3.8 (-8.4, 0.8)**	A Medium
		Fem-Pop	**Self-expand**						
Krankenberg 2007[40] 17592075	2004-2005 (66 yr)	SFA (3%)	Self-expanding	11%/nd (both)	12 mo	61 (75)	**2 (0)**	**3.3 (-1.2, 7.7)**	C Medium
Schillinger 2007[102] 17502568 [D]	2003-2004 (66 yr)	SFA (13%)	Self-expanding	32%/nd (ITT)	12 mo	51 (53)	**0 (0)**	**0**	A High
					24 mo	46 (52)	**0 (0)**	**0**	
							0 (1)	*-1.9 (-5.7, 1.8)*	
							4 (9)	*-3.8 (-8.8, 1.2)*	
			Balloon						
Becquemin 2003[93] 12618680	1995-1997 (67 yr)	SFA (21%)	Balloon	13%/1% (ITT)	4 yr	115 (112)	**1 (1)**	**0 (-2.5, 2.4)**	A Medium
		Tibial	**Balloon**						
Rand 2006[99] 16252079	nd (72 yr)	Tibial (Fontaine 3-4)	Balloon, treated [E]	3%/0% (no)	5.5 mo (mean)	24 (21)	**1 (0)**	**4.2 (-3.8, 12)**	C Medium
							1 (1)	*-0.6 (-12, 12)*	
Prospective									
		Tibial	**Mixed**						
Bosiers 2006[106] 16956473	2002-2005 (nd)	Tibial (nd)	Various [F]	Unclear	6 mo	158 [300 base] (37 [79 base])	**1.4% (3.3%)**	**NS** (survival analysis)	C High
Retrospective									
		Iliac	**Mixed**						
Kudo 2005[79] 16171589	1993-2004 (67 yr)	Iliac (50%)	Balloon or self-expanding	29%/NA (NA)	10 mo (median)	34 (117)	**nd** (limb salvage)	**NS**	C High

[A] Ischemic rest pain or greater severity.
[B] Percent assigned to PTA who received stent / Percent assigned to stent who received only PTA.
[C] Also 899470749, 9643685101, 1037707947, 1637158056.
[D] Also 16672699[101].
[E] Carbofilm.
[F] Balloon-expandable (bare, passive-coated, and absorbable metal) or self-expanding.

OR was 1.07 (95% CI 0.51 - 2.23), with evidence for possible between study heterogeneity (P=0.12, I^2=51%).

Subgroup analyses by clinical and methodological characteristics of the studies did not offer additional insights.

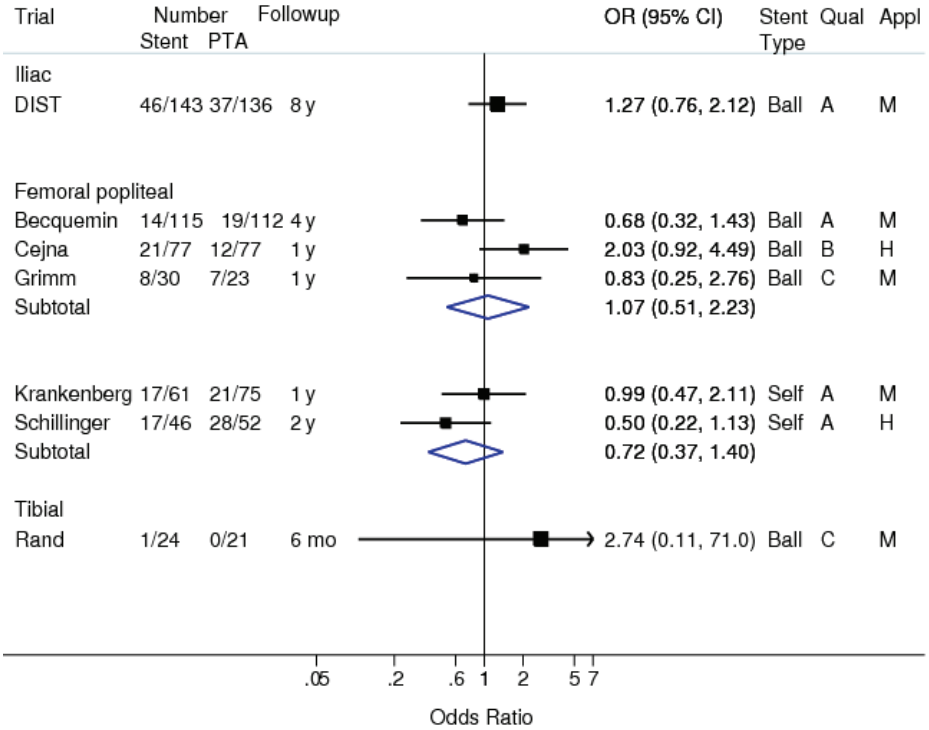
Tibial

One poor quality, small RCT[99] evaluated patients with tibial disease. The reintervention rates were low in both arms (4 percent with stent and 0 percent with PTA). This difference was not statistically significant. This study used a treated balloon stent.

Summary

The one good quality study on iliac artery intervention found no significant difference in rates of reinterventions comparing balloon-expandable stent with PTA. The two good quality studies of self-expanding stents in the femoral popliteal artery also did not find a statistically significant difference in the rates of reintervention when compared to PTA. The one poor quality study of treated balloon stent on tibial artery did not find a statistically significant difference. The body of evidence on reintervention rates is weak due to the heterogeneity of interventions and patients across studies, the generally small sizes of the studies, and the small number of studies. Furthermore, conclusions about reintervention rates will always be problematic due to the nature of the outcome (heterogeneous definitions and the interplay of clinician and patient preferences). The existing studies do not provide evidence of a difference in reintervention rates based on stenting versus PTA alone or planned PTA with conversion to stent placement.

Figure 11. Random effects model metaanalyses of odds ratio of reinterventions for stents versus PTA



Appl: applicability (H, high; M, medium; N, narrow); Ball: balloon expandable; CI: confidence interval; DIST: Dutch Iliac Stent Trial; mo: months; OR: odds ratio; PTA, percutaneous transluminal angioplasty; Qual: quality (A, good; B, fair; C, poor); Self: self expandable; y: years.

Table 26. Reinterventions: Stent versus PTA

Study Year UI	Intervention Years (Mean Age)	Artery (CLI, % [A])	Stent Type	Xover [B], % (ITT?)	Time	No. Analyzed Stent (Control)	No. Events Stent (Control)	RD, % (95% CI)	OR (95% CI)	Quality Applicability
RCTs										
		Iliac	**Balloon**							
Dutch Iliac Stent Trial 1998[56] 16371580 [C]	1993-1996 (58 yr)	Iliac (7%)	Balloon	43%/nd (ITT)	6-8yr	143 (136)	46 (37)	5.0 (-5.7, 16)	1.27 (0.76, 2.1)	A Medium
		Fem-Pop	**Self-expand**							
Krankenberg 2007[40] 17592075	2004-2005 (66 yr)	SFA (3%)	Self-expanding	11%/nd (both)	12 mo	ITT: 114 (115)	17 (21)	-3.4 (-13, 6)	0.78 (0.39, 1.58)	A Medium
						On treatment: 127 (102)	19 (19)	-3.7 (-14, 6)	0.77 (0.38, 1.54)	
Schillinger 2007[102] 17502568 [D]	2003-2004 (66 yr)	SFA (13%)	Self-expanding	32%/nd (ITT)	24 mo	46 (52)	17 (28)	-17 (-36, 2.6)	0.50 (0.22, 1.13)	A High
			Balloon							
Becquemin 2003[93] 12618680	1995-1997 (67 yr)	SFA (21%)	Balloon	13%/1% (ITT)	4 yr	115 (112)	14 (19)	-4.8 (-14, 4.4)	0.68 (0.32, 1.43)	A Medium
Cejna 2001[94] 11200349	1994-1997 (67 yr)	Fem-Pop (86%)	Balloon	13%/1% (ITT)	~12 mo	77 (77)	21 (12)	12 (-1.1, 25)	2.0 (0.92, 4.5)	B High
Grimm 2001[98] 9203369	nd (70 yr)	SFA (79%)	Balloon	0%/0% (nd)	7/11 mo (mean [E])	30 (23)	8 (7)	-3.8 (-28, 21)	0.83 (0.25, 2.8)	C Medium
		Tibial	**Balloon**							
Rand 2006[99] 16252079	nd (72 yr)	Tibial (Fontaine 3-4)	Balloon, treated [F]	3%/0% (no)	5.5 mo (mean)	24 (21)	1 (0)	4.2 (-3.8, 12)	--	C Medium
Prospective										
		Fem-Pop	**Self-expand**							
Do 1992[107] 1423291	nd	Fem-Pop (15%)	Self-expanding	NA	12 mo	26 (26)	10 (0)	38 (20, 57)	--	C Narrow
Retrospective										
		Iliac	**Mixed**							
Kudo 2005[79] 16171589	1993-2004 (67 yr)	Iliac (50%)	Balloon or self-expanding	29%/NA (NA)	10 mo (median)	34 (117)	9 (26)	4.2 (-12, 21)	1.26 (0.52, 3.0)	C High

[A] Ischemic rest pain or greater severity.
[B] Percent assigned to PTA who received stent / Percent assigned to stent who received only PTA.
[C] Also 8994707[57], 9643685[95], 10377079[55], 15286319[96].
[D] Also 16672699[101].
[E] Stent / PTA arms.
[F] Carbofilm.

All-cause mortality (Table 27, Figure 12)

Only mortality data from at least 6 months after the interventions are considered here. For 30-day mortality, which is a standard among interventionalists for procedure-related mortality, see page 107, under complications. For studies that did not state the timing of the reported mortality, we assumed that these were data from at least 6 months after the interventions.

Studies

Six RCTs reported on mortality rates comparing stent versus PTA.[40,56,93,94,98,101,102] Followup time in these studies ranged from about 1 to 5.6 years, though one study did not define the timeframe.[98] Four of the trials were rated to be of good quality for mortality outcomes with medium applicability in three and high applicability in one; there is one fair quality with high applicability and one poor quality with medium applicability.

Mean ages ranged from 58[56] to 70[98] years. Between 53[101] and 72[56] percent of patients were male. Diabetes was present in 10[56] to 40[94] percent of patients, a history of smoking in 44[101] and 90[56] percent, hypertension in 28[56] to 91[101] percent, hyperlipidemia in 25[56] and 89[101] percent, cardiac disease in 26[93] and 71[101] percent, and critical limb ischemia was present between 3[40] and 79[98] percent of patients (all in studies that reported the data). Judging by presence of cardiovascular risk factors and disease, the patients in the Dutch Iliac Stent Trial were at lower risk (except for their very high rate of smoking) and patients in Schillinger 2006[101] and Grimm 2001[98] were at relatively high risk.

Outcome definitions

All-cause mortality was the outcome assessed in all studies.

Results

Among four studies mortality rates at 1 year ranged between 2 and 16 percent after stent and 0 and 9 percent after PTA. One study had no deaths over about 30 months (although the duration being reported was unclear).[98]. One study had rates of death of 15 and 18 percent, respectively, at 3 years. The last study had similar mortality rates at 5.6 years: 15 and 16 percent, respectively. No study found a statistically different all-cause mortality rate at any time point. Risk differences ranged from -4.5 percent (favoring stent) at 12 months[93] to 6.5 percent (favoring PTA) also at about 12 months.[94]

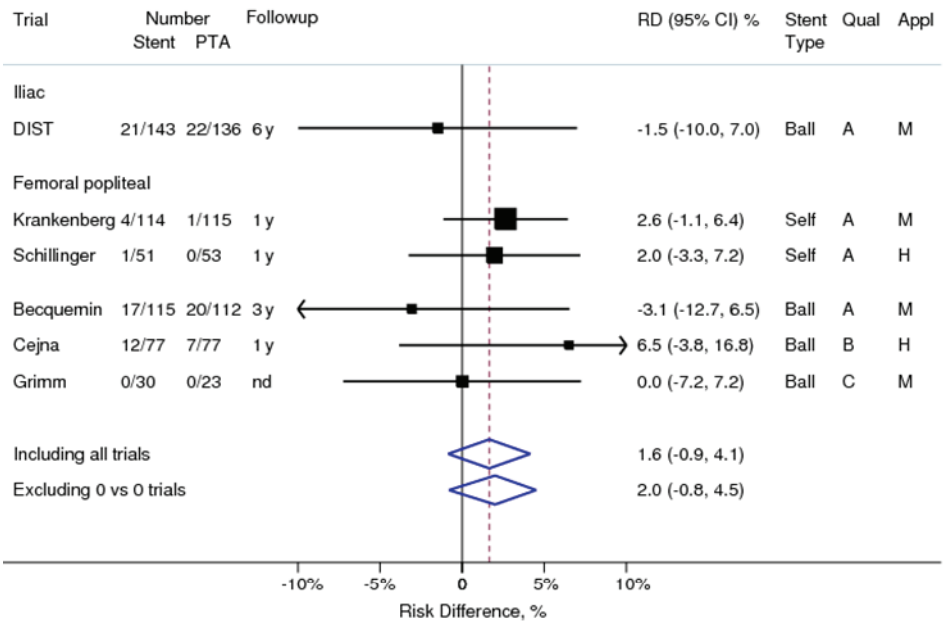
Figure 12 depicts the metaanalysis of the long term mortality (>30 days) in the 6 trials. On average, there was no statistically significant difference between stents and PTA (summary risk difference 1.6 percent, 95% CI -0.9, 4.1 percent). The metaanalysis was statistically homogeneous despite the clinical differences among studies. Subgroup analyses by clinical and methodological characteristics of the studies did not offer additional insights. Thus, the conclusions from these studies are similar for the three arterial sites and for self-expanding and balloon stents.

Summary

Though the data are limited and the studies were clinically heterogeneous in terms of arterial disease location, stent used, severity of patient disease, concomitant risk factors, duration of followup, methodological quality, and other factors, the studies consistently found no significant difference in mortality rates. However, the small number of studies and events may be masking true clinically important differences in mortality. Overall, while the studies do not

support any difference in all-cause mortality, actual differences between the interventions cannot be ruled out.

Figure 12. Random effects model metaanalysis of risk difference of mortality in stents versus PTA trials (after 30 days)



Appl: applicability (H, high; M, medium; N, narrow); Ball: balloon expandable; CI: confidence interval; DIST: Dutch Iliac Stent Trial; nd: not described; PTA, percutaneous transluminal angioplasty; Qual: quality (A, good; B, fair; C, poor); RD, risk difference; Self: self expandable; y: years.

Walking Distance (Table 28)

Studies

Four RCTs[40,55,98,102] reported on changes in walking distance comparing stent with PTA. Followup time in these studies ranged from 12 to 24 months. Methodological quality was rated good in two studies and poor in two studies for this outcome. One high quality study had high applicability, the other three trials had medium applicability. Three studies evaluated patients with femoral popliteal lesions, though they differed greatly in their rates of critical limb ischemia (3, 13 and 79 percent). One study included patients with iliac disease who mostly did not have critical limb ischemia.

Outcome definitions

The Dutch Iliac Stent Trial measured walking distance during a 5-minute walking test with a maximum of 300 meters. Krankenberg 2007 and Schillinger 2007 measured maximum walking distance on a treadmill (2 and 3.2 km/hr, respectively, at 12º slope). Grimm 2001 reported the absolute claudicating distance on a treadmill.

Table 27. Mortality: Stent versus PTA

Study Year UI	Intervention Years (Mean Age)	Artery (CLI, % [A])	Stent Type	Xover [B] % (ITT?)	Time	No. Analyzed Stent (Control)	No. Events Stent (Control)	RD, % (95% CI)	Quality Applicability
RCTs									
		Iliac	**Balloon**						
Dutch Iliac Stent Trial 1998[56] 16371580 [C]	1993-1996 (58 yr)	Iliac (7%)	Balloon	43%/nd (ITT)	5.6 yr	143 (136)	21 (22)	-1.5 (-10, 7.0)	A Medium
		Fem-Pop	**Self-expand**						
Krankenberg 2007[40] 17592075	2004-2005 (66 yr)	SFA (3%)	Self-expanding	11%/nd (ITT)	12 mo	114 (115)	4 (1)	2.6 (-0.1, 6.4)	A Medium
Schillinger 2007[102] 17502568 [D]	2003-2004 (66 yr)	SFA (13%)	Self-expanding	32%/nd (ITT)	12 mo	51 (53)	1 (0)	-2.0 (-1.8, 5.8)	A High
			Balloon						
Becquemin 2003[93] 12618680	1995-1997 (67 yr)	SFA (21%)	Balloon	13%/1% (ITT)	1 yr	115 (112)	3% (7%) [Survival analysis]	-4.5 (-10, 1.0)	A Medium
					3 yr	115 (112)	15% (18%) [Survival analysis]	-3.1 (-13, 6.5) [NS, 4 yr overall]	
Cejna 2001[94] 11200349	1994-1997 (67 yr)	Fem-Pop (86%)	Balloon	13%/1% (ITT)	~12 mo	77 (77)	12 (7)	6.5 (-3.8, 17)	B High
Grimm 2001[98] 9203369	nd (70 yr)	SFA (79%)	Balloon	0%/0% (nd)	Unclear	30 (23)	0 (0)	0	C Medium

[A] Ischemic rest pain or greater severity.
[B] Percent assigned to PTA who received stent / Percent assigned to stent who received only PTA.
[C] Also 8994707[57], 9643685[95], 10377079[55], 15286319[96].
[D] Also 16672699[101].

