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# Stenting for Peripheral Artery Disease of the Lower Extremities

## An Evidence-Based Analysis

*Presented to the Ontario Health Technology Advisory Committee in May 2010*

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# List of Abbreviations

| | |
|---|---|
| **AAA** | Abdominal Aortic Aneurysm |
| **ABI** | Ankle Brachial Index |
| **ABPI** | Ankle Brachial Pressure Index |
| **ACC/AHA** | American College of Cardiology / American Heart Association |
| **CAD** | Canadian Dollars |
| **CCI** | Canadian Classification of Health Interventions |
| **CCS** | Canadian Cardiovascular Society |
| **CEA** | Cost-Effectiveness Analysis |
| **CFA** | Common Femoral Artery |
| **CI** | Confidence Interval(s) |
| **CIA** | Common Iliac Artery |
| **CLI** | Chronic Limb Ischemia |
| **CT** | Computed Tomography |
| **CTA** | Computed Tomographic Angiography |
| **DSA** | Digital Subtraction Angiography |
| **DES** | Drug Eluting Stent |
| **EIA** | External Iliac Artery |
| **EUR** | European Union Euro Currency |
| **FP** | Femoral Popliteal |
| **ICER** | Incremental Cost-Effectiveness Ratio |
| **ITT** | Intention To Treat |
| **MAS** | Medical Advisory Secretariat |
| **MD** | Mean Difference |
| **MI** | Myocardial Infarction |
| **MRA** | Magnetic Resonance Angiography |
| **NACRS** | National Ambulatory Care Reporting System |
| **NHANES** | National Health and Nutrition Examination Survey |
| **OHISBF** | Ontario Health Insurance Schedule of Benefits and Fees |
| **OHTAC** | Ontario Health Technology Advisory Committee |
| **OR** | Odds Ratio |
| **PAD** | Peripheral Artery Disease |
| **PTA** | Percutaneous Transluminal Angioplasty |
| **RCT** | Randomized Controlled Trial |
| **QALY** | Quality-Adjusted Life Year |
| **QoL** | Quality of Life |
| **RD** | Risk Difference |

| | |
|---|---|
| **RR** | Relative Risk |
| **SCVIR** | Society of Cardiovascular and Interventional Radiology |
| **SD** | Standard Deviation |
| **SFA** | Superficial Femoral Artery |
| **SFPA** | Superficial Femoral-Popliteal Artery |
| **SVS-ISCVS** | Society of Vascular Surgery/International Society of Cardiovascular Surgery |
| **TASC II** | Trans Atlantic Inter-Society Consensus II Working Group |
| **TVR** | Target Vessel Revascularization |
| **USD** | United States Dollars |

# Executive Summary

## Background

## Objective

In January 2010, the Medical Advisory Secretariat received an application from University Health Network to provide an evidentiary platform on stenting as a treatment management for peripheral artery disease. The purpose of this health technology assessment is to examine the effectiveness of primary stenting as a treatment management for peripheral artery disease of the lower extremities.

## Clinical Need: Condition and Target Population

Peripheral artery disease (PAD) is a progressive disease occurring as a result of plaque accumulation (atherosclerosis) in the arterial system that carries blood to the extremities (arms and legs) as well as vital organs. The vessels that are most affected by PAD are the arteries of the lower extremities, the aorta, the visceral arterial branches, the carotid arteries and the arteries of the upper limbs. In the lower extremities, PAD affects three major arterial segments i) aortic-iliac, ii) femoro-popliteal (FP) and iii) infra-popliteal (primarily tibial) arteries. The disease is commonly classified clinically as asymptomatic claudication, rest pain and critical ischemia.

Although the prevalence of PAD in Canada is not known, it is estimated that 800,000 Canadians have PAD. The 2007 Trans Atlantic Intersociety Consensus (TASC) II Working Group for the Management of Peripheral Disease estimated that the prevalence of PAD in Europe and North America to be 27 million, of whom 88,000 are hospitalizations involving lower extremities. A higher prevalence of PAD among elderly individuals has been reported to range from 12% to 29%. The National Health and Nutrition Examination Survey (NHANES) estimated that the prevalence of PAD is 14.5% among individuals 70 years of age and over.

Modifiable and non-modifiable risk factors associated with PAD include advanced age, male gender, family history, smoking, diabetes, hypertension and hyperlipidemia. PAD is a strong predictor of myocardial infarction (MI), stroke and cardiovascular death. Annually, approximately 10% of ischemic cardiovascular and cerebrovascular events can be attributed to the progression of PAD. Compared with patients without PAD, the 10-year risk of all-cause mortality is 3-fold higher in patients with PAD with 4-5 times greater risk of dying from cardiovascular event. The risk of coronary heart disease is 6 times greater and increases 15-fold in patients with advanced or severe PAD. Among subjects with diabetes, the risk of PAD is often severe and associated with extensive arterial calcification. In these patients the risk of PAD increases two to four fold. The results of the Canadian public survey of knowledge of PAD demonstrated that Canadians are unaware of the morbidity and mortality associated with PAD. Despite its prevalence and cardiovascular risk implications, only 25% of PAD patients are undergoing treatment.

The diagnosis of PAD is difficult as most patients remain asymptomatic for many years. Symptoms do not present until there is at least 50% narrowing of an artery. In the general population, only 10% of persons with PAD have classic symptoms of claudication, 40% do not complain of leg pain, while the remaining 50% have a variety of leg symptoms different from classic claudication. The severity of symptoms depends on the degree of stenosis. The need to intervene is more urgent in patients with limb threatening ischemia as manifested by night pain, rest pain, ischemic ulcers or gangrene. Without successful revascularization those with critical ischemia have a limb loss (amputation) rate of 80-90% in one year.

Diagnosis of PAD is generally non-invasive and can be performed in the physician offices or on an

outpatient basis in a hospital. Most common diagnostic procedure include: 1) Ankle Brachial Index (ABI), a ratio of the blood pressure readings between the highest ankle pressure and the highest brachial (arm) pressure; and 2) Doppler ultrasonography, a diagnostic imaging procedure that uses a combination of ultrasound and wave form recordings to evaluate arterial flow in blood vessels. The value of the ABI can provide an assessment of the severity of the disease. Other non invasive imaging techniques include: Computed Tomography (CT) and Magnetic Resonance Angiography (MRA). Definitive diagnosis of PAD can be made by an invasive catheter based angiography procedure which shows the roadmap of the arteries, depicting the exact location and length of the stenosis / occlusion. Angiography is the standard method against which all other imaging procedures are compared for accuracy.

More than 70% of the patients diagnosed with PAD remain stable or improve with conservative management of pharmacologic agents and life style modifications. Significant PAD symptoms are well known to negatively influence an individual quality of life. For those who do not improve, revascularization methods either invasive or non-invasive can be used to restore peripheral circulation.

## Technology Under Review

A Stent is a wire mesh "scaffold" that is permanently implanted in the artery to keep the artery open and can be combined with angioplasty to treat PAD. There are two types of stents: i) balloon-expandable and ii) self expandable stents and are available in varying length. The former uses an angioplasty balloon to expand and set the stent within the arterial segment. Recently, drug-eluting stents have been developed and these types of stents release small amounts of medication intended to reduce neointimal hyperplasia, which can cause re-stenosis at the stent site. Endovascular stenting avoids the problem of early elastic recoil, residual stenosis and flow limiting dissection after balloon angioplasty.