Results

The Dutch Iliac Stent Trial analyzed 279 patients with iliac artery intervention and did not find a statistically significant difference in changes in walking distance comparing a balloon stent with PTA (where 43 percent of patients were converted to have a stent) at 24 months.[55] Krankenberg 2007 analyzed 136 patients with superficial femoral artery disease and found a statistically significant greater maximal walking distance among patients assigned to self-expanding stenting (P=.03); however, this outcome was poorly reported and the actual average difference in walking distance between the two groups is unclear. Schillinger 2007 analyzed 104 patients with superficial femoral artery intervention and found that patients in the stent group walked significantly farther on a treadmill than patients in the PTA group at 12 months (P=0.04), but not at 24 months (P=0.12).[102] Grimm 2001 analyzed 53 patients with femoral popliteal artery intervention and reported no statistically significant difference in the absolute claudicating distance between the stent and the PTA group; the time when the walking distance was assessed was not reported.[98]

Summary

Only four trials comparing stent with PTA reported changes in walking distance. Comparing stent with PTA, one good quality trial on iliac artery intervention did not find a significant difference in walking distance (with balloon stents); two trials (one good and one poor quality) on femoral artery intervention reported a statistically significant increase in walking distance at 12 months, but not at 24 months (in one trial) with a self-expanding stents. These limited data are insufficient to provide evidence of a clear benefit of stenting over PTA; though there is a suggestion that self-expanding stent placement may result in increased maximal walking distance, compared to PTA alone (or planned PTA with conversion to stenting) in patients with superficial femoral artery disease.

Ankle-brachial Index (ABI) (Table 29, Figure 13)

Studies

Eight RCTs,[40,56,93,98,100,103,105] one prospective[108] and three retrospective studies[113,115,117] reported on changes in ankle-brachial index (ABI) comparing stent versus PTA. Followup times in these studies ranged from 6 months up to 8 years. Methodological quality was rated good in two RCTs, fair in one RCT, and poor in five RCTs, one prospective, and three retrospective studies for this outcome. Only one RCT had high applicability; one of the RCTs and two retrospective studies had narrow applicability; the rest had medium applicability.

One RCT and the prospective study included patients with iliac lesions, and one retrospective study evaluated patients with infrarenal lesions; the other studies treated femoral popliteal lesions. Most studies had relatively few patients with critical limb ischemia, though three studies had critical limb ischemia rates over 50 percent.

Outcome definitions

ABI is a standard measurement used to diagnose and evaluate lower extremity PAD.[26] With a sphygmomanometer and a Doppler instrument the systolic pressure of the posterior tibial and dorsalis pedis arteries of the affected leg are measured. These pressures are then normalized (divided by) the brachial (arm) pressure. The test is usually performed with the patient at rest (as was done in all but one study[100]). The typical cut-off for diagnosing PAD is ABI≤0.90 at rest. Of note, patients with calcified vasculature due to diseases such as diabetes and chronic kidney

Table 28. Walking distance: Stent versus PTA

Study Year UI	Intervention Years (Mean Age)	Artery (CLI, % [A])	Stent Type	Xover [B], % (ITT?)	Time	N Stent (Control)	Baseline, m Stent (Control)	Final, m Stent (Control)	Net Change (95% CI)	Quality Applicability
RCTs										
		Iliac	**Balloon**							
Dutch Iliac Stent Trial 1998[56] 16371580 [C]	1993-1996 (58 yr)	Iliac (7%)	Balloon	43%/nd (ITT)	12 mo	143 (136)	190 [D] (204)	261 (263)	12 (-9, 33) [E]	A Medium
					24 mo			258 (255)	17 (-4, 38) [E]	
		Fem-Pop	**Self-expand**							
Krankenberg 2007[40] 17592075	2004-2005 (66 yr)	SFA (3%)	Self-expanding	11%/nd (ITT)	12 mo	61 (75)	~133, median (~130) [F]	185 (150)	P=.03	C Medium
Schillinger 2007[102] 17502568 [G]	2003-2004 (66 yr)	SFA (13%)	Self-expanding	32%/nd (ITT)	12 mo	51 (53)	92 [H], median (87)	375, mean (250)	P=0.04 [J]	A High
					24 mo	46 (52)	88, median (86)	302, median (196)	P=0.12 [J]	
			Balloon							
Grimm 2001[98] 9203369	nd (70 yr)	SFA (79%)	Balloon	0%/0% (nd)	Unclear	30 (23)	166 [K] (150)	384 (467)	-99 (-272, 74) [E]	C Medium

[A] Ischemic rest pain or greater severity.
[B] Percent assigned to PTA who received stent / Percent assigned to stent who received only PTA.
[C] Also 899470749, 9643685101, 1037707947, 15286319102.
[D] Test not described.
[E] Estimated from reported data.
[F] Approximated from reported data. At baseline, 97 of 121 stent patients had walking distance measured: median 110 m; only 61 had both baseline and final test. 99 of 123 PTA patients had median walking distance of 100 m; only 75 had both baseline and final test.
[G] Also 1667269956.
[H] Maximal distance on treadmill; assumed to be 0 m in patients with critical limb ischemia; 3.2 km/hr and 12° incline.
[J] Comparison of final values.
[K] Walking distance to claudication.

disease will have falsely elevated ABIs. These patients should be tested with other methods. None of the studies reported excluding these patients from this analysis.

The test can also be performed after exercise, as was done in two trials.[93,100] The post-exercise pressure may be lower than the resting pressure due to the effect of the increased blood flow requirements to muscles induced by exercise. This is particularly evident in stenoses which may be subcritical at rest, but become critical with exercise. Alternatively, the post exercise pressure may reflect the degree of collateral vessel formation around an occluded vessel.

Results

Iliac

Two studies evaluated resting ABI in patients with iliac lesions. The (high quality) Dutch Iliac Stent Trial found no significant difference in ABI 1, 2, or 6 to 8 years after the procedures regardless of whether patients were assigned to primary stenting or PTA. The prospective study (Schillinger 2002) and the retrospective study (Westcott 1998[117]) also found no significant difference. The trial and the retrospective study used balloon expandable stents. The prospective comparative study did not report stent type, but based on the publication date, it is likely that they too used balloon expandable stents.

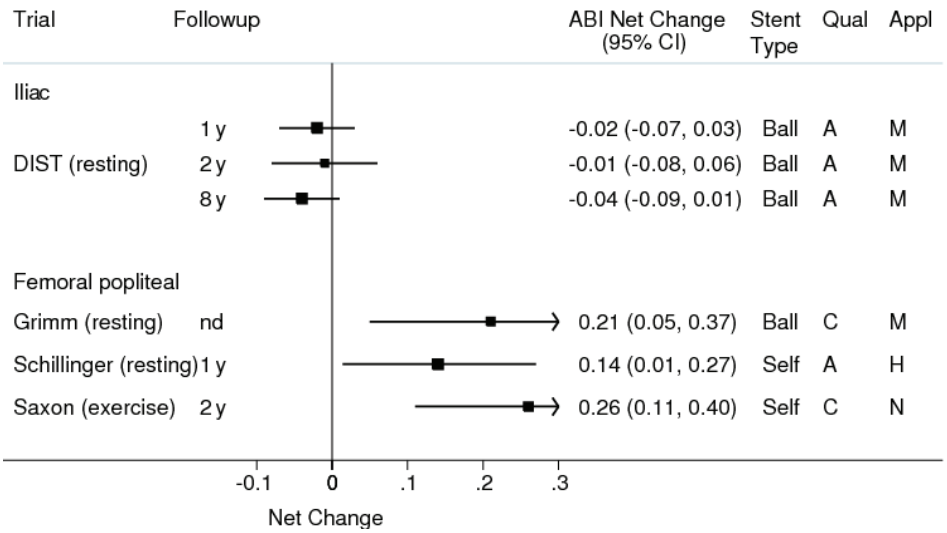
Femoral popliteal

Three trials and one retrospective study used self-expanding stents. The high quality trial among them (Schillinger 2006) found that ABI at 12 months was significantly higher (better) among patients assigned to stent; at 24 months ABIs were still higher after stent, but the difference was smaller and not statistically significant. Saxon 2003 and the retrospective analysis performed by Cho 2003 also found statistically significantly better ABI after self-expanding stent placement at both 6, and at 24 months in the trial. The remaining trial (Krankenberg 2007) found no significant difference in ABI at 12 months.

Four of the trials reported on comparisons of balloon stents versus PTA on ABI. One retrospective study (Pozzi Mucelli 2003) analyzed a cohort of patients for whom both balloon and self-expanding stents were used. Three out of four of the trials and the retrospective analysis found no difference in ABI at 12 months (or at an undefined time). Only one poor quality trial (Grimm 2001) found a significant improvement in ABI after balloon stenting compared to PTA alone.

The results of the few trials that provided sufficient data for graphing are presented in the Figure 13. Notably, the RCT of patients with iliac lesions found no difference in change in ABI between interventions, compared to the trials of femoral popliteal lesions. This difference may be due to intrinsic differences based on anatomy (iliac versus femoral disease) or may be related to the very high crossover rate in the Dutch Iliac Stent Trial, such that 43 percent of patients assigned to PTA had secondary stenting. However, there was a 32 percent crossover in the Schillinger 2006 trial. The difference may also be spurious, given that three trials of femoral popliteal disease with no significant differences in resting ABI (and a fourth trial that reported baseline resting ABI, but results only for exercise ABI) did not report adequate data for metaanalysis. Given all these issues, and the small number of similar studies, metaanalysis was not performed.

Figure 13. Forest plot of net change in ABI in stents versus PTA trials (no metaanalysis performed)



ABI: ankle-brachial index; Appl: applicability (H, high; M, medium: N: narrow); Ball: Balloon expandable; CI: confidence interval; DIST: Dutch Iliac Stent Trial; nd: not described; PTA, percutaneous transluminal angioplasty; Qual: Quality (A, good; B, fair; C, poor); Self: self-expanding; y: years

Summary

The evidence on the effect of balloon expandable stents on iliac disease are sparse, but suggest no difference in ABI, either short or long-term, based on whether stent use or PTA were planned. However, this conclusion is based largely on a trial in which almost half the patients with planned PTA were converted to stent placement. Among patients with superficial femoral artery disease, the evidence suggests, though is not conclusive, that patients assigned to self-expanding stents have better short term (6 to 12 month) ABI than those assigned to PTA, with possible better longer term results also. However, the trials that evaluated balloon expanded stents failed to find a benefit in ABI for stent compared to PTA.

Table 29. Ankle brachial index (ABI): Stent versus PTA

Study Year UI	Intervention Years (Mean Age)	Artery (CLI, % [A])	Stent Type	Xover [B], % (ITT?)	Time	N Stent (Control)	Baseline Stent (Control)	Final Stent (Control)	Net Change (95% CI)	Quality Applicability
RCTs										
		Iliac	**Balloon**							
Dutch Iliac Stent Trial 2006[56] 16371580 [C]	1993-1996 (58 yr)	Iliac (7%)	Balloon	43%/nd (ITT)	12 mo	118 [135 base] 112 [124 base]	0.75 (0.77)	0.94 (0.98)	-0.02 (-0.07, 0.03)	A Medium
					24 mo	107 99		0.97 (1.00)	-0.01 (-0.08, 0.06)	
					6-8 yr	101 85		0.90 (0.96)	-0.04 (-0.09, 0.01)	
		Fem-Pop	**Self-expand**							
Krankenberg 2007[40] 17592075	2004-2005 (66 yr)	SFA (3%)	Self-expanding	11%/nd (ITT)	12 mo	61 (75)	0.68 [D] median (0.72)	+0.21 [E] median (+0.15)	NS	C Medium
Schillinger 2007[102] 17502568 [F]	2003-2004 (66 yr)	SFA (13%)	Self-expanding	32%/nd (ITT)	12 mo	51 (53)	0.57 (0.54)	0.84 (0.67)	0.14 (P=0.03) [G]	A High
					24 mo		0.58 (0.54)	0.88 (0.77)	0.06 (P=0.09) [G]	
Saxon 2003[100] 12631634	1998-1999 (70 yr)	SFA (SVS 2.3, mean)	Covered, self-expanding	6%/0% (ITT)	6 mo	15 (13)	Exercise: 0.36 (0.43)	0.80 (0.50)	0.37 (0.23, 0.51)	C Narrow
					24 mo			0.86 (0.67)	0.26 (0.11, 0.40)	
			Balloon							
Becquemin 2003[93] 10069906	1995-1997 (67 yr)	SFA (21%)	Balloon	13%/1% (ITT)	≤12 mo	115 (112)	Rest: 0.74 (0.72) Post-Exercise: 0.52 (0.48)	nd	NS	C Medium
Grimm 2001[98] 9203369	nd (70 yr)	SFA (79%)	Balloon	0%/0% (nd)	Unclear	30 (23)	0.47 (0.62)	0.91 (0.85)	0.21 (0.05, 0.37) [H]	C Medium
Vroegindeweij 1997[103] 9354709	1993-1995 (65 yr)	Fem-Pop (18%)	Balloon	0%/8% (ITT)	12 mo	24 (27)	nd	0.78 (0.81)	(NS) [G]	B Medium
Zdanowski 1999[105] 10811511	nd (73 yr)	SFA (85%)	Balloon	0%/0% (no)	12 mo	15 (17)	0.48 (0.42) median	6 w/ABI ↑≥0.10 (8)	OR=0.63 (0.13, 3.1)	C Medium

continued

Table 29. Ankle brachial index (ABI): Stent versus PTA, continued

Study Year UI	Intervention Years (Mean Age)	Artery (CLI, % [A])	Stent Type	Xover [B], % (ITT?)	Time	N Stent (Control)	Baseline Stent (Control)	Final Stent (Control)	Net Change (95% CI)	Quality Applicability
Prospective										
		Iliac	**No Data**							
Schillinger 2002[108] 12083502	nd (61 yr)	Iliac (Fontaine IIa-4)	nd	NA	6 mo	63 (74)	0.55 (0.51) median	0.69 (0.73) median	[-0.07] [J] (NS) [G]	C Medium
Retrospective										
		Aorto-iliac	**Balloon**							
Westcott 1998[117] 9540904	nd (56 yr)	Infrarenal aorta (12%)	Balloon	NA	12 mo	9 (7)	0.61 (0.65)	0.85 (0.95)	-0.06 (-0.28, 0.16) [H]	C Narrow
		Fem-Pop	**Self-expand**							
Cho 2003[113] 12668846	1999-2002 (71 yr)	SFA (0%)	Self-expanding	NA	6 mo	14 (26)	0.61 (0.63)	0.93 (0.83)	+0.12 (+0.05, +0.19) [H,K]	C Narrow
			Mixed							
Pozzi Mucelli 2003[115] 12835627	1995-2001 (67 yr)	Fem-Pop (54%)	Balloon or self-expanding	NA	nd	23 (86)	nd	0.96 (0.91)	(NS) [G]	C High

[A] Ischemic rest pain or greater severity.
[B] Percent assigned to PTA who received stent / Percent assigned to stent who received only PTA.
[C] Also 899470749, 9643685101, 1037707947, 15286319102.
[D] In 97 (99) patients at baseline.
[E] Change from baseline in analyzed patients.
[F] Also 1667269956.
[G] Comparison of final values.
[H] Estimated from reported data.
[J] Net difference of median values.
[K] However analysis done by authors (statistical significance of final values) was nonsignificant.

Miscellaneous outcomes

Two RCTs that compared stent to PTA reported other long-term clinical outcomes that were not reported by other studies.

Other vascular events

Becquemin 2003[93] followed patients for up to 4 years after being randomized to Palmaz stent or PTA; 115 received stents and 112 had PTA, 13 percent of whom had secondary stent placement.

A Kaplan-Meier analysis of "survival free of a critical limb ischemia event" (rest pain or tissue necrosis) in the treated leg statistically significantly favored PTA over stent (P=0.02). An approximation of the hazard ratio drawn from the reported figure was 0.65. Notably, this finding was consistent with similar results for clinical status (Table 24), although rates of mortality, amputation, and vascular procedures did not significantly differ.

Acute ischemic events were more common among those with primary stents (3/115) than PTA (0/112), though this difference is not statistically significant (RD 2.6 (95% CI -0.3, 5.5) percent).

"Trash foot," distal embolization of microscopic atherosclerotic debris, was also more common after stent (4/115) than PTA (1/112), which again was not statistically significant (OR 4.0 (95% CI 0.44, 36); RD 2.6 (-1.2, 6.4) percent).

At this point it is worth noting that Becquemin 2003[93] came to the unique conclusion among the trials and other studies that patients had worse outcomes after primary stenting than after primary PTA (with secondary stenting in 13 percent of patients). The study was relatively large, and of good methodological quality and medium applicability. The interventions were performed about a decade ago. The study was not substantially different than other trials of stents versus PTA of femoral popliteal arteries, with one important exception. Almost uniquely, the trial reported using independent, blinded outcome assessors. In addition to the vascular findings above, this trial found that clinical status was also significantly worse in patients who received primary stents. However, no significant differences were found in amputation, reintervention, or mortality rates, or in ABI. The authors describe that intra-stent hyperplasia was responsible for most late failures. The occurrence of hyperplasia peaked within the first 18 months and was stable over longer terms.

Quality of life

The Dutch Iliac Stent Trial[55] compared primary Palmaz stent placement to PTA with secondary stent placement in 43 percent of patients. Quality of life was assessed with the SF-36 health survey[118] at 1, 2, and 5 years. Overall, health-related quality of life improved equally for both groups of patients across quality of life domains and over time. No significant differences were found.

Overall summary of stent versus PTA RCTs (Table 30)

Ten trials with 1190 patients met criteria; seven used balloon expandable stents and three self-expandable stents. Eight stent trials addressed femoral popliteal disease and the change to self-expandable nitinol stents appeared to extend the extent of the atherosclerotic lesion treated. Balloon-expandable stents of the Palmaz type were limited to treating lesions of less than 5 cm (e.g., 2.23 cm mean and 25% occlusions in Cejna 2001), while self-expandable stents permitted treatment of longer lesions and a greater proportion of occlusions (e.g., 10.1 cm mean in

Schillinger 2006 with 40% occlusions; 5.3 cm mean and 45% occlusions in Krankenberg 2007). One trial used treated stents and one used covered stents. Eight included patients with femoral popliteal disease, one iliac, and one tibial. Followup was 6 to 96 months. Three trials were rated good, one fair, and five poor quality.

Overall, the trials found no statistically significant difference in clinical outcomes between primary stent and PTA. When analyzed by specific segment treated the femoral popliteal RCTs did demonstrate some subtle differences. Limited metaanalyses of major amputations (OR 0.76, 95% CI 0.28, 2.05), reinterventions (OR 1.07, 95% CI 0.51, 2.23 for balloon expandable and 0.72, 95% CI 0.37, 1.40 for self-expanding stents in the femoral artery), and mortality (RD 2 percent , 95% CI -1, 4) found no significant differences. An important caveat to the amputation outcome, though, is that on the patients included in the studies mostly did not have chronic limb ischemia and therefore were not at substantial risk of amputation. One larger good quality trial of patients with femoral popliteal lesions (Becquemin 2003[93]) found that clinical status and survival free of critical limb ischemia favored primary PTA over primary stenting, which was ascribed to intrastent hyperplasia. The other good quality trial of femoral popliteal lesions (Schillinger 2002[108]) found that clinical status and survival free of critical limb ischemia favored primary PTA over primary stenting, which was also ascribed to intrastent hyperplasia. Becquemin 2003 demonstrated a higher proportion of adverse "vascular local events" in the PTA + stent group. With the newer nitinol stent Schillinger 2006 observed no difference in worsening by two Rutherford stages, thrombosis or need for ipsilateral reintervention between the PTA group and the stent groups, despite improved maximal walking distance and ABIs in the stent group. This study, however, was marked by a relatively high crossover from the PTA group to the stent group, due to the need for secondary stenting. The more recent study of Krankenberg 2007 similarly showed no difference in improved Rutherford stages and ABIs between the two groups, but an advantage in maximal walking distance for the stent group.

The Dutch Iliac Stent Trial was the only RCT of patients with aorto-iliac disease. It compared selective stenting in one arm (for a post-PTA mean pressure gradient of 10 mm Hg) to primary stenting. In the selective stenting group 43 percent of patients required stents. No differences in quality of life, 3 month ABIs, requirement for reintervention were seen for the two groups, but persistence of PAD symptoms were higher at late followup in the primary stenting group.

The available trials do not provide evidence that primary stenting results in better clinical outcomes than PTA. Except for one trial, studies found similar results despite heterogeneity in patients, disease anatomy, interventions, and study design. However, the trials were generally small, with few events occurring during followup, so the trials do not exclude the possibility of even large differences in effect.

Table 30. Study designs and clinical outcome rates

Study	Artery	Stent*	Xover	Quality	N	Clinical Outcomes (Times outcomes evaluated)					
						Clinical Status	Major Amputation	Reinter-vention	Mortality	Walking distance	Quality of Life
	Iliac	**Balloon**									
Dutch Iliac Stent Trial 1998	Iliac	Bb	43%	Good	279	NS 1-8 yr	NS 6-8 yr	NS 6-8 yr	NS 5.6 yr	NS 1-2 yr	NS 1-5 yr
	Fem-Pop	**Self-exp**									
Krankenberg 2007	SFA	Sb	11%	Good/ Poor	244	NS 1 yr		NS 1 yr	NS 1 yr	~+32 m‡ 1 yr	
Schillinger 2006	SFA	Sb	32%	Good	104	NS 1-2 yr	NS 1-2 yr	NS 2 yr	NS 1 yr	**+125 m‡** NS 1 yr 2 yr	
Saxon 2003	SFA	Sc	6%	Poor	28	NS 0.5-2 yr					
		Balloon									
Becquemin 2003	SFA	Bb	13%	Good	227	**OR 2†** 4 yr	NS 4 yr	NS 4 yr	NS 4 yr		
Cejna 2001	FP	Bb	13%	Fair	154	NS 1 yr		NS 1 yr	NS 1 yr		
Grimm 2001	SFA	Bb	0%	Poor	53			NS <1 yr	NS nd	NS nd	
Vroegindeweij 1997	FP	Bb	0%	Poor	51	NS 1 yr					
Zdanowski 1999	SFA	Bb	0%	Poor	29	NS 1 yr					
	Tibial	**Balloon**									
Rand 2006	Tibial	Bt	3%	Poor	45		NS 0.5 yr	NS 0.5 yr			
Metaanalysis (95% CI) [No. trials in metaanalysis]						--	OR 0.76 (0.28, 2.05) [5 trials]	--#	RD 2% (-1, 4%) [6 trials]	--	--

CI, confidence interval; FP, femoral popliteal; nd, no data; NS, nonsignificant; OR, odds ratio; SFA, superficial femoral artery; Xover, crossover; yr, year
* Stent type used: B, balloon; S, self-expanding; b, bare; c, covered; t, treated.
† Favor PTA; also significant differences in survival free of a chronic limb ischemia event (HR ~0.65, P=.02).
‡ Difference in walking distance at 12 mo, favor stent.
# Limited metaanalyses among 5 trials in the femoral popliteal arteries: OR 1.07 (0.51, 2.23) [3 trials; balloon expandable bare stents] and OR 0.72 (0.37, 1.40) [2 trials; self-expanding covered stents)

3.4.2 Stent versus Bypass

Description of studies (Tables 31 & 32)

One trial[76] and one retrospective study[111] compared patients who had stent insertion with patients who had bypass.

In the trial, a nitinol (self-expanding) stent exoskeleton supporting an ultrathin expanded ePTFE graft was compared to femoral popliteal bypass with either an ePTFE or Dacron conduit. The trial included 86 patients with superficial femoral artery lesions; 50 limbs in 40 patients were treated with stent versus 50 limbs in 46 patients which were treated with bypass. These patients had adequate runoff and were without significant aorto-iliac disease. The median followup was 18 months. After treatment patients took aspirin and clopidogrel for at least 3 months (or continued on warfarin instead of clopidogrel). Patients receiving stents were statistically significantly older (72 versus 67 years); patients ranged from 40 to 86 years; 39 percent had diabetes, 57 percent had a smoking history, 84 percent had hypertension, 52 percent had hyperlipidemia, and 41 percent had concomitant cardiac disease. Most patients had claudication (72 percent), 14 percent had rest pain, and 14 percent had tissue necrosis. The TASC classification of the patients was also reported: A 3 percent; B 14 percent; C 68 percent; D 15 percent. No data were reported regarding blinding, randomization method, allocation concealment, or use of intention-to-treat analyses. The methodological quality of the study was fair and applicability was rated medium.

In the retrospective study on patients with aorto-iliac disease, 65 patients who received stents (either Palmaz or Wallstent) were compared with 54 patients who received bypass. The mean followup was 22 months. The pattern of aorto-iliac disease was different between the two groups; more patients in the bypass group had category 4 (SVS) lesions, compared to patients in the stent group. The methodological quality of the study was poor and applicability was rated high.

Results

Randomized Controlled Trial

Clinical status: An improvement in SVS classification was reported in 100 percent of the limbs in the stent group compared to 92 percent of the limbs in the bypass group. The overall mean improvement was 2.4 grades in both groups.

Amputation: Limb salvage at 12 months was 98 percent for the stent group and 90 percent for the bypass group (P=0.09).

Mortality: The study reported four patients died during the study period; the result was not stratified by group assignment. The study reported that these patients died from causes unrelated to their infrainguinal atherosclerotic disease.

Ankle-brachial index: At 12 months, the mean improvement in ABI was 0.23 for the stent group versus 0.37 for the bypass group (P=0.11).

Retrospective Study

Mortality: No perioperative death was reported in the stent group; one perioperative death (1.9 percent) (myocardial infarction) was reported in the bypass group. At the time of followup, 3 (4.6 percent) other patients in the stent group and 2 (3.7 percent) other patients in the bypass group died. Two patients had myocardial infarction, one had respiratory failure, and two had metastatic cancer.

Ankle-brachial index: The mean improvement in ABI was 0.40 in both groups.

Summary

One fair quality RCT and one poorly reported retrospective study compared stent with bypass. These studies did not find any statistically significant differences between the use of stent or bypass in the treatment of femoral popliteal disease in terms of clinical improvement, limb salvage rate, mortality, or ABI in an average followup of 18 and 22 months.

Table 31. Amputation and mortality: Stent versus Bypass

Study Year UI	Intervention Years (Mean Age)	Artery (CLI, % [A])	Stent Type	Xover [B], % (ITT?)	Outcome	Time	No. Analyzed Stent (Control)	No. Events Stent (Control)	RD, % (95% CI)	Quality Applicability
RCT										
		Fem-Pop	**Self-expand**							
Kedora 2007[76] 1716520	2004-2005 (69 yr)	Fem-Pop (28%)	Self-expanding, covered	0%/0% (nd)	Clinical status, no improvement	nd	50 limbs (50)	0 (4)	-8.0 (-16, -0.5)	B Medium
					Major amputation	12 mo	50 limbs (50)	1 (5)	-8.0 (-17, 1.2)	
					Mortality	nd	40 (50)	4 (4)	2.0 (-10, 14)	
Retrospective										
		Aorto-iliac	**Balloon**							
Ballard 1998[111] 9685135	1992-1996 (65 yr)	Aorto-iliac (85%)	Balloon	NA	Mortality	22 mo	65 (54)	3 (2)	0.9 (-6.3, 8.1)	C High

[A] Ischemic rest pain or greater severity.
[B] Percent assigned to PTA who received stent / Percent assigned to stent who received only PTA.

Table 32. ABI: Stent versus Bypass

Study Year UI	Intervention Years (Mean Age)	Artery (CLI, % [A])	Stent Type	Xover [B], % (ITT?)	Time	No. Analyzed Stent (Control)	Baseline Stent (Control)	Final Stent (Control)	Net Change (95% CI)	Quality Applicability
RCTs										
		Fem-Pop	**Self-expand**							
Kedora 2007[76] 1716520	2004-2005 (69 yr)	Fem-Pop (27%)	Self-expanding, covered	0%/0% (nd)	12 mo	40 (46)	0.57 (0.46)	0.80 (0.83)	-0.14 (-0.31, 0.03)	B Medium
Retrospective										
		Aorto-iliac	**Balloon**							
Ballard 1998[111] 9685135	1992-1996 (65 yr)	Aorto-iliac (70%)	Balloon	NA	"Early"	65 (54)	nd	-0.4 overall	~0 (NS, implied)	C High

[A] Ischemic rest pain or greater severity.
[B] Percent assigned to PTA who received stent / Percent assigned to stent who received only PTA.

3.4.3 Stent versus Stent

Bare stent versus drug-eluting stent (Tables 33 & 34)

One trial[70,97,119] and one prospective study[109] compared patients who had bare stent insertion with patients who had drug-eluting stent insertion.

The trial compared 47 patients who received a sirolimus coated nitinol (self-expanding) stent with 46 patients who received a bare nitinol stent. All patients had chronic limb ischemia and TASC C superficial femoral artery disease. Mean followup was 24 months. Patients were treated with aspirin for at least 12 months and another antiplatelet drug for at least 3 or 4 weeks. The patients were on average 66 years old (range 38 to 84); 72 percent were male, 39 percent had diabetes, 38 percent were current smokers, 69 percent had hypertension, 63 percent had hyperlipidemia, and 44 percent had concurrent cardiac disease. Half the patients were in SVS classes 1 or 2, half 3 or 4. The authors noted that "the patients who received sirolimus-eluting stents were generally at greater risk of restenosis or complications than the control group"; 57 percent of patients with drug-eluting stents had moderate or severe calcification of their lesions while 35 percent of those with bare stents had calcification (P=0.03). No data were reported regarding blinding, randomization method, allocation concealment, or use of intention-to-treat analyses. The methodological quality of the study was rated fair and the applicability was rated medium. However, the quality of the ABI results was rated poor because the baseline data were not reported.

The prospective study reported 6 months outcomes on 29 patients who received sirolimus-eluting stents compared with 29 patients who received balloon-expandable bare metal stents for bailout after suboptimal PTA in the infrapopliteal arteries. All patients had chronic limb ischemia. More patients had symptomatic cardiac and carotid diseases in the sirolimus group, compared to the bare metal group (ASA 3, 24 versus 7 percent, P=0.03). The methodological quality of the study was poor and applicability was rated medium.

Results

Clinical status: In the trial, both groups of patients showed a sustained improvement in SVS classification over 24 months, any difference between groups was not reported. In the prospective study, the proportion of patients without rest pain at 6 months was 82 percent in the bare stent group versus 92 percent in the sirolimus group (P=0.12).

Reinterventions: In the trial, the target vessel revascularization at 24 months was 22 percent in the bare stent group versus 13 percent in the sirolimus group (difference NS). In the prospective study, target lesion revascularization was 17 percent in the bare stent group versus 4 percent in the sirolimus group (P=0.02). Also, target vessel revascularization was 24 percent in the bare stent group versus 18 percent in the sirolimus group (P=0.32).

Amputation: In the trial at 24 months followup, no patients in either group had amputations. There was no major amputation reported in the prospective study; minor amputation rates were 17 percent in the bare stent group versus 3 percent in the sirolimus group (P=0.04).

Mortality: In the trial, 2 patients (1 complication of coronary bypass, 1 cardiac failure) died in the bare stent group versus 7 patients (1 stroke, 1 pulmonary emboli, 1 cancer, 2 cardiac disease, 2 natural causes) died in the sirolimus group (difference NS). The 6-month mortality in

the prospective study was 2 patients in the bare stent group versus 3 patients in the sirolimus group (P=0.32). All patients died from cardiac causes.

ABI: In the trial, ABI remained increased in both groups for 24 months; there was no statistically significant difference between groups (0.84, bare stent versus 0.90, sirolimus; P=0.13). In the prospective study, ABI at 6 months was 0.90 in the bare stent group versus 0.96 in the sirolimus group (P=0.10).

Summary

One fair quality trial comparing bare stent with sirolimus stent did not find any statistically significant difference in clinical status, reintervention rates, amputation rates, mortality, and ABI outcomes at 24 months followup. One poor quality prospective study found that at 6-month followup, the target lesion reintervention rate and minor amputation rate were lower in the sirolimus group compared to the bare stent group. Baseline characteristics in this study were not entirely comparable as the sirolimus group had more patients with symptomatic cardiac and carotid diseases than the bare stent group.

Stent with brachytherapy versus stent (Tables 35 & 36)

One trial evaluated the effectiveness of vascular brachytherapy with iridium 192 (^{192}Ir) after femoral popliteal stent implantation.[104] This trial evaluated the effect of adding brachytherapy to stent placement; but it did not principally evaluate the relative effect of stents. All patients were at least 50 years old, had a history of claudication (SVS 2 or 3) for more than 3 months or critical limb ischemia, aorto-iliac vessels with adequate inflow, lesion located 10 cm or more from the femoral bifurcation, and residual stenosis greater than 30 percent, severe dissection, or both after PTA and stent implantation. The trial compared 42 patients with ^{192}Ir brachytherapy to 46 patients without. Patients had a mean age of 68 years; 65 percent were male, 39 percent had diabetes, 39 percent had a smoking history, 76 percent had hypertension, and 72 percent had hyperlipidemia. Women were significantly older than men in both groups (stent and ^{192}Ir: 72 versus 65, P=0.05; stent only: 72 versus 66, P=0.04). An ^{192}Ir source delivered a mean activity of 200 GBq (range, 150-366 GBq). Patients who had stents only received sham treatment. Followup was at 12 months. This was a double-blinded trial; patients and investigators in the followup examinations were blinded to the patients' group assignments. Randomization method and allocation concealment were not adequately reported. The analysis was effectively intention-to-treat as there were no crossovers or dropouts, except that fewer than half the patients had followup walking distance or ABI measured. Furthermore, mortality data were incompletely reported. Overall, the methodological quality of the study was rated fair, but ABI and walking distance data were rated poor, because a large proportion of patients did not have post-procedure testing. The study had narrow applicability.

Results

Clinical status: In the trial, clinical success was defined as immediate improvement by at least one clinical category of SVS classification; clinical patency was defined as sustained clinical success without further intervention. At 12 months, the clinical patency was 62 percent in the ^{192}Ir group versus 54 percent in the stent only group (difference NS).Reinterventions: In the trial, the target vessel revascularization at 6 months was 17 percent in the ^{192}Ir group versus 32 percent in the stent only (difference NS).

Mortality: In the trial, 4 patients died of causes unrelated to treatment after 12 months. One patient died of recurrence of disease in the segment treated with a stent. The report did not provide details as to which randomized groups these patients belonged to.

ABI: At 12 months, ABI was 0.91 in the ^{192}Ir group versus 0.71 in the stent only group (difference NS), although only 49 percent of the limbs (compared to before intervention) could be evaluated.

Walking Distance: At 12 months, walking distance was ABI was 384±294 meters in the ^{192}Ir group versus 329±216 meters in the stent only group (difference NS), although only 41 percent of the patients (compared to before intervention) could be evaluated.

Summary

Limited data from one small trial comparing stenting and the followup use of ^{192}Ir brachytherapy to stenting only without the use of brachytherapy did not find any statistically significant difference in clinical status, ABI, and walking distance outcomes at 12 months followup.

Table 33. Clinical outcomes: Drug-eluting stent versus bare stent

Study Year UI	Intervention Years (Mean Age)	Artery (CLI, % [A])	Stent Type	Xover [B], % (ITT?)	Outcome	Time	No. Analyzed Drug (Bare)	Events	Result	Quality Applicability
RCT										
		Fem-Pop								
Duda 2006[97] 17154704	≥2001 (66 yr)	SFA (SVS 3+4 57%)	Self-expanding (drug vs. bare)	0%/0% (nd)	Clinical status (SVS 3-4)	18 mo	39 (38)	1 (1)	OR 0.97 (NS)	B Medium
						24 mo	34 (38)	2 (3)	OR 0.73 (NS)	
					Major Amputation	24 mo	47 (46)	0 (0)	RD 0	
					Mortality	24 mo	47 (46)	7 (2)	RD 11 (-1.2, 22)	
					Reintervention	12 mo	47 (46)	4 (6)	RD -4.5 (-17, 8.1)	
						24 mo		6 (10)	RD -9.0 (-24, 6.3)	
Prospective										
		Infrapopliteal								
Siablis 2005[109] 16363898 [C]	2003-2004 (69 yr)	Infrapopliteal (100%)	Balloon (drug vs. bare)	NA	Clinical status (Symptom relief)	6 mo	26 (27)	24 (22)	OR 2.7 (NS)	C Medium
					Major Amputation	6 mo	29 (29)	0 (0)	RD 0	
						12 mo		1 (0)	RD 3 (-6, 13)	
					Minor Amputation	6 mo		1 (5)	RD -14 (-29, 1.5)	
						12 mo		3 (5)	RD -7 (-25, 11)	
					Mortality	6 mo	29 (29)	3 (2)	RD 3.4 (-11, 18)	
						12 mo		4 (3)	RD 3.4 (-13, 20)	
					Reintervention	6 mo	29 (29)	4 (5)	OR 0.77 (NS) RD 3.4 (-22, 15)	
						12 mo		7 (8)	OR 0.84 (NS) RD 3.4 (-26, 19)	

[A] Ischemic rest pain or greater severity.
[B] Percent assigned to PTA who received stent / Percent assigned to stent who received only PTA.
[C] Also 17484536110.