## Research Questions

1. In individuals with PAD of the lower extremities (superficial femoral artery, infra-popliteal, crural and iliac artery stenosis or occlusion), is primary stenting more effective than percutaneous transluminal angioplasty (PTA) in improving patency?

2. In individuals with PAD of the lower extremities (superficial femoral artery, infra-popliteal, crural and iliac artery stenosis or occlusion), does primary stenting provide immediate success compared to PTA?

3. In individuals with PAD of the lower extremities (superficial femoral artery, infra-popliteal, crural and iliac artery stenosis or occlusion), is primary stenting associated with less complications compared to PTA?

4. In individuals with PAD of the lower extremities (superficial femoral artery, infra-popliteal, crural and iliac artery stenosis or occlusion), does primary stenting compared to PTA reduce the rate of re-intervention?

5. In individuals with PAD of the lower extremities (superficial femoral artery, infra-popliteal, crural and iliac artery stenosis or occlusion) is primary stenting more effective than PTA in improving clinical and hemodynamic success?

6. Are drug eluting stents more effective than bare stents in improving patency, reducing rates of re-interventions or complications?

# Research Methods

## Literature Search

A literature search was performed on February 2, 2010 using OVID MEDLINE, MEDLINE In-Process and Other Non-Indexed Citations, OVID EMBASE, the Cochrane Library, and the International Agency for Health Technology Assessment (INAHTA). Abstracts were reviewed by a single reviewer and, for those studies meeting the eligibility criteria, full-text articles were obtained. Reference lists were also examined for any additional relevant studies not identified through the search. The quality of evidence was assessed as high, moderate, low or very low according to GRADE methodology.

### *Inclusion Criteria*

- English language full-reports from 1950 to January Week 3, 2010
- Comparative randomized controlled trials (RCTs), systematic reviews and meta-analyses of RCTs
- Proven diagnosis of PAD of the lower extremities in all patients.
- Adult patients at least 18 years of age.
- Stent as at least one treatment arm.
- Patency, re-stenosis, re-intervention, technical success, hemodynamic (ABI) and clinical improvement and complications as at least an outcome.

### *Exclusion Criteria*

- Non-randomized studies
- Observational studies (cohort or retrospective studies) and case report
- Feasibility studies
- Studies that have evaluated stent but not as a primary intervention

### *Outcomes of Interest*

The primary outcome measure was patency. Secondary measures included technical success, re-intervention, complications, hemodynamic (ankle brachial pressure index, treadmill walking distance) and clinical success or improvement according to Rutherford scale. It was anticipated, a priori, that there would be substantial differences among trials regarding the method of examination and definitions of patency or re-stenosis. Where studies reported only re-stenosis rates, patency rates were calculated as 1 minus re-stenosis rates.

## Statistical Analysis

Odds ratios (for binary outcomes) or mean difference (for continuous outcomes) with 95% confidence intervals (CI) were calculated for each endpoint. An intention to treat principle (ITT) was used, with the total number of patients randomized to each study arm as the denominator for each proportion. Sensitivity analysis was performed using per protocol approach. A pooled odds ratio (POR) or mean difference for each endpoint was then calculated for all trials reporting that endpoint using a fixed effects model. PORs were calculated for comparisons of primary stenting versus PTA or other alternative procedures. Level of significance was set at alpha=0.05. Homogeneity was assessed using the chi-square test, $I^2$ and by visual inspection of forest plots. If heterogeneity was encountered within groups ($P \leq 0.10$), a random effects model was used. All statistical analyses were performed using RevMan 5. Where sufficient data were

available, these analyses were repeated within subgroups of patients defined by time of outcome assessment to evaluate sustainability of treatment benefit. Results were pooled based on the diseased artery and stent type.

## Summary of Findings

**Balloon-expandable stents vs PTA in superficial femoral artery disease**

Based on a moderate quality of evidence, there is no significant difference in patency between primary stenting using balloon-expandable bare metal stents and PTA at 6, 12 and 24 months in patients with superficial femoral artery disease. The pooled OR for patency and their corresponding 95% CI are: 6 months 1.26 (0.74, 2.13); 12 months 0.95 (0.66, 1.38); and 24 months 0.72 (0.34. 1.55).
There is no significant difference in clinical improvement, re-interventions, peri and post operative complications, mortality and amputations between primary stenting using balloon-expandable bare stents and PTA in patients with superficial femoral artery. The pooled OR and their corresponding 95% CI are clinical improvement 0.85 (0.50, 1.42); ankle brachial index 0.01 (-0.02, 0.04) re-intervention 0.83 (0.26, 2.65); complications 0.73 (0.43, 1.22); all cause mortality 1.08 (0.59, 1.97) and amputation rates 0.41 (0.14, 1.18).

**Self-expandable stents vs PTA in superficial femoral artery disease**

Based on a moderate quality of evidence, primary stenting using self-expandable bare metal stents is associated with significant improvement in patency at 6, 12 and 24 months in patients with superficial femoral artery disease. The pooled OR for patency and their corresponding 95% CI are: 6 months 2.35 (1.06, 5.23); 12 months 1.54 (1.01, 2.35); and 24 months 2.18 (1.00. 4.78). However, the benefit of primary stenting is not observed for clinical improvement, re-interventions, peri and post operative complications, mortality and amputation in patients with superficial femoral artery disease. The pooled OR and their corresponding 95% CI are clinical improvement 0.61 (0.37, 1.01); ankle brachial index 0.01 (-0.06, 0.08) re-intervention 0.60 (0.36, 1.02); complications 1.60 (0.53, 4.85); all cause mortality 3.84 (0.74, 19.22) and amputation rates 1.96 (0.20, 18.86).

**Balloon expandable stents vs PTA in iliac artery occlusive disease**

Based on moderate quality of evidence, despite immediate technical success, 12.23 (7.17, 20.88), primary stenting is not associated with significant improvement in patency, clinical status, treadmill walking distance and reduction in re-intervention, complications, cardiovascular events, all cause mortality, QoL and amputation rates in patients with intermittent claudication caused by iliac artery occlusive disease. The pooled OR and their corresponding 95% CI are: patency 1.03 (0.56, 1.87); clinical improvement 1.08 (0.60, 1.94); walking distance 3.00 (12.96, 18.96); re-intervention 1.16 (0.71, 1.90); complications 0.56 (0.20, 1.53); all cause mortality 0.89 (0.47, 1.71); QoL 0.40 (-4.42, 5.52); cardiovascular event 1.16 (0.56, 2.40) and amputation rates 0.37 (0.11, 1.23). To date no RCTs are available evaluating self-expandable stents in the common or external iliac artery stenosis or occlusion.

**Drug-eluting stent vs balloon-expandable bare metal stents in crural arteries**

Based on a very low quality of evidence, at 6 months of follow-up, sirolimus drug-eluting stents are associated with a reduction in target vessel revascularization and re-stenosis rates in patients with atherosclerotic lesions of crural (tibial) arteries compared with balloon-expandable bare metal stent. The OR and their corresponding 95% CI are: re-stenosis 0.09 (0.03, 0.28) and TVR 0.15 (0.05, 0.47) in patients with atherosclerotic lesions of the crural arteries at 6 months follow-up. Both types of stents offer similar immediate success. Limitations of this study include: short follow-up period, small sample and no assessment of mortality as an outcome. Further research is needed to confirm its effect and safety.