Table 34. ABI: Drug-eluting stent versus bare stent

Study Year UI	Intervention Years (Mean Age)	Artery (CLI, % [A])	Stent Type	Xover [B], % (ITT?)	Time	No. Analyzed Drug (Bare) Stent	Baseline Drug (Bare) Stent	Final Drug (Bare) Stent	Net Change (95% CI)	Quality Applicability
RCT										
		Fem-Pop								
Duda 2006[97] 17154704	≥2001 (66 yr)	SFA (SVS 3+4 57%)	Self-expanding (drug vs. bare)	0%/0% (nd)	24 mo	35 [47 base] (37 [46 base])	~0.67 (~0.63)	0.90 (0.84)	(NS) [C]	C Medium
Prospective										
		Infrapopliteal								
Siablis 2005[109] 16363898 [D]	2003-2004 (69 yr)	Infrapopliteal (100%)	Balloon (drug vs. bare)	NA	6 mo	29 (29)	0.71 (0.76)	0.96 (0.90)	0.11 (0.02, 0.20) [E]	C Medium

[A] Ischemic rest pain or greater severity.
[B] Percent assigned to PTA who received stent / Percent assigned to stent who received only PTA.
[C] Comparison of final values.
[D] Also 17484536[110].
[E] Estimated from reported data.

Table 35. Clinical status and reintervention: Stent+Brachy versus Stent

Study Year UI	Intervention Years (Mean Age)	Artery (CLI, % [A])	Stent Type	Xover [B], % (ITT?)	Outcome	Time	No. Analyzed Stent+Brachy (Stent)	Events	OR (Significance)	Quality Applicability
RCT										
		Fem-Pop								
Wolfram 2005[104] 15987985	1999-2002 (68 yr)	Fem-Pop (13%)	Balloon or self-expanding	0%/0% (nd)	Clinical status (Improvement SVS)	12 mo	42 (46)	26 (25)	1.37 (NS)	B Narrow
						24 mo		24 (23)	1.33 (NS)	
					Reintervention	6 mo	42 (46)	14 (10)	1.78 (NS) [RD 12 (-7, 30)]	

[A] Ischemic rest pain or greater severity.
[B] Percent assigned to PTA who received stent / Percent assigned to stent who received only PTA.

Table 36. Walking distance and ABI: Stent+Brachy versus Stent

Study Year UI	Intervention Years (Mean Age)	Artery (CLI, % [A])	Stent Type	Xover [B], % (ITT?)	Outcome	Time	No. Analyzed Stent+Brachy (Stent)	Baseline Stent+Brachy (Stent)	Final Stent+Brachy (Stent)	Net Change (95% CI)	Quality Applicability
RCTs											
		Fem-Pop									
Wolfram 2005[104] 15987985	1999-2002 (68 yr)	Fem-Pop (Fontaine 2-4 100%)	Balloon or self-expanding	0%/0% (nd)	Walking distance	12 mo	17 [37 base] (12 [33 base])	147 [C] (113)	384 (329)	21 (-118, 160) [D]	C Narrow
					ABI	6 mo	30 [46 base] (28 [42 base])	0.55 (0.60)	0.74 (0.89)	-0.10 (-0.20, 0.001) [D]	
						12 mo	19 [46 base] (24 [42 base])		0.71 (0.91)	-0.15 (-0.26, -0.04) [D]	

[A] Ischemic rest pain or greater severity.
[B] Percent assigned to PTA who received stent / Percent assigned to stent who received only PTA.
[C] Only among those without chronic limb ischemia or orthopedic problems; 3.2 km/hr and 12° incline; maximal distance was 700 m.
[D] Estimated from reported data.

3.4.4 Procedure-Related Complications

Postoperative complications (Tables 37 & 38; Figure 14)

Studies

Fifteen studies reported on postoperative complications within 30 days of the procedures. All reported major complications (though one only implied that there were no complications[104]).[56,76,79,93,94,98,101,104,105,109,112-116] Six of the studies also explicitly reported minor complications.[76,94,101,104,109,112] Several studies reported complications for all evaluated patients but did not clarify which intervention the patients had, and are thus not included here.

Eight of the RCTs reported major complications.[56,76,93,94,98,101,104,105] The remaining studies included one prospective comparative study[109] and six retrospective comparative studies.[79,112-116] All but three of the studies compared stent placement with PTA. Wolfram 2005[104] compared stent with and without brachytherapy; Siablis 2005[109] compared bare and drug-eluting stents; Kedora 2007[76] compared stent to bypass surgery. The reporting times varied from peri- and postoperative to 30 days, including one study that included bleeding only during the hospitalization and one that did not report the timing.

Outcome definitions

This report uses the general definition for major complications used by most studies, namely a post-procedure complication, within 30 days of the procedure, that requires additional interventions such as surgery, medical therapy, prolonged hospitalization, or that has a substantive negative impact on patient health or well-being. When necessary, we reclassified complications to meet this definition. Minor complications were those that required at most conservative treatment, not requiring subsequent interventions.

Results

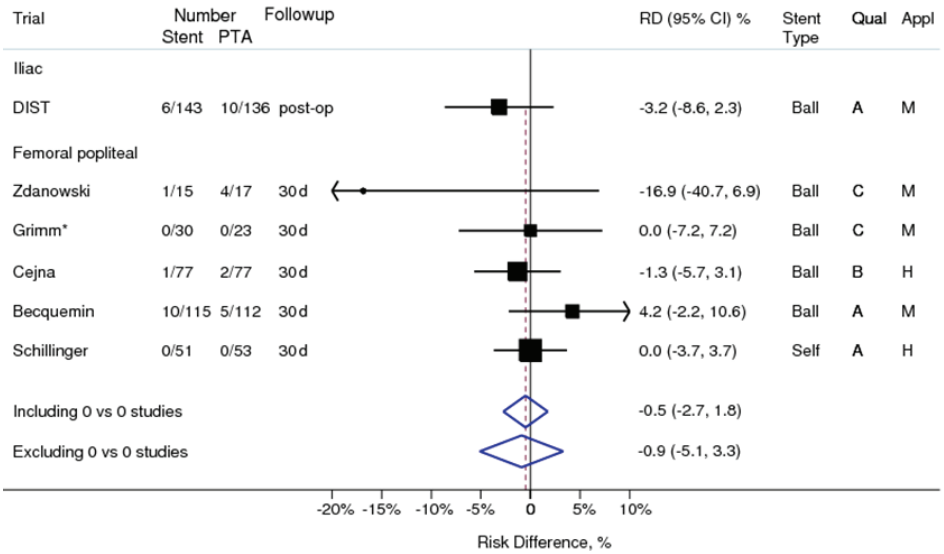
Across the studies the rate of major complications after stent placement ranged from 0 percent (5 studies) to 13 percent (3 of 23 patients), with a median of 3 percent (Table 37). In total, 31 of 792 patients (3.9 percent by metaanalysis) receiving stents were reported to have major complications. After PTA, between 0 percent (5 studies) and 24 percent (4/17) of patients had major complications, with a median of 1.5 percent. In total, 43 of 1212 patients (3.5 percent by metaanalysis) receiving PTA were reported to have major complications. One of the 46 patients who had bypass had major complications.

Among the six RCTs that compared stent and PTA, two had no major complications after either procedure and no statistically significant differences in rates of major complications were found between the two procedures (ranging from -17 to +4.2 percent). The summary risk difference of major complications was -0.5 percent (95% CI, –2.7 to 1.8 percent; favoring stents) (Figure 14). Among the six retrospective studies that compared PTA and stent, three had no episodes of major complications and the risk difference of major complications after stent versus PTA ranged from 0 to +11 percent, without statistical significance. The retrospective studies used a variety of stent types. The studies are insufficient to adequately assess differences in complication rates for differences in anatomy, stent or balloon types, patient characteristics, or other factors.

Six studies reported on minor complications after either stent, PTA, or bypass (Table 38). Interpretation of the results of this outcome is complicated by the inconsistent reporting of the

outcome and by the subjective nature of what constitutes a minor complication (as opposed to a nonreported event). One study[94] reported only that there was no significant difference in the number of minor complications between patients receiving stent or PTA. Minor complications were reported in 0 to 29 percent (6/29) of patients after stent and in 2 to 4 percent of patients after PTA. None of the risk differences was statistically significant. The RCT that compared stent to bypass found no difference in rates of minor complications. The two studies that compared different stent interventions also found no differences in minor complication rates.

Figure 14. Random effects model metaanalysis of risk difference for major complications in stent versus PTA trials



* Grimm implied that no major complications were observed, without clearly stating so.

Appl: applicability (H, high; M, medium; N, narrow); Ball: balloon expandable; CI: confidence interval; d: days; DIST: Dutch Iliac Stent Trial; Qual: quality (A, good; B, fair; C, poor); RD: Risk difference; Self: self-expanding.

Summary

Across 15 studies that compared either stent placement to PTA, stent to bypass, or different stent interventions, no consistent or statistically significant differences were found in either major or minor complication rates. Metaanalysis of stent versus PTA RCTs also found no difference in major complications rates The evidence suggests no difference in rates of major and minor complications among interventions, though the small number of studied patients precludes a definitive conclusion regarding relative risks of complications. The evaluation of minor complications is also inconclusive due to the incomplete reporting and the subjective nature of this outcome across studies. Whether differences in patient, clinician, or intervention characteristics affect complication rates could not be assessed.

Table 37. Major Complications

Study, Year UI	Intervention Years (Mean Age)	Artery (CLI, % [A])	Stent Type	Xover [B], % (ITT?)	Time	No. Analyzed Stent (Control)	No. Events (Details) Stent 1	Stent 2	PTA	Bypass	RD, % (95% CI)	Quality Applicability
RCT												
		Iliac										
Dutch Iliac Stent Trial 1998[56] 16371580 [C]	1993-1996 (58 yr)	Iliac (7%)	Balloon	43%/nd (ITT)	Post-op	143 (136)	6		10 [D]		1.9 (-1.7, 5.5)	A Medium
		Fem-Pop										
Krankenberg 2007[40] 17592075	2004-2005 (66 yr)	SFA (3%)	Self-expanding	11%/nd (both)	12 mo	121 (123)	2[E]		3[F]		-0.8 (-4.3, 2.8)	A Medium
Becquemin 2003[93] 12618680	1995-1997 (67 yr)	SFA (21%)	Balloon	13%/1% (ITT)	30 d	115 (112)	10 [G]		5 [G]		4.2 (-2.2, 11)	A Medium
Cejna 2001[94] 11200349	1994-1997 (67 yr)	Fem-Pop (86%)	Balloon	13%/1% (ITT)	30 d	77 (77)	1 [H]		2 [H]		-1.3 (-5.7, 3.1)	B High
Schillinger 2007[102] 17502568 [J]	2003-2004 (66 yr)	SFA (13%)	Self-expanding	32%/nd (ITT)	30 d	46 (42)	0		0		0	A High
Wolfram 2005[104] 15987985	1999-2002 (68 yr)	Fem-Pop (13%)	Balloon or self-expanding	0%/0% (nd)	<1 mo	46 (42 [K])	1 [L]	1 [L]				B Narrow
Kedora 2007[76] 1716520	2004-2005 (69 yr)	Fem-Pop (27%)	Self-expanding, covered	0%/0% (nd)	Post-op	40 (46)	1 [M]			1 [N]	0.3 (-6.1, 6.7)	B Medium
Grimm 2001[98] 9203369	nd (70 yr)	SFA (79%)	Balloon	0%/0% (nd)	Post-op	30 (23)	0		0		0	C Medium
Zdanowski 1999[105] 10811511	nd (73 yr)	SFA (85%)	Balloon	0%/0% (no)	30 d	15 (17)	1 [P]		4 [Q]		-17 (-41, 7)	C Medium
Prospective												
		Infrapopliteal										
Siablis 2005[109] 16363898 [R]	2003-2004 (69 yr)	Infrapopliteal (100%)	Balloon (drug vs. bare)	NA	30 d	29 (29)	1 [S]	0 [T]			3.4 (-3.2, 10)	C Medium
Retrospective												
		Mixed										
Burns 2000[112] 11232893	1997-1998 (69 yr)	Aorto-iliac 47% Fem-Pop 43% (nd, included gangrene)	nd	NA	Hospitalization	34 (206)	3 [U]		2 [V]		7.8 (-1.8, 17)	C High
		Aorto-iliac										
Kudo 2005[79] 16171589	1993-2004 (67 yr)	Iliac (50%)	Balloon or self-expanding	29%/NA (NA)	Peri-op	34 (117)	0		0		0	C High
Laxdal 2007[114] 17258418	1990-2003 (55 yr)	Infrarenal aorta (0%)	Balloon or self-expanding	NA	30 d	17 (13)	0		0		0	C Narrow

continued.

Table 37. Major Complications, continued.

Study, Year UI	Intervention Years (Mean Age)	Artery (CLI, % [A])	Stent Type	Xover [B], % (ITT?)	Time	No. Analyzed Stent (Control)	No. Events (Details)		RD, % (95% CI)	Quality Applicability
Retrospective										
		Fem-Pop								
Schillinger 2003[116] 12877612	1998-2000 (71 yr)	SFA (29%)	Balloon	NA	Peri-op	58 (357)	3	18 [W]	0.1 (-6.0, 6.3)	C High
Pozzi Mucelli 2003[115] 12835627	1995-2001 (67 yr)	Fem-Pop (54%)	Balloon or self-expanding	NA	30 d	23 (86)	3 [X]	2 [X]	11 (-3, 25)	C High
Cho 2003[113] 12668846	1999-2002 (71 yr)	SFA (0%)	Self-expanding	NA	nd	14 (26)	0	0	0	C Narrow

[A] Ischemic rest pain or greater severity.
[B] Percent assigned to PTA who received stent / Percent assigned to stent who received only PTA.
[C] Also 8994707[57], 9643685[95], 10377079[55], 15286319[96].
[D] Hematoma, arterial wall perforation, acute occlusion, embolism, vasovagal collapse.
[E] False aneurysm.
[F] False aneurysm, arteriovenous fistula.
[G] Thrombosis, embolus, arterial rupture, introducer site problems.
[H] Unclear what the complication was.
[J] Also 16672699[101].
[K] Plus brachytherapy.
[L] Distal embolization requiring embolectomy (classified as minor complication by authors).
[M] Limb pain.
[N] Lymphocele.
[P] Bleed, embolus.
[Q] Myocardial infarction, bleed.
[R] Also 17484536[110].
[S] Sirolimus; myocardial infarction.
[T] Bare.
[U] Hematoma, false aneurysm, immediate occlusion, embolus.
[V] Arterial rupture, embolus.
[W] Vessel ruptures, emboli, AVF, pseudoaneurysm
[X] Hematoma, embolism.

Table 38. Minor Complications

Study, Year UI	Intervention Years (Mean Age)	Artery (CLI, % [A])	Stent Type	Xover [B], % (ITT?)	Time	No. Analyzed Stent (Control)	No. Events (Details) Stent 1	Stent 2	PTA	Bypass	RD, % (95% CI)	Quality Applicability
RCT												
		Fem-Pop										
Krankenberg 2007[40] 17592075	2004-2005 (66 yr)	SFA (3%)	Self-expanding	11%/nd (both)	12 mo	121 (123)	6[C]		1[D]		-4.1 (-0, 8.3)	A Medium
Cejna 2001[94] 11200349	1994-1997 (67 yr)	Fem-Pop (86%)	Balloon	13%/1% (ITT)	30 d	77 (77)	NS [E]		NS [E]		nd	B High
Wolfram 2005[104] 15987985	1999-2002 (68 yr)	Fem-Pop (13%)	Balloon or self-expanding	0%/0% (nd)	<1 mo	46 (42 [F])	4 [G]	3 [F,H]			0.6 (-11, 10)	B Narrow
Schillinger 2007[102] 17502568 [J]	2003-2004 (66 yr)	SFA (13%)	Self-expanding	32%/nd (ITT)	30 d	46 (42)	0		1 [K]		-2.4 (-7.0, 2.2)	A High
Kedora 2007[76] 1716520	2004-2005 (69 yr)	Fem-Pop (27%)	Self-expanding, covered	0%/0% (nd)	Post-op	40 (46)	3 [L]			2 [M]	3.2 (-6.9, 13)	B Medium
Prospective												
		Infrapopliteal										
Siablis 2005[109] 16363898 [N]	2003-2004 (69 yr)	Infrapopliteal (100%)	Balloon (drug vs. bare)	NA	30 d	29 (29)	6 [P, Q]	5 [Q, R]			3.4 (-17, 24)	C Medium
Retrospective												
		Mixed										
Burns 2000[112] 11232893	1997-1998 (69 yr)	Aorto-iliac 47% Fem-Pop 43% (nd, included gangrene)	nd	NA	Hospitalization	34 (206)	1 [S]		8 [T]		-0.9 (-7.2, 5.3)	C High

[A] Ischemic rest pain or greater severity.
[B] Percent assigned to PTA who received stent / Percent assigned to stent who received only PTA.
[C] Hematoma, dissection, closure device failure.
[D] Dissection.
[E] No significant difference between interventions. Number of events not reported.
[F] Plus brachytherapy.
[G] Pseudoaneurysm, bleed.
[H] Pseudoaneurysm.
[J] Also 16672699[101].
[K] Peripheral embolization.
[L] Dissection, edema, hematoma.
[M] Seroma, superficial wound dehiscence.
[N] Also 17484536[110].
[P] Sirolimus.
[Q] Hematoma, pseudo-aneurysm.
[R] Bare.
[S] Hematoma.
[T] Hematoma, embolus.