# Background

## Objective of Analysis

In January 2010, the Medical Advisory Secretariat received a verbal application from the University Health Network to provide an evidentiary platform on stenting as a treatment management for peripheral artery disease. The purpose of this health technology assessment is to examine the effectiveness of stenting as a treatment management for peripheral artery disease of the lower extremities.

## Clinical Need and Target Population

Peripheral artery disease (PAD) is a progressive disease occurring as a result of plaque accumulation (atherosclerosis) in the arterial system that carries blood to the extremities (arms and legs) as well as vital organs. (1) The vessels that are most affected by PAD are the aorta, its visceral arterial branches and the arteries of the lower extremities. In the lower extremities, PAD affects three major arterial segments i) aortic-iliac, ii) femoral-popliteal (FP) and iii) infra-popliteal (primarily tibial) arteries. The disease is commonly classified clinically as asymptomatic claudication, rest pain and critical ischemia (Appendix 1).

Although the prevalence of PAD in Canada is not known, it is estimated that 800,000 Canadians have PAD. (2) The 2007 Trans Atlantic Intersociety Consensus (TASC) II Working group for the Management of Peripheral Disease estimated that the prevalence of PAD in Europe and North America to be 27 million of whom 88, 000 are hospitalizations involving lower extremity. (3;4) A higher prevalence of PAD among elderly individuals has been reported to range from 12% to 29% (5;6). The National Health and Nutrition Examination Survey (NHANES) estimated that the prevalence of PAD is 14.5% among individuals 70 years of age and over. (5)

Modifiable and non-modifiable risk factors associated with PAD include advanced age, male gender, family history, smoking, diabetes, hypertension and hyperlipidemia. (7-10) PAD is a strong predictor of myocardial infarction (MI), stroke and cardiovascular death. Annually approximately 10% of ischemic cardiovascular and cerebrovascular events can be attributed to the progression of PAD. (11) Compared with patients without PAD, the 10 year risk of all-cause mortality is 3-fold higher in patients with PAD with a 4-5 times greater risk of dying from cardiovascular event. (11) The risk of coronary heart disease is 6 times greater and increases 15-fold in patients with advanced or severe PAD. (11) Among patients with diabetes, the risk of PAD increases two to four fold (10;12) and PAD is often severe and extensive with a greater degree of calcification. The results of the Canadian survey of public survey of knowledge of PAD demonstrated that Canadians are unaware of the morbidity and mortality associated with PAD. (2) Despite its prevalence and cardiovascular risk implications, only 25% of PAD patients are undergoing treatment. (10;13)

The diagnosis of PAD is difficult as most patients remain asymptomatic for many years. Symptoms do not present until there is at least 50% narrowing of an artery. In the general population, only 10% of persons with PAD have classic symptoms of claudication, 40% do not complain of leg pain, while the remaining 50% have a variety of leg symptoms different from classic claudication. (3) The severity of symptoms depends on the degree of stenosis. The need to intervene is more urgent in patients with limb threatening ischemia as manifested by rest pain, ischemic ulcers or gangrene. Without successful revascularization those with critical ischemia have a limb loss (amputation) rate of 80-90% in one year. (11)

Diagnosis of PAD is generally non-invasive and can be performed in the physician office or on an outpatient basis in a hospital. The most common diagnostic procedures include: 1) Ankle Brachial Index

(ABI), a ratio of the blood pressure readings between the highest ankle pressure and the highest brachial (arm) pressure; (Appendix 2); and 2) Doppler ultrasonography, a diagnostic imaging procedure that uses sound waves to evaluate blocked vessels and determine the severity of the disease. Other non invasive imaging techniques include Computed Tomography (CT) and Magnetic Resonance Angiography (MRA). Definitive diagnosis of PAD can be made by an invasive catheter based angiography procedure which shows the roadmap of the arteries, depicting the exact location, length and severity of the stenosis / occlusion. Angiography is the standard method against which all other imaging procedures are compared for accuracy. An overall strategy for evaluating patients in whom PAD is susceptible is shown in Appendix 3.

## Treatment Options for PAD

More than 70% of the patients diagnosed with PAD remain stable or improve with conservative management of pharmacologic agents and life style modifications. Significant PAD symptoms are well known to negatively influence an individual quality of life. For those who do not improve, revascularization methods both invasive and non-invasive can be used to restore peripheral circulation. Treatment for PAD is aimed at improving the blood flow and includes:

***Life style modifications:***

- Smoking cessation
- Controlling diabetes and blood pressure
- Physical activity including supervised walking programs
- Diet with low saturated-fat and low cholesterol

***Pharmacologic Agents:***

Pharmacologic agents for PAD include drugs that are aimed to improve functional status, quality of life (QoL), reduce platelet aggregation, lower cholesterol and improve peripheral blood flow. Primary medications for treatment of PAD include: antiplatelets therapies such as acetylsalicylic acid (ASA), pentoxifylline and cilostazol aimed to prevent blood clots formation; lipid lowering agents such as HMG-CoA reductase inhibitors "statins" are recommended to lower serum cholesterol concentrations and to improve endothelial function and other markers of atherosclerotic risk such as P-selection concentrations; blood pressure lowering therapies such as agiotensin converting (ACE) inhibitors and glucose control agents (oral hypoglycemic agents or insulin) are also recommended. Clopidogrel bisulfate is indicated for the secondary prevention of atherothrombotic events (MI, stroke and vascular death) in patients with athresclerosis documented by stroke, MI or established PAD. The American College of Cardiology / American Heart Association (ACC/AHA) and Canadian Cardiovascular Society (CCS) recommends that PAD be treated with antithrombotic therapy and life-long ASA therapy unless contraindicated. (14;15)

***Balloon Angioplasty:***

Angioplasty is a technique of mechanically widening a narrowed or obstructed blood vessel as a result of atherosclerosis. An empty and collapsed balloon on a guide wire, known as a balloon catheter, is passed into the narrowed locations and then inflated to a fixed size using water pressures. The balloon is then collapsed and withdrawn. It is often called percutaneous transluminal angioplasty (PTA). Balloon angioplasty allows slow vessel stretching to enhance lumen enlargement.

***Atherectomy:***

Atherectomy devices cut and remove atherosclerotic plaque from a vessel wall or grind the atheroma into small particles, allowing them to embolize distally. Elastic recoil is reduced after atherectomy because the lumen is widened without stretching the arterial wall.

***Endarterectomy:***

An endarterectomy involves making an incision in the leg to remove the plaque contained in the inner lining of the diseased artery. This leaves a wide-open artery and restores blood flow through the leg artery. The effectiveness of this method depends upon the particular location and extent of the arterial blockage.

***Bypass Surgery***

Bypass surgery creates a detour around a narrowed, or blocked, section of a leg artery. Bypass, uses one of the veins or a tube made from man-made materials to attach the bypass above and below the area that is blocked. This creates a new path for the blood to flow to the affected leg tissues and is particularly effective for extensive artery blockages.

A summary of known treatment strategies for PAD are shown in Appendix 4.

## Technology Under Review

A stent is a wire mesh "scaffold" that is implanted and remains in the artery to keep the artery open. It can be combined with angioplasty to treat PAD. There are two types of stents: i) balloon-expandable and ii) self-expandable stents and are available in varying length. The former uses an angioplasty balloon to expand and set the stent within the arterial segment. Recently, drug-eluting stents have been developed and these types of stents release small amounts of medication intended to reduce neointimal hyperplasia, which can cause re-stenosis at the stent site. Endovascular stenting avoids the problem of early elastic recoil, residual stenosis and flow limiting dissection after balloon angioplasty. A summary of comparisons of balloon expanding and self expanding stent properties (16) are shown in Table 1.

**Table 1: Comparison of Balloon Expandable and Self Expandable Stents**

| Balloon-Expandable Stent | Self-Expandable Stent |
|---|---|
| • Manufactured in a crimped state and expanded to the vessel diameter by inflating a balloon. | • Manufactured at the vessel diameter or slightly above and are crimped and constrained to a smaller diameter until the intended delivery site is reached. |
| • Can collapse if a critical external pressure is exceeded. Collapse is usually a buckling phenomenon i.e. flattening to a half moon shape. Thus the resistance to collapse is dependent upon lesion eccentricity, localized irregularities etc. | • Have no strength limitations and elastically recover even after complete flattening.<br>• Ideally suited to superficial locations such as femoral and carotid arteries. |
| • Resist balloon expansion process.<br>• Recoils after balloon deflation | • Assist vessel expansion. There is no recoil after inflation. |
| • Without subsequent balloon dilation, balloon expandable stents become smaller in diameter over time. | • Properly oversized self-expandable stents will continue to apply force acting to expand the vessel over time remodeling the vessel profile. |
| • Direct stenting is common with balloon expandable stents. The stent is advanced to the site and expanded. | • Self-expandable stent do not have sufficient stiffness to directly open calcified lesions. They must be pre or post dilated |
| • Crimped onto a balloon and can be | • Are housed in delivery catheters |

dislodged, though rare, during delivery.

## Lower Limb Procedures in Ontario

Figure 1 shows that the number of discharged lower limb procedures in Ontario has been steadily increasing each year from about 1100 in 2004 to about 1300 in 2008. About 29% of these procedures are percutaneous stent implantations.

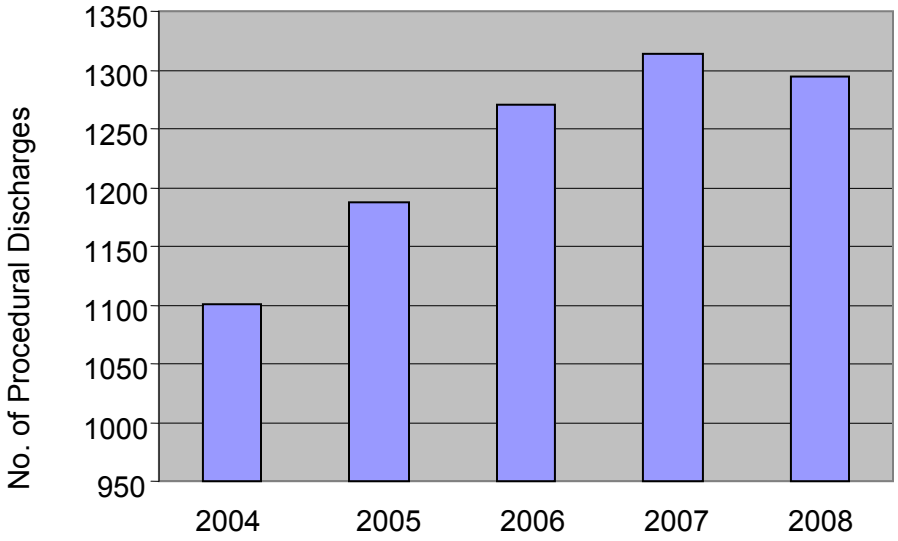



*Figure 1: Number of Lower Limb Procedures in Ontario Over the Last 5 Years*

## Regulatory Status

There are nine types of stents licensed by Health Canada for treatment of PAD of the lower extremities. These stents are licensed as Class IV devices. Table 2 provides their indication.

**Table 2: Endovascular Stents Licensed by Health Canada as of January 2010**

| Manufacturer | Trade Name | License | First Issue Date | Indications |
|---|---|---|---|---|
| ANGIOMED GMBH & CO. MEDIZINTECHNIK KG | Lifestent Vascular Stent and Life Stent XL | 81651 | 2010-01-07 | Intended for primary stenting of de novo or restenotic lesions of the peripheral arteries. |
| ANGIOMED GMBH & CO. MEDIZINTECHNIK KG | Bard E-Luminex Vascular Stent | 74541 | 2007-07-25 | Indicated for the treatment of peripheral occlusive arterial disease (POAD) and is intended to be placed in the iliac and femoral arteries after percutaneous recanalization to keep the vessel open. |
| ANGIOMED GMBH & CO. MEDIZINTECHNIK KG | Bard –Luminex 3 Vascular Stent | 65531 | 2004-08-19 | The Bard LUMINEX 3 Vascular Stent is a stenting device designed to maintain the patency of iliac and femoral arteries. The device includes the self-expanding Bard LUMINEXX 3 Vascular Stent pre-loaded on a flexible delivery system.<br><br>Indicated for residual stenoses with impaired perfusion (pressure gradient) following balloon dilation, especially in stages III and IV according to Fontaine (Appendix 5), dissection- detached arterioschlerotic plaque material and luminal obstruction following balloon dilation, occlusion after thrombolysis or after aspiration and before dilation and re-stenosis or reocclusion |
| ATRIUM MEDICAL CORPORATION | Advanta V12 Iliac PTFE Covered Stent | 81129 | 2009-11-06 | Balloon-expandable stent made of stainless steel and encapsulated with EPTFE graft material. The delivery system comprises an over the wire catheter with a non-compliant balloon. Two radiopaque marker bands indicate the dilating section of the balloon and aid in stent positioning during fluoroscopy. The advanta V12 PTFE encapsulated stent is indicated for restoring and improving the patency of the iliac artery and the renal artery in diameters 5mm-7mm. |
| BIOTRONIK SE & CO. KG | Peripheral Stent System | 67035 | 2005-01-10 | Peripheral self-expanding Nitinol stent system. Indicated for use in patients with atherosclerotic disease of the iliac and femoral arteries and for the treatment of insufficient results after PTA for treating obstructed peripheral arterial diseases by improving luminal diameter. |

| Manufacturer | Trade Name | License | First Issue Date | Indications |
|---|---|---|---|---|
| BOSTON SCIENTIFIC PLYMOUTH TECHNOLOGY CENTRE | Wallstentiliac Endoprosthesis | 9625 | 1999-08-10 | Indicated for use as an adjunct to angioplasty for the treatment of peripheral vascular disease in common and external iliac and superficial femoral arteries of adult patients with a sub optimal PTA result. |
| EV3 INC | Intra Stent Double Strut Stent | 64561 | 2004-05-20 | Indicated for improving luminal diameter in patients with symptomatic atherosclerotic disease of the common and / or external iliac arteries. |
| EV3 INC | IntraCoil Peripheral Vascular Stent | 3251 | 1999-11-16 | The IntraCoil stent is indicated for use in peripheral arteries in the leg in which balloon angioplasty has been applied. The IntraCoil stent is indicated for placement in flexing regions and at tortuous lesions. |
| WILLIAM COOK EUROPE APS | Zilver Vascular Stent | 73251 | 2007-02-05 | Intended for use as an adjunct to PTA in the treatment of symptomatic vascular disease of the iliac arteries. Patients should be suitable for PTA and/or stent treatment. |
| | Drug Eluting Stents | Currently not licensed by Health Canada for peripheral artery disease | | |

## Practice Guidelines for the Management of Patients with PAD

Several practice guidelines including the ACC/AHA and the Canadian Cardiovascular Society Consensus (CCS) for management for PAD are available. (15;17) Most of these guidelines refer to TASC Working Group on management of PAD. This Working Group was formed in 2000 and represents 16 professional societies including vascular surgery, interventional radiology, angiology and cardiology. (4;18) These guidelines represent a consensus among the various specialities that treat PAD. The TASC document provides a clear standardization by anatomic description of the extent and degree of disease in both the 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 of the extent of the lesions. Table 3 below summarizes TASC classification and treatment recommendations for aorto-iliac and femoral-popliteal segments. Although the TASC recommendations are internationally accepted, the Canadian Cardiovascular Society Consensus recommendations expanded the role of percutaneous endovascular intervention taking into account recent improved outcomes as of 2005. (17) The CCS proposed recommendations for using percutaneous endovascular interventions are shown in Table 4.