Postoperative bleeding (Tables 39-41; Figure 15)

Studies

Fourteen studies reported on postoperative bleeding within 30 days of the procedure. Seven of these studies explicitly reported major bleeding events[93,94,100,105,112,114,115] while seven reported other postoperative complications but did not describe major bleeding, implying that no patients experienced this complication.[76,79,98,103,104,109,117] Six of these studies also reported minor bleeding events.[76,79,104,109,112,117]

Eight of the RCTs reported on bleeding.[76,93,94,98,100,103-105] The remaining studies included one prospective comparative study[109] and five retrospective comparative studies.[79,112,114,115,117] All but three of the studies compared stent placement with PTA. Wolfram 2005[104] compared stent with and without brachytherapy; Siablis 2005[109] compared bare and drug-eluting stents; Kedora 2007[76] compared stent to bypass surgery. The reporting times varied from peri- and postoperative to 30 days, including one study that included bleeding only during the hospitalization and one that did not report the timing.

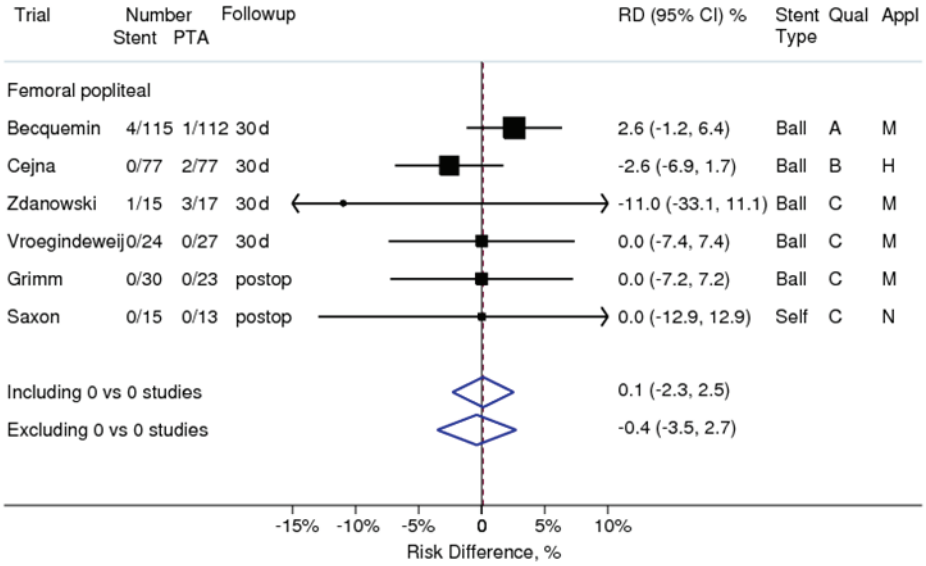
Outcome definitions

Slightly different definitions were used for major bleeding, though the general concept was the same for all studies. Bleeding was defined as major if the patients required blood transfusions, surgery or other invasive intervention to stop the bleeding, or that prolonged hospital stay or affected the patient's general health. Across studies, bleeding was defined as minor if only local hematomas occurred that required only conservative treatment (such as local pressure).

Results

Across the studies the rate of major bleeding after stent placement (Tables 39 & 40) ranged from 0 percent (10 studies) to 7 percent (1 of 15 patients). In total, 7 of 554 patients (1.3 percent by metaanalysis) receiving stents were reported to have major bleeding. After PTA, between 0 percent (5 studies) and 18 percent (3/17) of patients had major bleeding. In total, 10 of 597 patients (1.7 percent by metaanalysis) receiving PTA were reported to have major bleeding. None of the 40 patients who had bypass had major bleeding. Among the six RCTs that compared stent and PTA, three had no episodes of major bleeding after either procedure and no statistically significant differences in rates of major bleeding were found between the two procedures. The summary risk difference of major bleeding was 0 percent (95% CI -2.3 to 2.5 percent). Excluding trials with no events in both arms resulted in similar estimates (Figure 15). One study had 3 percent more bleeding (absolute difference) after stent placement[93] and two had 3 and 11 percent more bleeding after PTA[94,105]; these three studies used balloon-expanded stents so all patients effectively had balloon angioplasty. Among the four retrospective studies that compared PTA and stent, two had no episodes of major bleeding and the risk difference of major bleeding after stent versus PTA ranged from 0 to +2.5 percent, without statistical significance. The retrospective studies used a variety of stent types. The studies are insufficient to adequately assess differences in bleeding rates for differences in anatomy, stent or balloon types, patient characteristics, or other factors.

Figure 15. Random effects model metaanalysis of risk differences for major bleeding in trials comparing stents versus PTA



Appl: Applicability (H, high; M, medium; N, narrow); :Ball: balloon expandable; CI: confidence interval; d, days; postop: postoperative period (not clearly defined); PTA, percutaneous transluminal angioplasty; Qual: quality (A, good; B, fair; C, poor); RD: Risk difference; Self: self-expanding.

Only three retrospective studies reported on minor bleeding after either stent (a variety of types) or PTA (Table 41). Minor bleeding was reported in 0 to 8 percent (1/12) of patients after stent and in 1 to 31 percent (4/13) of patients after PTA. None of the risk differences was statistically significant. The RCT that compared stent to bypass found no difference in rates of minor bleeding. The two studies that compared different stent interventions also found no differences in minor bleeding rates.

Summary

Across 14 studies that compared either stent placement to PTA, stent to bypass, or different stent interventions, no consistent or statistically significant differences were found in either major or minor bleeding rates. However, only about 1 percent of patients experienced major bleeding and the studies were relatively small. Metaanalysis of stent versus PTA RCTs also found no difference in major complications rates. The evidence suggests no difference in rates of major and minor bleeding between interventions, though the small number of studied patients precludes a definitive conclusion regarding relative risks of bleeding. It could not be assessed whether differences in patient, clinician, or intervention characteristics affect complication rates.

Table 39. Major Bleeding

Study, Year UI	Intervention Years (Mean Age)	Artery (CLI, % [A])	Stent Type	Xover [B], % (ITT?)	Time	No. Analyzed Stent (Control)	No. Events				RD, % (95% CI)	Quality Applicability
							Stent 1	Stent 2	PTA	Bypass		
RCT												
		Fem-Pop										
Becquemin 2003[93] 12618680	1995-1997 (67 yr)	SFA (21%)	Balloon	13%/1% (ITT)	30 d	115 (112)	4		1		2.6 (-1.2, 6.4)	A Medium
Cejna 2001[94] 11200349	1994-1997 (67 yr)	Fem-Pop (86%)	Balloon	13%/1% (ITT)	30 d	77 (77)	0		2		-2.6 (-6.2, 1.0)	B High
Zdanowski 1999[105] 10811511	nd (73 yr)	SFA (84%)	Balloon	0%/0% (no)	30 d	15 (17)	1		3		-11 (-33, 11)	C Medium
Saxon 2003[100] 12631634	1998-1999 (70 yr)	SFA (SVS 2.3, mean)	Covered, self-expanding	6%/0% (ITT)	Post-op	15 (13)	0		0		0	C Narrow
Retrospective												
		Mixed										
Burns 2000[112] 11232893	1997-1998 (69 yr)	Aorto-iliac 47% Fem-Pop 43% (nd, included gangrene)	nd	NA	Hospitalization	34 (206)	1		1		2.5 (-3.3, 8.2)	C High
		Aorto-iliac										
Laxdal 2007[114] 17258418	1990-2003 (55 yr)	Infrarenal aorta (0%)	Balloon or self-expanding	NA	30 d	17 (13)	0		0		0	C Narrow
		Fem-Pop										
Pozzi Mucelli 2003[115] 12835627	1995-2001 (67 yr)	Fem-Pop (54%)	Balloon or self-expanding	NA	30 d	23 (86)	1		3		0.9 (-8.3, 10)	C High

[A] Ischemic rest pain or greater severity.
[B] Percent assigned to PTA who received stent / Percent assigned to stent who received only PTA.

Table 40. Major Bleeding – No Events

The following studies implied that there was no major bleeding in either arm. They reported adverse events but did not explicitly document major bleeding.

Study, Year UI	Intervention Years (Mean Age)	Artery (CLI, % [A])	Stent Type	Xover [B], % (ITT?)	Time	No. Analyzed				Quality Applic.
						Stent 1	Stent 2	PTA	Bypass	
RCT										
		Fem-Pop								
Wolfram 2005[104] 15987985	1999-2002 (68 yr)	Fem-Pop (13%)	Balloon or self-expanding	0%/0% (nd)	<1 mo	46	42 [C]			B Narrow
Kedora 2007[76] 1716520	2004-2005 (69 yr)	Fem-Pop (27%)	Self-expanding, covered	0%/0% (nd)	Post-op	46			40	B Medium
Grimm 2001[98] 9203369	nd (70 yr)	SFA (79%)	Balloon	0%/0% (nd)	Post-op	30		23		C Medium
Vroegindeweij 1997[103] 9354709	1993-1995 (65 yr)	Fem-Pop (18%)	Balloon	0%/8% (ITT)	1 mo	24		27		C Medium
Prospective										
		Infrapopliteal								
Siablis, 2005[109] 16363898 [D]	2003-2004 (69 yr)	Infrapopliteal (100%)	Balloon (drug vs. bare)	NA	nd	29 [E]	29 [F]			C Medium
Retrospective										
		Aorto-iliac								
Kudo 2005[79] 16171589	1993-2004 (67 yr)	Iliac (50%)	Balloon or self-expanding	29%/NA (NA)	Peri-op	34		117		C High
Westcott 1998[117] 9540904	nd (56 yr)	Infrarenal aorta (12%)	Balloon	NA	Immediate post-op	12		13		C Narrow

[A] Ischemic rest pain or greater severity.
[B] Percent assigned to PTA who received stent / Percent assigned to stent who received only PTA.
[C] Plus brachytherapy.
[D] Also 17484536[110].
[E] Sirolimus.
[F] Bare.

Table 41. Minor Bleeding

Study, Year UI	Intervention Years (Mean Age)	Artery (CLI, % [A])	Stent Type	Xover [B], % (ITT?)	Time	No. Analyzed Stent (Control)	No. Events				RD, % (95% CI)	Quality Applicability
							Stent 1	Stent 2	PTA	Bypass		
RCT												
		Fem-Pop										
Krankenberg 2007[40] 17592075	2004-2005 (66 yr)	SFA (3%)	Self-expanding	11%/nd (both)	12 mo	121 (123)	3		0		2.5 (-0.3, 5.2)	A Medium
Wolfram 2005[104] 15987985	1999-2002 (68 yr)	Fem-Pop (13%)	Balloon or self-expanding	0%/0% (nd)	<1 mo	46 (42 [C])	1	0 [C]			2.2 (-2.0, 6.4)	B Narrow
Kedora 2007[76] 1716520	2004-2005 (69 yr)	Fem-Pop (27%)	Self-expanding, covered	0%/0% (nd)	Post-op	40 (46)	1			0	2.5 (-2.4, 7.3)	B Medium
Prospective												
		Infrapopliteal										
Siablis 2005[109] 16363898 [D]	2003-2004 (69 yr)	Infrapopliteal (100%)	Balloon (drug vs. bare)	NA	30 d	29 (29)	45 [E]	[F]			3.4 (-15, 22)	C Medium
Retrospective												
		Mixed										
Burns 2000[112] 11232893	1997-1998 (69 yr)	Aorto-iliac 47% Fem-Pop 43% (nd, included gangrene)	nd	NA	Hospitalization	34 (206)	1		8		-0.9 (-7.2, 5.3)	C High
		Aorto-iliac										
Kudo 2005[79] 16171589	1993-2004 (67 yr)	Iliac (50%)	Balloon or self-expanding	29%/NA (NA)	Peri-op	34 (117)	0		1		-0.9 (-2.5, 0.8)	C High
Westcott 1998[117] 9540904	nd (56 yr)	Infrarenal aorta (12%)	Balloon	NA	Immediate post-op	12 (13)	1		4		-22 (-52, 7)	C Narrow

[A] Ischemic rest pain or greater severity.
[B] Percent assigned to PTA who received stent / Percent assigned to stent who received only PTA.
[C] Plus brachytherapy.
[D] Also 17484536[110].
[E] Sirolimus.
[F] Bare.

Embolic events (Table 42; Figure 16)

Studies

Seven studies reported on embolic events within 30 days of the procedures.[93,94,100,101,103,104,115] Six of the RCTs reported on emboli and one retrospective comparative study.[115] All but one compared stent placement with PTA. Wolfram 2005[104] compared stent with and without brachytherapy. None evaluated bypass surgery. The reporting times varied from postoperative to 30 days.

Outcome definitions

All but one study reported on emboli that required intervention, presumably due to signs or symptoms of compromised blood flow. Removal of the emboli was achieved with either thrombolysis, aspiration, or embolectomy. Only Becquemin 2003[93] reported on emboli without either describing how the emboli were diagnosed or treated. Saxon 2003[100] reported on both emboli that were asymptomatic and diagnosed by angiography alone and one embolus that required treatment. Only treated emboli are included here.

Results

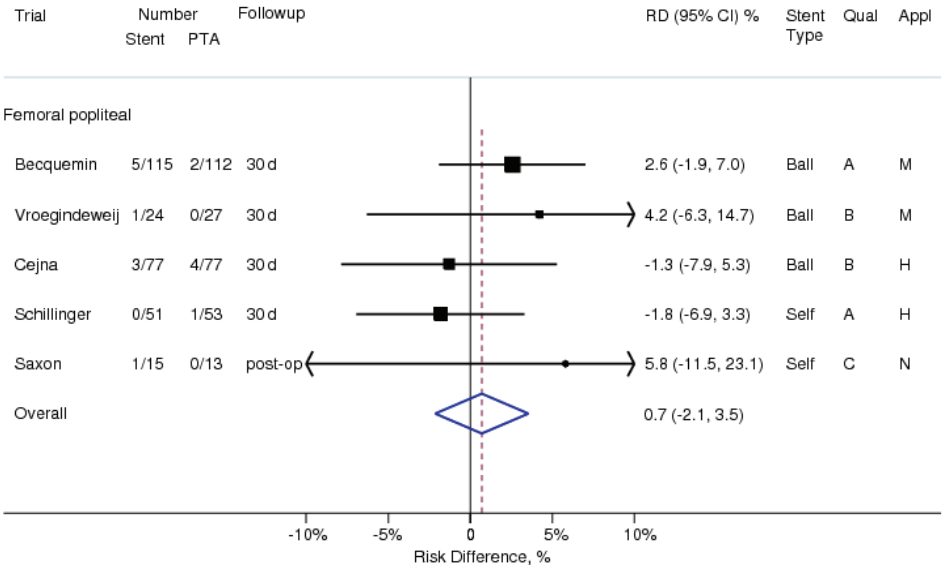
Across the studies the rate of emboli after stent placement ranged from 0 percent (1 study) to 7 percent (1 of 15 patients), with a median of 4 percent. In total, 12 of 393 patients (3.4 percent by metaanalysis) receiving stents had emboli requiring treatment. After PTA, between 0 percent (2 studies) and 5 percent (4/77) of patients had emboli, with a median of 1.5 percent. In total, 8 of 368 patients (2.6 percent by metaanalysis) receiving PTA had emboli.

Among the five RCTs that compared stent and PTA, there were no statistically significant differences in emboli rates between the two procedures (ranging from -1.9 to +6.7 percent). The summary risk difference of major complications was 0.7 percent (95% CI, –2.1 to 3.5 percent; favoring PTA); the RCTs had statistically homogeneous results (Figure 16). The retrospective study similarly found no significant difference in emboli rates. The studies are insufficient to adequately assess differences in emboli rates for differences in anatomy, stent or balloon types, patient characteristics, or other factors.

Summary

Across seven studies that compared either stent placement to PTA, or stent to bypass no consistent or statistically significant differences were found in rates of postoperative emboli requiring treatment. Metaanalysis of stent versus PTA RCTs also found no difference in emboli rates. The evidence suggests no difference in emboli rates among interventions, though the small number of studied patients precludes a definitive conclusion regarding relative risks of complications. It could not be assessed whether differences in patient, clinician, or intervention characteristics affect complication rates.

Figure 16. Random effects model metaanalysis of risk difference for emboli within 30 days in stent versus PTA trials



Appl: Applicability (H, high; M, medium; N, narrow); Ball: balloon expandable; CI: confidence interval; d, days; post-op, postoperative period (not clearly defined); PTA, percutaneous transluminal angioplasty; Qual: quality (A, good; B, fair; C, poor); RD: Risk difference; Sekf: self-expanding.

30-day mortality (Table 43; Figure 17)

Studies

Eight studies reported all-cause mortality within 30 days of followup. These included three RCTs,[93,94,105] one prospective comparative study[109], and four retrospective comparative studies.[79,111,114,115] Six of the studies compared stent to PTA; the prospective study compared bare stents to drug-eluting stents, and one retrospective study compared stent to bypass. Two retrospective studies reported "perioperative" deaths; the rest clearly reported 30-day mortality.

Results

Six of the eight studies had no deaths within 30 days of the procedures. Cejna 2001[94] had two deaths after PTA. One patient died of a myocardial infarction on day 17 and one patient died of sepsis 27 days after PTA. Ballard 1998[111] had one death after surgical bypass in a patient who had a myocardial infarction and cardiac failure. Overall across studies, none of 404 patients who had stents died within 30 days, 2 of 422 patients assigned to PTA died, and 1 of 54 patients who had bypass died perioperatively. None of studies found a significant difference in 30-day mortality between stent and an alternate intervention. The summary risk difference across the three RCTs comparing stents and PTA was –0.3 percent (95% CI -1.9, 1.2 percent).