**Table 3: TASC Classification and Treatment Recommendations for Aorto-Iliac and Femoral-Popliteal Lesions**

| Classification | Aorto-Iliac Lesions | Femoral Popliteal Lesions | Treatment Consensus |
|---|---|---|---|
| TASC A | Unilateral or bilateral stenoses of CIA<br>Unilateral or bilateral single (≤ 3 cm) stenosis of EIA | Single stenosis ≤ 10 cm in length<br>Single occlusion ≤ 5 cm in length | Endovascular therapy is the treatment of choice. |
| TASC B | Short (≤ 3 cm) stenosis of infrarenal aorta.<br>Unilateral CIA occlusion.<br>Single or multiple stenoses totaling 3-10cm involving the EIA not extending into the CFA.<br>Unilateral EIA occlusion not involving the origins of the internal iliac CFA. | Multiple lesions, each ≤ 5 cm (stenosis / occlusions).<br>Single stenosis / occlusion ≤ 10 cm not involving the infrageniculate popliteal artery.<br>Single or multiple lesions in the absence of continuous tibial vessels to improve inflow for distal bypass.<br>Heavily calcified occlusions ≤ 5 cm in length.<br>Single popliteal stenosis. | Endovascular therapy is the preferred treatment.<br><br>The patient's comorbidities, fully informed patient preference, and the local operator'<br><br>s long term success rates must be considered when making treatment recommendations. |
| TASC C | Bilateral CIA occlusions.<br>Bilateral EIA stenosis 3-10cm long, not extending into the CFA.<br>Unilateral EIA stenosis extending in the CFA.<br>Unilateral EIA occlusion that involves the origins of internal iliac and / or CFA.<br>Heavily calcified unilateral EIA occlusion with or without involvement of the origins of internal iliac and / or CFA. | Multiple stenosis or occlusions totaling >15 cm, with or without heavy calcification.<br>Recurrent stenosis or occlusions that need treatment after two endovascular interventions. | Surgery is the preferred treatment for low-risk patients.<br><br>The patient's comorbidities, fully informed patient preference, and the local operators long-term success rates must be considered when making treatment recommendations. |
| TASC D | Infrarenal aorto iliac occlusion.<br>Diffuse disease involving the aorta and both iliac arteries requiring treatment.<br>Diffuse multiple stenoses involving the unilateral CIA, EIA, and CFA.<br>Unilateral occlusions of both CIA and EIA.<br>Bilateral occlusions of EIA.<br>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 (>20cm, involving the popliteal artery and the proximal trifurcation vessels). | Surgery is the treatment of choice |

*Common iliac artery (CIA), external iliac artery (EIA), abdominal aortic aneurysm (AAA), common femoral artery (CFA)*

**Table 4: Canadian Cardiovascular Society Indications and Recommendations for Use of Percutaneous Endovascular Intervention for PAD**

| | Grade |
|---|---|
| 1. Clinical indications for percutaneous interventions of PAD (where technically feasible*) | |
| (a) Severe intermittent claudication that interferes with work or lifestyle despite pharmacological and exercise therapy. | IIC |
| (b) Chronic critical limb ischemia (rest pain, non healing ulcer, gangrene) | |
| 2. Recommendations for iliac artery interventions | |
| (a) Provisional iliac stenting (either balloon-expandable or self-expanding) should be performed following suboptimal PTA results (flow limiting dissection, residual stenosis greater than 30%, residual mean pressure gradient than 5 mmHg, treatment of chronic total occlusions or re-stenosis of previous PTA). | IA |
| 3. Recommendations for femoro-popliteal interventions | |
| (a) Femoral popliteal stents should be deployed in the setting of suboptimal PTA (residual stenosis greater than 30%, flow limiting dissection, mean pressure gradient than 5mmHg or re-stenosis | IB |
| 4. Recommendations for infra-popliteal interventions | |
| (a) Limb salvage of acute or chronic critical limb ischemia | IIC |
| (b) To improve long-term patency of femoral popliteal interventions by improving distal runoff. | IIIC |

**Technical feasibility depends on lesion anatomy, operator experience and equipment availability. Surgery is indicated if the lesions is suitable for or failed percutaneous endovascular intervention.*

# Evidence-Based Analysis

## Research Questions

1. In individuals with PAD of the lower extremities (superficial femoral artery, infra-popliteal, crural and iliac artery stenosis or occlusion), is primary stenting more effective than PTA in improving patency?

2. In individuals with PAD of the lower extremities (superficial femoral artery, infra-popliteal, crural and iliac artery stenosis or occlusion), does primary stenting provide immediate success compared to PTA?

3. In individuals with PAD of the lower extremities (superficial femoral artery, infra-popliteal, crural and iliac artery stenosis or occlusion), is primary stenting associated with less complications compared to PTA?

4. In individuals with PAD of the lower extremities (superficial femoral artery, infra-popliteal, crural and iliac artery stenosis or occlusion), is primary stenting compared to PTA reduce the rate of re-intervention?

5. In individuals with PAD of the lower extremities (superficial femoral artery, infra-popliteal, crural and iliac artery stenosis or occlusion) is primary stenting more effective than PTA in improving clinical and hemodynamic success?

6. Are drug eluting stents more effective than bare stents in improving patency, reducing rates of re-interventions or complications?

## Research Methods

### Literature Search

A literature search was performed on February 2, 2010 using OVID MEDLINE, MEDLINE In-Process and Other Non-Indexed Citations, OVID EMBASE, the Cochrane Library, and the International Agency for Health Technology Assessment (INAHTA). Abstracts were reviewed by a single reviewer and for studies meeting the eligibility criteria; full-text articles were obtained. Reference lists of retrieved articles were also scanned for any additional relevant studies not identified through the initial search. Data were extracted using a standardized data abstraction form.

#### *Inclusion Criteria*

- English language full-reports from 1950 to January Week 3, 2010
- Comparative randomized controlled trials (RCTs), systematic reviews and meta-analyses
- Proven diagnosis of PAD of the lower extremities in all patients.
- Adult patients at least 18 years of age.
- Stent used in at least one treatment arm.
- Patency, re-stenosis, re-intervention, technical success, hemodynamic (ABI) and clinical improvement, mortality, amputation, treadmill walking distance and complications as at least an outcome.

***Exclusion Criteria***

- Non-randomized studies
- Observational studies (cohort or retrospective studies) and case report.
- Feasibility studies
- Not licensed by Health Canada
- Studies that have evaluated stent but not as a primary intervention

***Outcomes of Interest***

The primary outcome measure was primary patency. Secondary measures included technical success, re-intervention, complications, hemodynamic (ABI, treadmill walking distance) and clinical improvement as defined by Rutherford et al (19) (Appendix 6). It was anticipated, a priori, that there would be substantial differences among trials regarding the method of examination and definitions of patency or re-stenosis or secondary outcomes. Where studies reported only re-stenosis rates, patency rates were calculated as 1 minus the re-stenosis rates. Results were pooled based on disease artery location and stent type.

***Statistical Analysis***

Odds ratios (for binary outcomes) or mean difference (for continuous outcomes) with 95% confidence intervals (CI) were calculated for each endpoint. An intention to treat principle (ITT) was used, with the total number of patients randomized to each study arm as the denominator for each proportion. Sensitivity analysis was performed using per protocol approach. A pooled odds ratio (POR) or mean difference for each endpoint was then calculated for all trials reporting that endpoint using a fixed effects model. PORs were calculated for comparisons of primary stenting versus PTA or other alternative procedures. Level of significance was set at alpha=0.05. Homogeneity was assessed using the chi-square test, $I^2$ and by visual inspection of forest plots. If heterogeneity was encountered within groups ($P \leq 0.10$), a random effects model was used. All statistical analyses were performed using RevMan 5. Where sufficient data were available, these analyses were repeated within subgroups of patients defined by time of outcome assessment to evaluate sustainability of treatment benefit. Results were pooled based on the diseased artery.

## Quality of Evidence

The quality of the body of evidence was assessed as high, moderate, low, or very low according to the GRADE Working Group criteria (20) as presented below.

- Quality refers to the criteria such as the adequacy of allocation concealment, blinding and follow-up.
- Consistency refers to the similarity of estimates of effect across studies. If there are important and unexplained inconsistencies in the results, our confidence in the estimate of effect for that outcome decreases. Differences in the direction of effect, the magnitude of the difference in effect, and the significance of the differences guide the decision about whether important inconsistency exists.
- Directness refers to the extent to which the interventions and outcome measures are similar to those of interest.

As stated by the GRADE Working Group, the following definitions of quality were used in grading the quality of the evidence:

| | |
|---|---|
| **High** | Further research is very unlikely to change confidence in the estimate of effect. |
| **Moderate** | Further research is likely to have an important impact on confidence in the estimate of effect and may change the estimate. |
| **Low** | Further research is very likely to have an important impact on confidence in the estimate of effect and is likely to change the estimate. |
| **Very Low** | Any estimate of effect is very uncertain |

# Results

## Literature Search

The results of the literature search identified 390 citations; a detailed literature search strategy is shown in Appendix 7. Two additional articles were identified through scanning reference of included studies and a search of the Agency for Health Care Research and Quality Technology Assessment (AHRQ) database. Titles and abstracts of retrieved articles were reviewed for potential inclusion. A total of 20 published papers met the inclusion criteria: 5 systematic reviews; and 15 published results from RCTs. Of the 15 RCTs publications, 9 were identified as primary publications (21-29); 6 were follow-up results (30-35) from these primary studies. Characteristics of included studies are described in Appendix 8. Reasons for study exclusion are provided in Appendix 9. A flow diagram of articles retrieved and inclusion progress through the stages of the evidence based review is shown below.

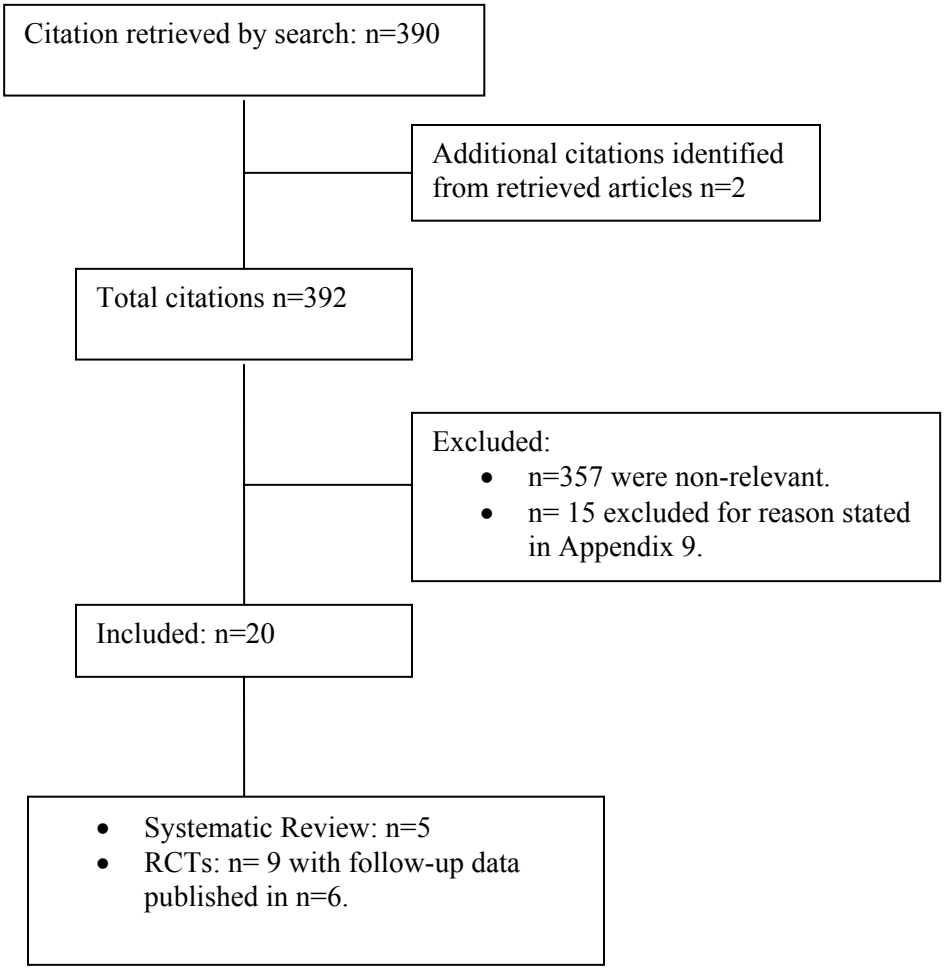



*Figure 2: Flow Diagram of the Systematic Literature Search*

## Quality of Evidence

The quality of the evidence of the studies that met the inclusion criteria is presented in Table 5.

**Table 5: Quality of Evidence of Included Studies**

| Study Design | Level of Evidence† | Number of Eligible Studies |
|---|---|---|
| Systematic review and meta-analyses | 1a | 5 |
| Large RCT, systematic review of RCTs | 1 | 6 RCTs ( plus 6 follow –up results of RCTs), |
| Large RCT unpublished but reported to an international scientific meeting | 1(g) | |
| Small RCT | 2 | 3 |
| Small RCT unpublished but reported to an international scientific meeting | 2(g) | |
| Non-RCT with contemporaneous controls | 3a | |
| Non-RCT with historical controls | 3b | |
| Non-RCT presented at international conference | 3(g) | |
| Surveillance (database or register) | 4a | |
| Case series (multisite) | 4b | |
| Case series (single site) | 4c | |
| Retrospective review, modelling | 4d | |
| Case series presented at international conference | 4(g) | |
| | Total | 20 |

For each included study, level of evidence was assigned according to a ranking system proposed by Goodman(36)

## Systematic Reviews and Meta-Analyses on Peripheral Artery Disease of the Lower Extremities

Five systematic reviews and meta-analyses of RCTs were reviewed. One was conducted by Agency for HealthCare Research and Quality (AHRQ), (37) two were published in the Cochrane Database of Systematic Reviews (38;39) and two were published in a peer reviewed journals. (40;41) Detailed summary of the findings for each review are provided below.