Table 42. Embolic Events

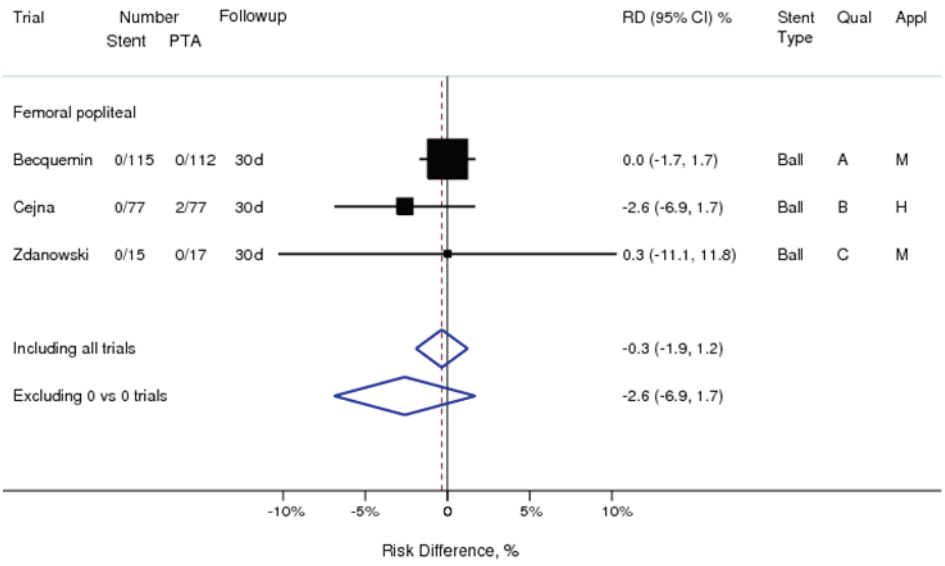
Study, Year UI	Intervention Years (Mean Age)	Artery (CLI, % [A])	Stent Type	Xover [B], % (ITT?)	Time	No. Analyzed Stent (Control)	No. Events				RD, % (95% CI)	Quality Applicability
							Stent 1	Stent 2	PTA	Bypass		
RCT												
		Fem-Pop										
Krankenberg 2007[40] 17592075	2004-2005 (66 yr)	SFA (3%)	Self-expanding	11%/nd (both)	12 mo	121 (123)	0		0		0	A Medium
Becquemin 2003[93] 12618680	1995-1997 (67 yr)	SFA (21%)	Balloon	13%/1% (ITT)	30 d	115 (112)	5		2		2.6 (-1.9, 7.0)	A Medium
Cejna 2001[94] 11200349	1994-1997 (67 yr)	Fem-Pop (86%)	Balloon	13%/1% (ITT)	30 d	77 (77)	3		4		-1.3 (-7.9, 5.3)	B High
Schillinger 2007[102] 17502568 [C]	2003-2004 (66 yr)	SFA (13%)	Self-expanding	32%/nd (ITT)	30 d	51 (53)	0		1		-1.9 (-5.6, 1.8)	A High
Wolfram 2005[104] 15987985	1999-2002 (68 yr)	Fem-Pop (13%)	Balloon or self-expanding	0%/0% (nd)	<1 mo	46 (42 [D])	1	0 [D]			2.2 (-2.0, 6.4)	B Narrow
Vroegindeweij 1997[103] 9354709	1993-1995 (65 yr)	Fem-Pop (18%)	Balloon	0%/8% (ITT)	1 mo	24 (27)	1		0		4.2 (-3.8, 12)	B Medium
Saxon 2003[100] 12631634	1998-1999 (70 yr)	SFA (SVS 2.3, mean)	Covered, self-expanding	6%/0% (ITT)	Post-op	15 (13)	1 [E]		0		6.7 (-6.0, 19)	C Narrow
Retrospective												
		Fem-Pop										
Pozzi Mucelli 2003[115] 12835627	1995-2001 (67 yr)	Fem-Pop (54%)	Balloon or self-expanding	NA	30 d	23 (86)	1		1		3.2 (-5.5, 12)	C High

[A] Ischemic rest pain or greater severity.
[B] Percent assigned to PTA who received stent / Percent assigned to stent who received only PTA.
[C] Also 16672699[101].
[D] Plus brachytherapy.
[E] Also 2 asymptomatic emboli discovered by angiography alone. No treatment required.

Summary

The perioperative mortality after PTA or stent placement is very low. The very small number of perioperative deaths among the studies (none for PTA) precludes an accurate estimate of perioperative mortality. From these studies, though the approximate estimates of perioperative deaths are less than 1 in 400 after stent, about 1 in 200 after PTA, and about 1 in 50 after bypass. However, the evidence does not support any meaningful differences in perioperative mortality.

Figure 17. Random effects model of risk difference of 30 day mortality in stent versus PTA trials



Appl: applicability (H, high; M, medium); Ball: balloon expandable; CI: confidence interval; d: days; RD: Risk difference; PTA, percutaneous transluminal angioplasty; Qual: Quality (A, good; B, fair; C, poor).

Stent Fractures (Table 44)

Studies

Four studies reported rates of stent fractures. These included three RCTs[40,97,101] and one prospective comparative study.[109] The three RCTs all evaluated self-expanding stents in the superficial femoral artery; the prospective study evaluated balloon expanded stents in the infrapopliteal segments. All studies primarily evaluated stent fractures based on ultrasonography, though two of the trials also reported clinical consequences.

Results

The studies found widely varying rates of stent fractures. In the small prospective study of balloon expanded stents in the infrapopliteal arteries, none of 58 stents were found to be fractured at 30 days. Schillinger 2006 also found a low rate of stent fracture (2 percent) in 49 patients receiving self-expanding stents in the superficial femoral artery at 1 year. The article provided no data regarding any clinical consequences of the stent fracture in the on one patient.

Table 43. 30-day mortality

Study, Year UI	Intervention Years (Mean Age)	Artery (CLI, % [A])	Stent Type	Xover [B], % (ITT?)	Time	No. Analyzed Stent (Control)	No. Events (Details) Stent 1	Stent 2	PTA	Bypass	RD, % (95% CI)	Quality Applicability
RCT												
		Fem-Pop										
Becquemin 2003[93] 12618680	1995-1997 (67 yr)	SFA (21%)	Balloon	13%/1% (ITT)	30 d	115 (112)	0		0		0	A Medium
Cejna 2001[94] 11200349	1994-1997 (67 yr)	Fem-Pop (86%)	Balloon	13%/1% (ITT)	30 d	77 (77)	0		2		-2.6 (-6.2, 1.0)	B High
Zdanowski 1999[105] 10811511	nd (73 yr)	SFA (85%)	Balloon	0%/0% (no)	30 d	15 (17)	0		0		0	C Medium
Prospective												
		Infrapopliteal										
Siablis 2005[109] 16363898 [C]	2003-2004 (69 yr)	Infrapopliteal (100%)	Balloon (drug vs. bare)	NA	30 d	29 (29)	0 0 [D]	[E]			0	C Medium
Retrospective												
		Aorto-iliac										
Ballard 1998[111] 9685135	1992-1996 (65 yr)	Aorto-iliac (85%)	Balloon	NA	Peri-op	65 (54)	0			1	-1.9 (-5.4, 1.7)	C High
Kudo 2005[79] 16171589	1993-2004 (67 yr)	Iliac (50%)	Balloon or self-expanding	29%/NA (NA)	Peri-op	34 (117)	0		0		0	C High
Laxdal 2007[114] 17258418	1990-2003 (55 yr)	Infrarenal aorta (0%)	Balloon or self-expanding	NA	30 d	17 (13)	0		0		0	C Narrow
		Fem-Pop										
Pozzi Mucelli 2003[115] 12835627	1995-2001 (67 yr)	Fem-Pop (54%)	Balloon or self-expanding	NA	30 d	23 (86)	0		0		0	C High

[A] Ischemic rest pain or greater severity.
[B] Percent assigned to PTA who received stent / Percent assigned to stent who received only PTA.
[C] Also 17484536[110].
[D] Sirolimus.
[E] Bare.

Krankenberg 2007 found a higher rate of stent fractures (12 percent) in 83 patients with self-expanding stents also in the superficial femoral artery. The article did not report what clinical consequences ensued from the stent fractures, except to note that there was no difference in restenosis rates between those patients with and without stent fractures. The remaining study, Duda 2006, had the highest rate of stent fractures (26 percent, overall) in 65 patients treated with self-expanding stents in the superficial femoral artery at 18 months. This study included patients who were treated earlier (including prior to 2003) than the other studies. All the patients were asymptomatic, though one patient had a prophylactic graft stent placed due to a 12 mm ulcer that was visible at the strut fracture site.

Summary

Overall, only a few studies evaluated stent fracture rates in a total of 255 patients. The rates of stent fractures ranged from 0 percent in the prospective study to 26 percent in a trial that included patients treated prior to those included in other studies. Reporting on clinical consequences were incomplete, but no patients were reported to have clinical symptoms due to the stent fractures while one patient had a prophylactic reintervention due to an ulcer forming at the site of the stent fracture.

Patient or Lesion Characteristics as Predictors of Clinical Outcomes (Table 45)

Only two studies reported subgroup analyses that evaluate potential predictors of clinical outcomes, including one RCT[96] and one retrospective study[79] comparing stent to PTA. The majority of trials that reported analyses of predictors of outcomes evaluated various definitions of patency as the outcome. A review of direct and indirect comparisons of patients by TASC category is in Section 3.3.

The Dutch Iliac Stent Trial compared primary balloon-expandable stent placement in the iliac artery with selective stent placement (43 percent of patients had secondary stent placement based on hemodynamically significant gradients after angioplasty). In a Cox regression, multivariable analysis, they evaluated the risk of reintervention. Since they found no difference in outcome based on intervention group, this variable (primary versus selective stent) was not included in the model.

Kudo 2005 was a retrospective analysis of balloon-expandable stent versus PTA in the iliac artery. In a Cox regression, multivariable analysis, they evaluated the risk of clinical failure, defined as failure to improve by at least one clinical category in the SVS/ISCVS system. It is implied in the article that the variable stent versus PTA was not included in the model.

Table 45 presents the evaluated risk factors in the 2 studies. The only agreement between the two studies of risk factors that predict poor outcome was clinical severity of PAD. The Dutch Iliac Stent Trial found as trend that those with Fontaine III or IV disease were twice as likely to require a reintervention; Kudo 2005 found a similar trend for patients with rest pain (HR=2.45, P=.10) and a strong association of gangrene with clinical failure (HR=6.3, P=.0002).

The two studies came to opposite conclusions as to whether women or men were at higher risk of outcome failure; the Dutch trial found that elevated serum creatinine was not a risk factor, but Kudo 2005 found that patients on hemodialysis faired significantly worse. The Dutch trial also found as a trend that iliac stenosis over 2 cm in length predicted poor outcomes (not evaluated by Kudo 2005) and Kudo found that ipsilateral superficial femoral artery stenosis of at

Table 44. Stent fractures

Study, Year UI	Intervention Years (Mean Age)	Artery (CLI, % [A])	Stent Type	Xover [B], % (ITT?)	Time	No. Events				Clinical Consequences	Quality Applicability
						Balloon, bare	Balloon, drug eluting	Self-expanding, bare	Self-expanding, drug eluting		
RCT											
		Fem-Pop									
Krankenberg 2007[40] 17592075	2004-2005 (66 yr)	SFA (3%)	Self-expanding	11%/nd (both)	12 mo			10/83 (12%)		No difference in restenosis rate between those with and without stent fracture	A Medium
Duda 2006[97] 17154704	≥2001 (66 yr)	SFA (SVS 3+4 57%)	Self-expanding (drug vs. bare)	0%/0% (nd)	18 mo			8/40 (20%)	9/25 (36%)	All asymptomatic. 1 patient had covered graft stent placed prophylactically due to 12 mm ulcer at strut fracture site	B Medium
Schillinger 2006[101,102] 16672699	2003-2004 (66 yr)	SFA (13%)	Self-expanding	32% (ITT)	12 mo			1/49 (2%)		nd	A High
Prospective											
		Infrapopliteal									
Siablis 2005[109] 16363898 [C]	2003-2004 (69 yr)	Infrapopliteal (100%)	Balloon (drug vs. bare)	N/A	30 d	0/29	0/29			NA	C Medium

least 50 percent (compared to vessel occlusion) predicted clinical failure (not evaluated by the Dutch trial).

The two studies agreed that the classic cardiovascular risk factors (tobacco use, hypertension, diabetes, and hypertension) did not predict worse clinical outcomes. Other measures of lesion characteristics or PAD severity (including ABI and walking distance) failed to independently predict poor clinical outcomes.

It is important to note that no study evaluated whether any intervention may be superior to another for any subgroup of patients (for example, whether those with longer occlusions should receive a stent instead of PTA).

Table 45. Predictors of clinical outcomes by multivariable analysis (Cox regression).

Predictor		**Dutch Iliac Stent Trial HR (95% CI)**	**Kudo 2005 HR [P value]**
	Artery (Stent):	Iliac (Balloon)	Iliac (Balloon)
	Outcome:	Reintervention	Clinical Failure*
	Study Design:	RCT	Retrospective
Demographic			
Sex		Female 2.1 (1.2, 3.7)	Male 2.51 [.053]
Age ≥65 yr			2.78 [.025]
Cardiovascular Risk Factors			
Tobacco use		NS	NS
Hypertension		NS	NS
Diabetes		NS	NS
Hyperlipidemia		NS	NS
Kidney disease		NS (elevated Cr)	3.16 [.03] (hemodialysis)
CAD			NS
PAD Severity			
Fontaine III/IV		2.0 (0.9, 4.7)	
Rest pain			2.45 [.10]
Ulcer or gangrene			6.28 [.0002]
ABI (rest or exercise)		NS	
Walking distance		NS	
PAD Characterization			
Iliac stenosis >2 cm		1.6 (0.9, 2.7)	
Common vs. external iliac artery		NS	NS
Lesion morphology		NS	
Patency of runoff vessels		NS	
Former recanalization		NS	
Ipsilateral SFA patent (vs. occluded)			NS
Ipsilateral SFA stenosis >50% (vs. occluded)			3.31 [.02]

* Failure to improve by at least 1 clinical category per SVS/ISCVS.

ABI, ankle brachial index; CI, confidence interval; Cr, serum creatinine; HR, hazard ratio; NS, not statistically significant (not included in multivariable model); RCT, randomized controlled trial; SFA, superficial femoral artery.

Chapter 4. Discussion

Horizon Scan

Key Question 1. Perform horizon scan of published literature on invasive vascular procedures for the treatment of infrarenal PAD (surgical bypass grafting, angioplasty, angioplasty with stent placement, atherectomy). Categorize studies based on intervention; preoperative characteristics of PAD defined by clinical, anatomic, and hemodynamic features (based primarily on TASC II classification schemes[26]); primary outcomes; study design; and sample size.

The systematic horizon scan of the vascular procedures for the treatment of PAD in the lower extremities gives clinicians, researchers, and policymakers a snapshot of the literature, which can be used to identity gaps in knowledge and can help to determine which questions are likely to have been addressed by the literature. The horizon scan gives a broad, but superficial, look at the interventions that have been evaluated, the study designs used, the populations included in studies, and an indication of the outcomes that have been reported. It is important to remember that the horizon scan was based on abstracts and titles, without delving into the full articles or attempting to remove multiple publications of the same studies. The frequencies of variables of interest are only as accurate and complete as what could be gleaned from the abstracts and titles. Notably, 11 percent of citations did not include abstracts, which may have led to an underestimation of the outcomes assessed as well as the number of studies that evaluated the safety of the interventions. However, most of the citations without abstracts were classified as having an unknown study design, and for the comparisons among study designs (where we did not consider the unknown design citations), at least 93 percent of citations had abstracts. Overall, it was common that information about patient characteristics, and even study designs or interventions, were either lacking or too unclear to assess. It also should be assumed that the outcomes reported in the abstracts underrepresent the outcomes analyzed in the full text articles. In general, the findings of the present horizon scan should not be used as an accurate indication of the adequacy of reporting or the quality of the studies.

Review of findings

With these caveats, the most common study design in the published PAD literature is the single arm study. For each intervention, published uncontrolled studies greatly outnumber comparative studies. An argument can be made that there are only a few situations in which a report of a single cohort of patients is of scientific value. One such is when the use of a comparator results in a known outcome rate. For example, if lack of treatment is universally fatal. In this situation, the relative benefit of the tested intervention (compared to the alternate treatment) can be confidently assessed. Data from single cohort studies could also be incorporated into properly adjusted regression analyses to determine predictors of favorable and unfavorable outcomes. In addition, if there is an incremental improvement in technique, then noncomparative studies may help advance clinical knowledge. For PAD interventions, the latter situation is more common, as there have been many incremental changes to surgical, angioplasty, and stent techniques and instrumentation. There is a clear value of disseminating this information without the effort of directly comparing new and old techniques. However, it is unlikely that the approximately 2,000 single arm studies that included hundreds of thousands of patients mostly

represent improvements that could be put into practice by clinicians. Very few of the single arm studies reported evaluation of predictors of outcomes, whether properly adjusted or not. The clinical value, therefore, of the high volume of single arm studies is questionable.

The RCT is the best study design to evaluate efficacy and safety, but RCTs comprise only about 6 percent of the published literature and the sample sizes in these trials were small. The limited number and small sizes of these RCTs not only make the evaluation of the relative efficacy and safety of the interventions difficult, it also calls into question the reliability of the reported findings. A small sample size is likely to counteract the main goal of randomization, achieving groups with similar risks before the start of the intervention. These imbalances could lead to false positive results (concluding that one intervention is superior when it is not); though with small trials, in the setting of a true difference between interventions it is more likely that false negative results will occur, since confidence intervals will be large and statistical significance will be hard to achieve.

In the present horizon scan, we extracted from the abstracts whether or not authors reported statistically significant results as an indication that one intervention was superior to another. We found that 42 percent of studies reported statistically significant results. However, these findings could be misleading, since we counted any statistically significant result regardless of the importance of the outcomes. It is clear that authors preferentially report significant results in their abstracts.