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

Balk and colleagues (37) undertook a horizon scan and a systematic review for Centers for Medicare and Medicaid Services to evaluate the safety and effect of peripheral artery stenting with other vascular procedures for occlusive PAD. The authors conducted a comprehensive search of scientific literature from Medline (1950- July 2007) and the Cochrane Clinical Trial Registry to identify relevant articles. The methodological quality of studies was graded using a three category system and scored as A (good-least bias based on randomization, clear description of the population, setting, interventions and comparisons groups, appropriate measurement of outcomes, appropriate statistical and analytic methods and reporting, less than 20% drop out and accounting of dropouts and no obvious bias); B (fair-susceptible to some bias but not sufficient to invalidate the results, but none likely to cause major bias); C (poor-significant bias that may invalidate the results-serious problem related to design, analysis or reporting or large amounts of missing information). Study applicability was scored as High (sample representative of the Medicare population in relevant settings with no substantial exclusion criteria that would make the sample atypical of patients with PAD receiving invasive procedures); Moderate (sample is an important subgroup of the population of interest possibly limited by age range, type of disease, gender and restrictive eligibility criteria); and Narrow (sample represents only a narrow, atypical subgroup of population of interest). Clinical outcomes measured included clinical success, complications, mortality, amputation, hemodynamic success, symptom relief, re-intervention, mortality and quality of life (QoL). Below is a summary of the findings and conclusions by type of group comparison.

### *Stent vs PTA*

Table 6 summarizes the results of the pooled estimates from studies comparing effectiveness of stent with PTA on re-intervention, amputation, mortality and complications rates.

**Table 6: Pooled Estimates for Re-intervention, Mortality, Amputation and Complications –Stent vs PTA**

| | No. of Patients (# of studies) | | | Pooled Estimates RD (95%CI) | | | |
|---|---|---|---|---|---|---|---|
| **Outcome** | **Iliac** | **Femoral Popliteal** | **Tibial** | **Iliac** | **Femoral Popliteal** | **Tibial** | **Overall** |
| Re-intervention | 279(1) | 668(5) | 45(1) | *1.27 ( 0.76, 2.12) | [a]*1.07 (0.51, 2..23)<br>[o]*0.72 (0.37, 1.40) | *2.74 (0.11, 71.0) | Not Provided |
| Major Amputation | 279(1) | 467(3) | 45(1) | *0.37 (0.11, 1.23) | Not provided | *6.52 (0.13, 332) | *0.76 (0.28, 2.05) |
| >30 days Mortality | 279(1) | 767(5) | No studies | -1.5 (-10.0, 7.0) | Not provided | N/A | 1.6 (-0.9, 4.1) |
| 30 day Mortality | No studies | 413(3) | No studies | N/A | -0.3 (-1.9, 1.2) | N/A | -0.3 (-1.9, 1.2) |
| Within 30 days Emboli | No studies | 464(5) | No studies | N/A | 0.7(-2.1, 3.5) | N/A | 0.7 (-2.1, 3.5) |
| Major Complications | No studies | 464(5) | No studies | N/A | -0.5(-2.7, 1.8) | N/A | -0.5 (-2.7, 1.8) |
| Major Bleeding | No studies | 546(1) | No studies | N/A | 0.1(-2.3, 2.5) | N/A | 0.1 (-2.3, 2.5) |

[o] Balloon expandable stent vs PTA
[a] Self expandable stent vs PTA
* Odds ratios

*Source: Balk E, Cepeda MS, Ip S, Trikalinos T, O'Donnell T. Horizon Scan of invasive interventions for lower extremity peripheral artery disease and systematic review of studies comparing stent placement to other interventions. ARTS0407, -157. 10-10-2008. Boston, MA, Agency for Healthcare Research and Quality. 1-12-2010.*

The authors concluded that there were no significant differences in the rates of re-intervention, amputation, mortality and complications between the two treatment groups. The available trials do not provide evidence that primary stenting results in better clinical outcomes.

### *Stent Graft Vs Bypass*

The AHRQ technology assessment report also summarized the results of a single randomized control trial conducted by Kedora et al (42) that compared the effectiveness of Viabahn stent graft vs bypass in patients with superficial femoral arterial occlusive disease. The trial included 86 patients (100 limbs). Fifty limbs (40 patients) were randomized to receive stent graft and 50 limbs (46 patients) to receive femoral above knee popliteal bypass. The patients had adequate runoff and were without significant aorto-iliac disease. Follow-up assessments of ABI and color flow duplex sonography imaging were performed at 3, 6, 9 and 12 months. The median follow-up was 18 months. Patients receiving stent graft were older. The mean age varied from 40 to 86 years; 39% had diabetes, 57% had a history of smoking; 84% were hypertensive; 52% had hyperlipidemia and 41% had concomitant cardiac disease. Seventy-two

percent had claudication; 14% rest pain; and14% tissue necrosis. The methodological quality was rated poor and applicability rated high. The summary of the results are presented in Table 7.

**Table 7: Summary of Study Findings for Clinical improvement, Limb Salvage, Mortality and Ankle Brachial Index- Stent Graft Vs Bypass**

| Outcome at 12 months | Stent Graft | Bypass | P-Value |
|---|---|---|---|
| Clinical improvement (%) | 100 | 92 | Not significant |
| Limb salvage (%) | 98 | 90 | Not significant |
| Mortality (n) | 4 | 4 | Not significant |
| ABI (net change) | 0.80 | 0.83 | Not significant |

*Source: Balk E, Cepeda MS, Ip S, Trikalinos T, O'Donnell T. Horizon Scan of invasive interventions for lower extremity peripheral artery disease and systematic review of studies comparing stent placement to other interventions. ARTS0407, -157. 10-10-2008. Boston, MA, Agency for Healthcare Research and Quality. 1-12-2010.*

The authors concluded that there were no statistically significant differences between the use of stent graft or bypass in the treatment of femoro-popliteal disease in terms of clinical improvement, limb salvage, rate, mortality or ABI at 12 months of follow-up.

***Drug Eluting Stents Vs Bare Stents***

The AHRQ technology assessment report also summarized the results of an RCT (43-45), comparing patients who received bare metal stents to those receiving drug eluting stents (DES) in patients with superficial femoral artery disease. The trial included 93 patients, 46 received bare nitinol stents and 47 received sirolimus coated nitinol self expanding stent. Patients were followed on average for 24 months. Patient mean age was 66 years; 72% were female; 39% had diabetes; 38% were current smokers; 69% had hypertension; 63% had hyperlipidemia. Fifty percent of the patients were classified according to the Society for Vascular Surgeons (SVS) as category 3 or 4 and the other half as 1 and 2. The authors noted that patients on DES were at greater risk of re-stenosis or complications than the control group. Post operatively, patients were placed on aspirin and either ticlopidine or clopidogrel for 12 months and 3 to 4 weeks respectively. The methodological quality of the trial was rated fair and applicability was rated medium. The summary of the study findings are provided in Table 8.