The abstracts emphasized outcomes such as imaging – primarily aimed at patency and percent stenosis – or hemodynamic success. Only about one-third of abstracts reported clinical outcomes. It is plausible that patient-centered outcomes such as symptom relief or changes in quality of life were reported in the full publications but not in the abstracts. However, our analyses of the association between outcomes and TASC grade and our systematic review confirm that clinical outcomes are incompletely reported. There appears to be a reliance among study researchers on the concept that patency, or other surrogate outcomes, are a good indicator of long-term success for the investigated procedures. This is the case despite the unproven value of imaging success as a surrogate measure for clinical outcomes of importance to the patients.[43] Besides being ingrained into both surgical and interventional radiologist literature as the standard there are several likely reasons for the continued frequent measurement of this outcome, including patency's ease of measurement and that the use of patency allows for smaller numbers of patients to be enrolled for the same statistical power than clinical outcomes would require. In addition, there is the appeal of demonstrating that a once-blocked vessel can be successfully cleared. However, this has not been demonstrated for nonacute coronary artery disease[120] nor possibly for renal artery stenosis;[44] mechanical opening might not fully translate into improvement of symptoms. Fewer than a third of the studies reported hemodynamic success (in their abstracts). Despite consensus documents that encourage the use of clinical outcomes,[4,44] fewer than a quarter of studies report symptomatic relief or need for reintervention. Very few studies report quality of life or economic evaluations, clearly important factors to help patients and clinicians to determine the best management. Only about a third of the studies report complication rates in their abstracts, though it is likely that this underestimates the reporting of adverse events in the publications. Nevertheless, given the potentially dire consequences of the more common complications from invasive arterial interventions, increased reporting of complications as primary outcomes would be of value.

Among the studies that reported followup durations, most followed patients for at least 18 to 24 months about a quarter followed patients for at least 3 years. For a simple assessment of the

clinical value of the different interventions, this timeframe is adequate, but longer term followup, of at least 5 years, is needed to provide clinicians and patients with full information for decisionmaking regarding the optimal treatment.

Interestingly, RCTs were twice as likely to evaluate femoral popliteal disease as either nonrandomized comparative studies or single arm studies; however only 10 to 15 percent of studies reported disease anatomy in their abstracts. The explanation for this may simply be that the nonrandomized studies were more likely to take all-comers, instead of having strict eligibility criteria, thus these studies included many more patients with lesions in multiple vessels. This does suggest, however, that patients with aorto-iliac disease may be underrepresented among RCTs. Similarly, though severity of disease was difficult to assess, the horizon scan suggests that RCTs are substantially more likely to include patients with at most claudication (i.e., excluding critical limb ischemia) than noncomparative studies, suggesting an underrepresentation of this population also.

The interventions evaluated were fairly similar across study design types, with the exception that nonrandomized comparative studies were substantially more likely to evaluate surgical bypass than other study designs. Only about 17 percent of studies overall evaluated stent placement; almost half the studies evaluated PTA and/or evaluated bypass. Atherectomy has not been commonly studied. Other treatments have been rarely studied. The most common comparative studies were those in which one surgical intervention was compared to another. Other common comparisons have been between different versions of PTA, PTA versus stent, and (at least among nonrandomized studies) PTA versus bypass. Medical (noninvasive) interventions have been compared to PTA and bypass in 16 and 10 publications, respectively, but only with stents in 2 publications. Brachytherapy has been reported in abstracts of 33 primary studies (in conjunction with an invasive intervention). Overall, bypass surgery and PTA have been heavily studied, but the newer advances in therapy – stents, atherectomy, and brachytherapy – have relatively few studies. In part, this may be due to these therapies' recent development; however, the continued dominance of publications on PTA over stents (and atherectomy) has continued at least through 2006.

The horizon scan demonstrated that there has been a change in research over time. Encouragingly, the exponential growth in single-arm studies stopped in about 1990, while there continues to be rapid growth in comparative studies. Currently, about 20 to 30 comparative studies are published annually. This may signify that frequent assessments for the need for updating any systematic reviews in the field are necessary. Systematic reviews have likewise been growing rapidly in number over the past decade. The interventions being investigated have also changed with time. The number of studies of stents has been growing exponentially since the late 1980, but these studies are still less common than those of PTA alone or bypass. Among single arm studies, the number of studies of PTA peaked in about 1990. For both single-arm and comparative studies, currently, approximately equal numbers of single arm studies of PTA and bypass are published annually. The proportion of studies evaluating different arteries has remained fairly constant since about 1990. Studies evaluating femoral popliteal arteries and those evaluating a combination of arteries are about twice as common as studies of the aorto-iliac arteries.

Finally, the majority of the studies appear to be broadly applicable to the Medicare population in that the average age of patients included in most studies is well over 65 years. Fewer than one-quarter of studies evaluated patients with mean ages below age 65. Relatively few studies excluded patients under age 65.

Horizon scan process

The main purpose of the horizon scan was to learn something about a large body of literature concerning a single topic in an efficient manner. In general, given limited resources, it would not be feasible to conduct a systematic review of all studies across such a large body of literature. A horizon scan permits an overview of the nature of the studies conducted concerning a broad topic. Data obtained from the horizon scan can help focus the formulation of the key questions that could reasonably be asked and answered from conducting a systematic review of relevant and qualifying studies.

Our horizon scan reviewed only data obtained from abstracts; this is not an unreasonable approach given the thousands of abstracts on peripheral arterial vascular interventions. Even though data obtained from abstracts are limited, it is vital that the horizon scan itself be conducted in a systematic manner; otherwise, the information obtained could be fragmented and may not be meaningful. To this end, the kinds of questions that should be asked before undertaking a horizon scan include: what elements of the body of literature are of interest and why? and how is the information gathered from such a scan to be used, given the inherent limitations of abstracts? The answers to these questions are dependent on who is asking the questions and who will use the information (e.g., researcher versus clinician versus payer versus patient versus advocacy group). Therefore, it is important to identify all the stakeholders prior to conducting a horizon scan so that all the relevant questions and issues could be raised and anticipated. Feedback from users of this report should inform future horizon scans.

Our horizon scan and systematic review were conducted as a single project. In the future, it may be preferable to perform a horizon scan first, and then using the results to inform a subsequent systematic review. Data gathered from the horizon scan could help to further refine key questions, by using the knowledge of what studies have been performed and understanding the kinds and quality of the data that are available. This process ought to minimize redundancy and promote efficiency.

We foresee two main challenges for using the horizon scan data. The first is to keep the horizon scan up to date so that policy makers, researchers, and health care providers can base their decisions on a current picture of the field. The second is to create ways to share the actual horizon scan with a greater community. It is crucial that stakeholders have access to the ongoing product to capitalize on the huge enterprise that is necessary in performing a horizon scan. This would require a dedication of resources to update, maintain, and make available the database.

Horizon scan conclusions

In summary, the study publications on invasive interventions for lower extremity PAD are heavily weighted toward single arm (noncomparative) studies of PTA and bypass surgery. Among the comparative studies, most evaluated comparisons between different bypass techniques or different PTA interventions. Relatively few studies compare different categories of interventions. To inform clinicians, patients, and policymakers of the relative value of different techniques, the area that may be most fruitful for summarizing appears to be the comparison between PTA and stent. This comparison is what constituted the second half of our review. The horizon scan suggests that reviews of comparative studies of atherectomy or of brachytherapy are likely to be premature, given the small number of publications. It is reasonable to assume that, similar to what was found for the systematic review of stents, about two-thirds of the potentially interesting publications for other topics would not meet criteria for systematic review. There may however, be some interesting insights to be drawn from the literature of comparisons

between invasive and noninvasive interventions. Most studies appear to follow patients for a reasonable period of time (at least 18 months), but there has been a disproportionate use of imaging outcomes instead of clinically meaningful outcomes. Thus, a large proportion of the evidence provides information only on the mechanical success of opening individual vessels without providing evidence of clinical benefit. As suggested by the rate of reporting in abstracts, complications due to the procedures ought to be given greater prominence also. Future systematic reviews of topics with multiple interventions, patient differences (such as anatomy of disease), and outcomes of interest could well benefit from preliminary horizon scans to help focus (or expand) topics and key questions for the subsequent systematic reviews. For example, with PAD, the limited data found on brachytherapy in the horizon scan or the range of noninvasive interventions in comparative studies could have usefully altered the questions asked and the eligibility criteria of the systematic review.

TASC II Citation Analysis

Key Question 2. Review and describe the studies cited in the TASC II report[26] that support the recommendations regarding choice of intervention. Judge whether the cited studies adequately support the recommendations.

The TASC document made recommendations for the type of interventional therapy, surgery versus endovascular, based on the extent of atherosclerotic involvement.[4] The TASC anatomic categories relate to the extent of disease (length of involvement) and luminal involvement (degree of stenosis or occlusion). In general surgery was recommended for more extensive involvement – TASC C or D – while endovascular therapy was recommended for TASC A or B disease. One would expect that the studies cited as evidence supporting these recommendations would have an anatomic description of the patients treated by a specific therapy. Preferably, the outcomes measured by the studies to assess the effect of the interventions should have been clinically based. However, the cited aorto-iliac surgery studies did not describe the preoperative anatomy and no clinically relevant outcomes were reported. The majority of studies cited for the endovascular treatment of the aorto-iliac segment did have anatomic descriptions of the studied patients, but none used the TASC classification. Most of these studies did report on clinical outcomes.

Similarly, studies cited for recommending endovascular treatment of femoral popliteal disease mostly did not provide anatomic descriptions of the involved segment sufficiently adequate to categorize by TASC classification. Clinically relevant outcomes, however, were employed in almost all of the studies. However, it was striking that only a minority of the relevant evidence for endovascular treatment of PAD was cited by the TASC II report, as compared to our systematic review of the stent literature.

The TASC II report did not fully describe their methods for reviewing or incorporating the evidence into the guideline statements. They stated only that "the Working Group reviewed the literature."[4] They used a 1993 AHRQ guideline on acute pain management to grade the recommendations.[121] This system accounts for the presence of RCTs or other well-conducted clinical studies. It is not clear whether the Working Group used a systematic review approach or if they used a systematic approach to incorporate the evidence known to them into the grades. It is apparent from this review that expert opinion from the TASC participants supplemented the literature citations relating therapeutic recommendations to TASC anatomic classification. It is notable that specific formal recommendations were not made regarding the choice of surgery or

endovascular treatment and that all the recommendations about choice of intervention were graded C "based on evidence obtained from expert committee reports or opinions and/or clinical experiences of respected authorities (i.e., no applicable studies of good quality)."

Systematic Review of TASC Analyses

Key Question 3. Perform a systematic review across invasive vascular interventions for infrarenal PAD for the association between the TASC I or II classification schemes and rates of clinical outcomes (mortality, amputation, clinical stage, reinterventions, and quality of life) after the intervention, accounting for differences in anatomy and interventions.

The TASC classification scheme is a prognostic indicator that also intends to provide guidance on treatment planning. We therefore performed a systematic appraisal of how different TASC grades are associated with clinical outcomes (testing its value as a prognostic indicator), as well as how bypass and PTA compare among patients who have lesions of the same TASC grade (testing its value as a guide to treatment).

It is notable that the majority (85 percent) of 399 papers that evaluated clinical outcomes for invasive vascular procedures that were published after the first TASC report (i.e., 2001) did not report TASC classifications. This is indicative of the small uptake of TASC in clinical research over 7 years since its introduction. Since 2005, the percentage of studies that reported clinical outcomes for patients within specific TASC classifications remains low at 16 percent. It is therefore not surprising that the TASC classification does not have an extensive direct support from clinical data and empirical research.

Only 11 studies reported data providing direct comparisons (among patients included in the same study) of clinical outcomes among TASC grades or between bypass and PTA for a specific TASC grade, and only six reported relevant statistical analyses. These studies tended to be underpowered to detect statistically significant differences across TASC classifications, largely because of small numbers of patients within specific TASC levels. Nevertheless, among direct comparisons across interventions, arteries, and outcomes, there was the common trend that patients with higher levels of disease (more extensive atherosclerotic involvement) had worse clinical outcomes.

We also performed overall graphical analyses of the frequency of clinical events per intervention, artery and TASC subgroup across all studies with available evidence. We provide an overall snapshot of the frequency of clinical events across interventions, TASC grades and arteries. Again, as in the case of direct data, we observed a common trend that poor clinical outcomes occurred more frequently with worsening TASC categories. To some extent, these observations lend support to the face validity of TASC as a predictive classification scheme. However, this body of studies did not provide evidence that any specific treatment resulted in better clinical outcomes for patients in a specific TASC classification.

The majority of the data came from single cohorts of patients where no direct comparisons were reported between interventions or among TASC grades. There were numerous confounding factors related to differing baseline characteristics, eligibility criteria, and treatment thresholds across the studies. Therefore, the current evidence should not be used to draw definitive conclusions on the relative effectiveness of different interventions across arteries or TASC categories. Future analyses of larger studies are needed, focusing on the clinical

significance of a TASC classification as it pertains to expected clinical outcomes and to choice of intervention.

Systematic Review of Stent Studies

Key Question 4. Perform systematic review of the relative safety and effect of peripheral artery stenting with other invasive vascular procedures for occlusive PAD of infrarenal vessels. Also evaluate comparisons of different stents and/or different procedures with stents.

In keeping with our philosophy regarding imaging versus clinical outcomes, this review emphasized the reporting of meaningful and objective clinical outcomes, such as changes in clinical stages of the patients after intervention, walking distance, rate of amputation, rate of reinterventions, complications,- and mortality. We did not evaluate the reporting of primary or secondary patency, commonly used surrogates to gauge clinical success.

Given the large number of possible differences in the manifestations of lower extremity PAD and the large number of different specific interventions possible, there are few comparative studies covering this topic. There are only 10 RCTs comparing PTA to stent that analyzed a total of 1190 patients, with a median of 78 patients per trial. Only one study each compared three other sets of interventions.

Lower extremity PAD mostly affects people in their 60s or older. It was not surprising therefore, to find that the average age of patients in most studies was mid-60s or greater. From this perspective, then, the trials and other comparative studies are moderately to highly applicable to the Medicare population. Many of the studies, though, implicitly or explicitly excluded patients with kidney disease, and therefore on dialysis as well. All the studies were conducted in the US or other western, developed countries, though the racial or ethnic makeup of the patients was rarely reported. As was also found in the horizon scan, the large majority of these studies evaluated patients with femoral popliteal disease alone, even though review of the nonrandomized and noncomparative studies of PAD interventions in general suggests that a large percentage of patients have interventions in multiple arteries.

These trials included patients with either femoral popliteal, superficial femoral artery alone, aorto-iliac, iliac alone, or tibial disease. They included a very wide range in percent of patients with critical limb ischemia (almost the complete range from 0 to 100 percent) and a wide range of patients with cardiovascular risk factors or concomitant cardiac disease. The older trials of balloon expanded stents included only patients with relatively short vascular lesions (e.g., <5 cm). The studies used a variety of stent types, including bare, covered, or treated; and balloon-expandable or self-expanding. Importantly, it is evident that angioplasty and stent technologies continue to change rapidly. Therefore, only a minority of the available evidence are directly applicable to contemporary clinical practice. Though we have evaluated the range of stents that have been researched, several of the stents may have limited applicability in the US, such as the Palmaz stents used by several of the RCTs and the Wallstents and Strecker stents used in other trials. While it may be inevitable, and in many situations appropriate, that the field advances ahead of the publication of definitive evidence, it should be recognized that the evidence for any specific intervention technique for any specific artery segment or severity of disease is sparse at best.

The studies also varied widely in their use of stenting as a secondary intervention in their PTA arms; one of the larger, better quality trials had a crossover rate of 43 percent. Thus, we

found that for each outcome of interest, very few trials, with few patients total, examined sufficiently similar patients with sufficiently similar interventions to allow for confident determinations as to the relative values of the interventions. Despite these limitations, we took the approach of performing metaanalyses (or at least drawing forest plots) for outcomes when feasible and clinically meaningful. Our aim was to use these analyses to form hypotheses about which patients may most benefit from which specific interventions. Unfortunately, as we discuss below, this goal is not yet achievable given the limitations of the data.

Other than the clinical heterogeneity of the studies, the principal limitation of the studies for most outcomes was that too few patients were analyzed, possibly for too short of a duration. This resulted in very small numbers of event rates for most clinical outcomes. The likely reason for this is that most, if not all, investigators designed their studies with imaging success (i.e., patency and/or restenosis) as the primary outcome. The result of this is that for many outcomes fewer than 2 patients in either arm, and often zero, had outcomes of interest. The statistical tools available to analyze these data are generally weak and the levels of uncertainty about any estimate are poor. For this reason, we were forced to use risk difference as the outcome measure, since it can most reliably handle no events in one arm and can provide a meaningful estimate where there are no events in either arm (namely 0), although it does not provide a reliable estimate of the confidence interval. However, summarizing risk differences across studies, particularly with metaanalysis, is problematic, since a particular risk difference must be interpreted in light of a particular underlying risk of the event (the rate in the control arm, control rate). While odds ratios and relative risks are generally stable over a range of control rates across studies, risk differences tend to change considerably with different control rates. However, despite these caveats, we found that trial results were generally statistically homogeneous (similar) for risk difference or odds ratio even given the clinical heterogeneity of the studies and a range of control rates. Despite the general statistical homogeneity, our conclusions about the summary estimates of relative rates must remain weak, given the great limitations of the analyses and the clinical heterogeneity of the studies.

Individual trials (and other studies) did find statistically significantly better clinical outcomes with one intervention or the other, but overall, the trials and other comparative studies failed to provide adequate data to show that any one intervention is superior for any outcome over any other intervention in any group of patients. However, for the most part, the data cannot be said to convincingly show that stent and PTA (or the other comparisons) are equivalent. The studies are clinically too heterogeneous and both individually and collectively too small to accurately estimate relative differences in clinical event rates.

Notably, the ACC/AHA guidelines document commented on the lack of difference between PTA and stenting for femoral popliteal lesions and was based on many of the RCTs presented in the current analysis with the exception of the recently published Krankenberg 2007. The group did suggest that stenting may have a higher technical success rate and may help salvage an immediate failure of a PTA. They did conclude that there has been an improved technical success rate with stents, their advantage in salvaging immediate PTA failures or correcting arterial stenosis after PTA.

Clinical status was measured with a wide range of metrics, with little uniformity, though most studies that reported changes in clinical status did report a measure related to the SVS (Rutherford) categories. While most of the trials did report clinical status, greater consistency in metrics would have been of greater value to compare and summarize the studies and to inform patients and clinicians. The studies mostly found no difference in clinical status regardless of

planned (primary) intervention. The principal exception was one good quality, medium applicability trial (Becquemin 2003[93]), which found that patients assigned to stent had significantly worse clinical status during 4 years of followup. As described in the Results section (Miscellaneous), this trial came to the unique conclusion that overall for femoral popliteal disease, primary stent patients with Palmaz stents had worse clinical (and imaging) outcomes than primary PTA (with 13 percent crossover) patients. It is unclear why the patients in this trial faired differently from those in similar trials, though the investigators did describe that intra-stent hyperplasia was responsible for most failures. Across studies, about three-quarters of patients reported clinical improvement compared to baseline at 1 and 2 years, about two-thirds at 4 years, but (in one trial[56]) only about one-third of patients maintained clinical improvement by 6 to 8 years. At 1 or 2 years, critical limb ischemia occurred between 0 and about 7 percent of patients, though it affected 16 percent of patients at 6 to 8 years.

There is no evidence for differences in major or minor amputation rates between interventions, though the estimates are very uncertain and even large effects favoring either intervention cannot be excluded. In addition, the patients included in the studies mostly did not have chronic limb ischemia and therefore were not at substantial risk of amputation. Only 4 RCTs and one other study evaluated this outcome for PTA versus stent. About half the studies reported rates of reinterventions, including repeat PTA or stent placement, or bypass surgery, at least 6 months after the initial procedure. As with amputations, no difference was found between interventions but large effects cannot be excluded. Across 5 RCTs, there was no significant difference in all-cause mortality rates, with a wide confidence interval (a risk difference of about 3 to 4 percent around zero).

Only 3 RCTs measured treadmill walking distance, though each used a different specific measure. One trial of patients with superficial femoral artery disease found a statistically significant increase in walking distance after stent at 12, but not 24 months. The other two trials found no difference. The evidence regarding the relative effect of stenting on ankle-brachial index (ABI) is heterogeneous, with some studies finding a significantly greater improvement after stent placement than PTA alone, but overall, the studies mostly suggest no difference in ABI at followup, regardless of intervention; however, transient improvement after stent placement for superficial femoral artery lesions is possible. Of note, among the outcomes evaluated, ABI is the one outcome that is imperceptible to the patient and that may be only a poor surrogate outcome for true clinical outcomes.

Quality of life was investigated by only one trial of primary Palmaz stenting and primary PTA with secondary stenting in 43 percent of patients. At 1, 2, and 5 years, health-related quality of life improved equally for both groups of patients across quality of life domains.

Five studies (3 RCTs) evaluated either stent versus bypass, drug-eluting versus bare stent, or stent with and without brachytherapy. No significant differences in clinical outcomes were found for stent versus bypass or bare versus drug-eluting stents, with the exception of a significant improvement in ABI 6 months after stent, in a small unadjusted nonrandomized study. No significant difference in clinical outcomes was reported in one small trial of brachytherapy.

Overall, across studies, only two provided analyses of risk factors for poor clinical outcomes. Both an RCT and a retrospective study of stent versus PTA (or selective stenting) for iliac disease performed multivariable analyses. The trial evaluated reinterventions and the retrospective study evaluated clinical failure. Both had found no difference between the interventions, so these were not included in the regression. Only clinical severity of disease

predicted poor clinical outcomes in both studies (though as a trend only in the trial). The two studies came to opposite conclusions about which sex was at higher risk of a poor outcome, but both agreed that the classic cardiovascular risk factors failed to predict poor clinical outcomes. Importantly, no study evaluated whether any one intervention was superior for a particular group of patients based on demographics, comorbid conditions, or PAD characteristics.

Complication rates (within 30 days) were reported in 10 of 12 RCTs, only 1 of 4 prospective nonrandomized studies, and all 8 retrospective studies. The outcomes were major and minor complications (overall), major and minor bleeding, embolic events requiring intervention, and 30-day mortality (all-cause). For all complications, no significant differences in events were reported or were evident from metaanalysis, although as with clinical outcomes, the analyses suffered from clinical heterogeneity and insufficient event rates (sample sizes) to accurately estimate rates. Overall, almost 4 percent of patients had major complications (requiring additional intervention or that had a substantial negative impact on patient health or well-being), regardless of PAD intervention. Less than 2 percent of patients had major postprocedural bleeding (requiring transfusion or an intervention to halt the bleeding). About 3 percent of patients had an embolic event related to the invasive intervention. Thirty-day mortality was rare; perioperatively, none of about 400 patients assigned to stent died, 2 of about 400 patients assigned to PTA died, and 1 of 54 patients who had bypass died.

In summary, despite a large volume of literature that has evaluated interventions for PAD, including 10 RCTs that directly compare primary stenting with PTA (or selective stenting), there is little definitive evidence of the relative benefits or harms of the different invasive interventions. There is a dearth of trials of patients with either aorto-iliac or infrapopliteal disease. The newer nitinol stents were used by only three of these trials (plus one RCT of stent versus bypass and two RCTs comparing different stents). The predominant primary outcome of the trials remains patency (variously defined), which has not yet been adequately shown to be an excellent predictor of clinical outcomes. True clinical outcomes have frequently been inadequately or incompletely reported and analyzed. This is a major limitation of the quality of the clinical outcomes data for several of the trials. Examples include failure to measure the outcome (e.g., ABI) in a large percentage of patients, failure to fully define the outcome (e.g., major versus minor amputation, reintervention), and failure to adequately analyze the outcome (e.g., walking distance). Furthermore, few patients have been enrolled and analyzed in the currently available trials. Only 1190 patients have been analyzed in the 10 PTA versus stent trials, with a median of 78 patients per trial. These numbers are inadequate to measure long-term clinical outcomes, the outcomes of most interest to patients and decisionmakers.

To be able to assess the true relative value of stent placement compared to PTA, it is important that future trials analyze more clearly defined questions, use greater methodological rigor, and use appropriate clinical outcomes. This includes clearly defining what the population being analyzed is (by diseased artery, lesion morphology, and clinical severity) and what the intervention and comparator is (preferably analyzing stent to PTA, with minimal crossover, since high rates of secondary stenting make the study results difficult to interpret). The primary outcomes should be important clinical outcomes, not surrogate outcomes such as patency (or even ABI). Researchers should choose the best standardized, clinically meaningful and useful measures of outcomes, particularly for potentially subjective outcomes such as “clinical status.” Trials should be adequately powered to fully evaluate these clinical outcomes, with allowance made to capture long-term followup. And complications and other safety outcomes should be fully and actively solicited and analyzed. Until high quality trials are published that address these

issues and study the patients for whom the interventions are actually being used, the value of stent placement compared to PTA for patients with PAD will remain unclear.

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Appendix A. Search Strategy

Databases:
Ovid MEDLINE(R) (mesz), Ovid MEDLINE(R) Daily Update (mesx), Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations (prem), CCTR

#	Search History	Results
1	Exp Stents/ or exp Vascular Surgical Procedures/ or exp Angioplasty, Balloon/	100,204
2	Exp Atherectomy/	1,690
3	Exp Limb Salvage/	634
4	Exp Brachytherapy/	11,438
5	embolectomy/ or endarterectomy/ or thrombectomy/ or saphenous vein/ or blood vessel prosthesis implantation/	26,032
6	or/1-5	119,355
7	Exp Intermittent Claudication/ or exp Peripheral Vascular Diseases/ or peripheral artery disease.mp.	13,868
8	Arterial occlusive diseases/ or arteriosclerosis/	74,855
9	Arteriosclerosis Obliterans/	3,571
10	Critical limb ischemia.mp.	527
11	or/7-10	88,845
12	Exp graft occlusion, vascular/	6,711
13	*femoral artery/ or *iliac artery/ or *popliteal artery/ or *tibial arteries/	16,553
14	12 or 13	22,595
15	6 and 11	10,758
16	6 and 14	8,553
17	15 or 16	16,270
18	Limit 17 to humans [Limit not valid in: Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations,CCTR; records were retained]	**14,815**

Appendix B. Excluded Articles (and Reasons)

Abando A, Akopian G, Katz SG. Patient sex and success of peripheral percutaneous transluminal arterial angioplasty. Archives of Surgery. 2005. 16103285
Not stent vs other

Ansel GM, Silver MJ, Botti CF, Rocha-Singh K, Bates MC, Rosenfield K, Schainfeld RM, Laster SB, Zander C. Functional and clinical outcomes of nitinol stenting with and without abciximab for complex superficial femoral artery disease: a randomized trial. Catheterization & Cardiovascular Interventions. 2006. 16408299
Not stent vs other

Aoki J, Colombo A, Dudek D, Banning AP, Drzewiecki J, Zmudka K, Schiele F, Russell ME, Koglin J, Serruys PW, TAXUS II Study Group. Peristent remodeling and neointimal suppression 2 years after polymer-based, paclitaxel-eluting stent implantation: insights from serial intravascular ultrasound analysis in the TAXUS II study. Circulation. 2005. 16344384
No clinical outcomes (st v other)

Ascher E, Marks NA, Hingorani AP, Schutzer RW, Mutyala M. Duplex-guided endovascular treatment for occlusive and stenotic lesions of the femoral-popliteal arterial segment: a comparative study in the first 253 cases. Journal of Vascular Surgery. 2006. 17055689
Not stent vs other

Ascher E, Marks NA, Schutzer RW, Hingorani AP. Duplex-guided balloon angioplasty and stenting for femoropopliteal arterial occlusive disease: an alternative in patients with renal insufficiency. Journal of Vascular Surgery. 2005. 16376200
Not stent vs other

Bauermeister G. Endovascular stent-grafting in the treatment of superficial femoral artery occlusive disease. Journal of Endovascular Therapy: Official Journal of the International Society of Endovascular Specialists. 2001. 11491267
Not stent vs other

Beier F, Gyongyosi M, Raeder T, von Eckardstein-Thumb E, Sperker W, Albrecht P, Spes C, Glogar D, Mudra H. First in-human randomized comparison of an anodized niobium stent versus a standard stainless steel stent--an intravascular ultrasound and angiographic two-center study: the VELA study. Clinical Research in Cardiology. 2006. 16799877
Not PAD

Benedek I. Interventional treatment with autoexpandable stents in iliofemoral arterial diseases. Romanian Journal of Internal Medicine. 2005. 16812983
Not stent vs other

Bonvini R, Baumgartner I, Do DD, Alerci M, Segatto JM, Tutta P, Jager K, Aschwanden M, Schneider E, mann-Vesti B, Greiner R, Mahler F, Gallino A. Late acute thrombotic occlusion after endovascular brachytherapy and stenting of femoropopliteal arteries. Journal of the American College of Cardiology. 2003. 12575967
Not stent vs other

Cambria RA, Farooq MM, Mewissen MW, Freischlag JA, Seabrook GR, Crain MR, Goldblatt MI, Paz-Fumagalli R, Towne JB. Endovascular therapy of iliac arteries: routine application of intraluminal stents does not improve clinical patency. Annals of Vascular Surgery. 1999. 10541614
Not stent vs other

Costanza MJ, Queral LA, Lilly MP, Finn WR. Hemodynamic outcome of endovascular therapy for TransAtlantic InterSociety Consensus type B femoropopliteal arterial occlusive lesions. Journal of Vascular Surgery. 2004. 14743134
No clinical outcomes (st v other)

Duda SH, Bosiers M, Lammer J, Scheinert D, Zeller T, Tielbeek A, Anderson J, Wiesinger B, Tepe G, Lansky A, Mudde C, Tielemans H, Beregi JP. Sirolimus-eluting versus bare nitinol stent for obstructive superficial femoral artery disease: the SIROCCO II trial. Journal of Vascular & Interventional Radiology. 2005. 15758128
Early subgroup of later publication

Duda SH, Pusich B, Richter G, Landwehr P, Oliva VL, Tielbeek A, Wiesinger B, Hak JB, Tielemans H, Ziemer G, Cristea E, Lansky A, Beregi JP. Sirolimus-eluting stents for the treatment of obstructive superficial femoral artery disease: six-month results. Circulation. 2002. 12234956
Early subgroup of later publication

Funovics MA, Lackner B, Cejna M, Peloschek P, Sailer J, Philipp MO, Maca T, Ahmadi A, Minar E, Lammer J. Predictors of long-term results after treatment of iliac artery obliteration by transluminal angioplasty and stent deployment. Cardiovascular & Interventional Radiology. 2002. 12447561
Not stent vs other

Galaria II, Davies MG. Percutaneous transluminal revascularization for iliac occlusive disease: long-term outcomes in TransAtlantic Inter-Society Consensus A and B lesions. Annals of Vascular Surgery. 2005. 15818461
No clinical outcomes (st v other)

Greenberg D, Rosenfield K, Garcia LA, Berezin RH, Lavelle T, Fogleman S, Cohen DJ. In-hospital costs of self-expanding nitinol stent implantation versus balloon angioplasty in the femoropopliteal artery (the VascuCoil Trial). Journal of Vascular & Interventional Radiology. 2004. 15466792
No original data

Hanekamp CE, Koolen JJ, den HP, Schalij MJ, Piek JJ, Bar FW, De S, Bonnier HJ, Pijls NH, Venestent Study Group. Randomized study to compare balloon angioplasty and elective stent implantation in venous bypass grafts: the Venestent study. Catheterization & Cardiovascular Interventions. 2003. 14624420
Graft lesion

Hassen-Khodja R, Sala F, Declemy S, Bouillanne PJ, Batt M, Staccini P. Value of stent placement during percutaneous transluminal angioplasty of the iliac arteries. Journal of Cardiovascular Surgery. 2001. 11398035
<80% stent arm actually had stent

Hausegger KA, Lammer J, Hagen B, Fluckiger F, Lafer M, Klein GE, Pilger E. Iliac artery stenting--clinical experience with the Palmaz stent, Wallstent, and Strecker stent. Acta Radiologica. 1992. 1633038
Not stent vs other

Henry M, Amor M, Ethevenot G, Henry I, Mentre B, Tzvetanov K. Percutaneous endoluminal treatment of iliac occlusions: long-term follow-up in 105 patients. Journal of Endovascular Surgery. 1998. 9761574
No clinical outcomes (st v other)

Kiesz RS, Buszman P, Martin JL, Deutsch E, Rozek MM, Gaszewska E, Rewicki M, Seweryniak P, Kosmider M, Tendera M. Local delivery of enoxaparin to decrease restenosis after stenting: results of initial multicenter trial: Polish-American Local Lovenox NIR Assessment study (The POLONIA study). Circulation. 2001. 11136681
Not PAD

Krajcer Z, Sioco G, Reynolds T. Comparison of Wallgraft and Wallstent for treatment of complex iliac artery stenosis and occlusion. Preliminary results of a prospective randomized study. Texas Heart Institute Journal. 1997. 9339507
N<10 per arm

Kruse JR, Cragg AH. Safety of short stay observation after peripheral vascular intervention. Journal of Vascular & Interventional Radiology. 2000. 10693712
Not stent vs other

Kudo T, Chandra FA, Ahn SS. The effectiveness of percutaneous transluminal angioplasty for the treatment of critical limb ischemia: a 10-year experience. Journal of Vascular Surgery. 435. 15838475
Not stent vs other

Kuribayashi S, Takamiya M, Homma S. Intravascular ultrasound observations during iliac stent deployment. International Angiology. 1999. 10811513
No clinical outcomes (st v other)

Long AL, Page PE, Raynaud AC, Beyssen BM, Fiessinger JN, Ducimetiere P, Relland JY, Gaux JC. Percutaneous iliac artery stent: angiographic long-term follow-up. Radiology. 1991. 1831274
Not stent vs other

Lopez-Galarza LA, Ray LI, Rodriguez-Lopez J, Diethrich EB. Combined percutaneous transluminal angioplasty, iliac stent deployment, and femorofemoral bypass for bilateral aortoiliac occlusive disease. Journal of the American College of Surgeons. 1997. 9060920
Not stent vs other

Lorenzi G, Domanin M, Costantini A, Rolli A, Agrifoglio G. Role of bypass, endarterectomy, extra-anatomic bypass and endovascular surgery in unilateral iliac occlusive disease: a review of 1257 cases. Cardiovascular Surgery. 1994. 8049976
<80% stent arm actually had stent

Madera FA, Orecchia PM, Razzino RA, Razzino J, Calcagno D. Balloon angioplasty by vascular surgeons. American Journal of Surgery. 1997. 9293833
Not stent vs other

Martin EC, Katzen BT, Benenati JF, Diethrich EB, Dorros G, Graor RA, Horton KM, Iannone LA, Isner JM, Ramee SR. Multicenter trial of the wallstent in the iliac and femoral arteries. Journal of Vascular & Interventional Radiology. 1995. 8850658
Not stent vs other

Mehilli J, Kastrati A, Wessely R, Dibra A, Hausleiter J, Jaschke B, Dirschinger J, Schomig A, Intracoronary Stenting and Angiographic Restenosis-. Randomized trial of a nonpolymer-based rapamycin-eluting stent versus a polymer-based paclitaxel-eluting stent for the reduction of late lumen loss. Circulation. 2006. 16391155
Not PAD

Minar E, Pokrajac B, Maca T, Ahmadi R, Fellner C, Mittlbock M, Seitz W, Wolfram R, Potter R. Endovascular brachytherapy for prophylaxis of restenosis after femoropopliteal angioplasty : results of a prospective randomized study. Circulation. 2000. 11094034
Not stent

Mousa A, Rhee JY, Trocciola SM, Dayal R, Beauford RB, Kumar N, Henderson P, McKinsey J, Morrissey NJ, Kent KC, Faries PL. Percutaneous endovascular treatment for chronic limb ischemia. Annals of Vascular Surgery. 2005. 15782274
Not stent vs other

Murphy TP, Khwaja AA, Webb MS. Aortoiliac stent placement in patients treated for intermittent claudication. Journal of Vascular & Interventional Radiology. 1998. 9618100
Not stent vs other

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<80% had de novo treatment

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Not stent vs other

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Not stent vs other

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No clinical outcomes (st v other)

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Not stent vs other

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Not stent vs other

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No clinical outcomes (st v other)

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Not stent

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Graft lesion

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Not stent vs other

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Not PAD

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No clinical outcomes (st v other)

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No clinical outcomes (st v other)

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Not stent vs other

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Not stent vs other

Appendix C. Comparative Studies and Systematic Reviews in Horizon scan

RCTs that evaluate PTA

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Nonrandomized comparative studies that evaluate PTA

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