**Table 8: Summary of study findings for Amputation, Re-intervention, Mortality, Clinical Status and Ankle Brachial Index- Drug Eluting Stents Vs Bare Stents***

| | Number of Events | | |
|---|---|---|---|
| **Outcome at 24 Months** | **DES (N=47)** | **Bare Stent( N=46)** | **P-Value** |
| Major Amputation (%) | 0 | 0 | Not Significant |
| Re-interventions (%) | 13 | 22 | Not Significant |
| Major Mortality (n) | 7 | 2 | Not Significant |
| ABI (mean) | 0.90 | 0.84 | Not Significant |
| Clinical status | Both groups showed a sustained improvement in SVS classification. | | Not Significant |

*Source: Balk E, Cepeda MS, Ip S, Trikalinos T, O'Donnell T. Horizon Scan of invasive interventions for*

*lower extremity peripheral artery disease and systematic review of studies comparing stent placement to other interventions. ARTS0407, -157. 10-10-2008. Boston, MA, Agency for Healthcare Research and Quality. 1-12-2010.*

The authors concluded that there was no significant difference between the two treatment groups on clinical status, re-interventions, mortality, amputation rates and ABI.

Overall, the ARHQ review reported no evidence of statistically significant difference in any outcome assessed, regardless of the disease artery location or stent type. However, the authors noted methodological limitations such as small number of patients studied, rarity of event such as amputations or mortality and clinical heterogeneity in terms of higher risk of amputation prior to intervention, severity of disease and concomitant risk factors.

## Percutaneous Transluminal Angioplasty (PTA) Alone versus PTA with Balloon Expandable Stent Placement for Short-Segment Femoro-popliteal Artery Disease: A Meta-Analysis of Randomized Trials

YaJun and colleagues (41) undertook a systematic review and meta-analyses of randomized control trials comparing the effect of PTA alone and PTA with balloon expandable stent for short segment femoro-popliteal artery occlusive disease. The authors performed a comprehensive literature search of abstracts in MEDLINE, OVID, Springer and Cochrane library of database published from 1999 to 2007 and additional search of references obtained from bibliographies of retrieved articles. Data were abstracted by two independent reviewers. A total of nine studies were eligible for inclusion. Two were excluded because data could not be pooled. (25;26) Thus seven studies (22;24;29;46-49) were included for analysis. Risk of bias was assessed by performing sensitivity analysis and publication bias. Outcome assessment included primary patency at 6, 12 and 24 months and secondary patency at 24 months. The results of the meta-analysis are summarized in Table 9.

**Table 9: Pooled Estimates for Primary and Secondary Patency–Balloon Expanding Stent vs PTA Alone***

| Outcome | No. of studies | No. of patients | OR (95%CI) |
|---|---|---|---|
| Primary Patency | | | |
| 6 months | 4 | 304 | 0.47(0.27, 0.84) |
| 12 months | 6 | 519 | 1.27(0.87, 1.86) |
| 24 Months | 4 | 417 | 1.22(0.81, 1.82) |
| Secondary Patency | | | |
| 12 Months | 4 | 401 | 1.34(0.78, 2.30) |

*Source: E Y, He N, Wang Y, Fan H. Percutaneous transluminal angioplasty (PTA) alone versus PTA with balloon-expandable stent placement for short-segment femoro-popliteal artery disease: a meta-analysis of randomized trials. J Vasc Interv Radiol 2008; 19(4):499-503.*

The authors concluded that in the treatment of femoro-popliteal artery occlusive disease (≤10 cm), higher primary patency rates can be expected 6 months after PTA followed by balloon expandable stents compared with PTA alone. But PTA with stent placement does not produce better long term primary results and secondary patency rates than PTA alone.

## Routine Stent Implantation vs. Percutaneous Transluminal Angioplasty in Femoro-popliteal Artery Disease: A Meta-Analysis of Randomized Controlled Trials.

Kasapis and colleagues (40) performed a meta-analysis of RCTs comparing routine stenting with PTA for symptomatic SFPA (intermittent claudication and CLI) and included studies with at least 6 months outcome follow-up on primary patency, re-stenosis, technical success /failure, mortality, amputation rate, vascular complications, early thrombo-embolic events, and bleeding, and rate of target vessel revascularization (TVR). Immediate technical success / failure was defined as residual stenosis <30% without flow limiting dissection unless otherwise defined by study investigators. Crossover to bailout stenting was considered as immediate technical failure of PTA. TVR was defined as repeat revascularization of the same SFPA proximal or distal to or involving the index lesions or surgical bypass. Re-stenosis was defined as a reduction in luminal diameter >50% on duplex ultrasound peak velocity ratio in 9-24 months of follow up.
The authors searched MEDLINE (1960 to October 2007), EMBASE, ISI Web of Knowledge, Current Contents, International Pharmaceutical Abstracts databases and the Cochrane Central Register of Controlled Trials abstracts list from 2006 and 2007 conference meetings of the AHA/ACC and the European College of Cardiology and the Transcatheter Cardiovascular Therapeutics. A total of 10 RCTs (21;22;24-26;28;29;50-52) were included. Two independent reviewers abstracted data and differences were resolved by consensus. In cases of discrepancies in the interpretation of reported data, original study authors were contacted for clarification. The quality of trials was assessed by Jadad criteria. The authors evaluated each trial for adequacy of allocation concealment, ITT and blind assessment of the outcome. In cases of trials that enrolled by limbs and could possibly enroll a patient more than once, a correction for within-patient clustering was evaluated as an additional quality check. The summary of the pooled estimates comparing stent with PTA and subgroup analysis of studies using different stent types (Palmaz, nitinol and stent graft) on outcomes assessed are shown in Table 10 and Table 11 respectively.

**Table 10: Pooled Estimates for Immediate Failure, Re-stenosis and Target Vessel Revascularization- Stent vs PTA***

| Outcome | No. of studies | No. of Patients | RR (95% CI) |
|---|---|---|---|
| Immediate Failure | 8 | 1357 | 0.43 (0.15, 0.54) |
| Re-stenosis | 10 | 1442 | 0.85 (0.69, 1.06) |
| TVR | 9 | 1091 | 0.98 (0.78, 1.23) |

*Source: Kasapis C, Henke PK, Chetcuti SJ, Koenig GC, Rectenwald JE, Krishnamurthy VN et al. Routine stent implantation vs. percutaneous transluminal angioplasty in femoro-popliteal artery disease: a meta-analysis of randomized controlled trials. Eur Heart J 2009; 30(1):44-55.*

**Table 11: Pooled Estimates: Subgroup analysis by Type of Stent**

| Outcome | RR (95% CI) |
|---|---|
| Nitinol Stent | |
| Immediate Failure | 1.198 ( 1.028, 1.396) |
| Re-stenosis | 0.870 ( 0.609, 1.244) |
| TVR | 0.792 (0.591, 1.062) |
| Palmaz Stent | |
| TVR | 1.46 (0.99, 2.16) |

*Source: Kasapis C, Henke PK, Chetcuti SJ, Koenig GC, Rectenwald JE, Krishnamurthy VN et al. Routine stent implantation vs. percutaneous transluminal angioplasty in femoro-popliteal artery disease: a meta-analysis of randomized controlled trials. Eur Heart J 2009; 30(1):44-55.*

The authors concluded that despite higher immediate success, routine stenting was not associated with a significant reduction in the rate of re-stenosis or TVR. Complications (vascular, mortality, thrombo-embolic event and bleeding) were lower in both groups. With regard to other outcomes, mortality and amputation rates were similar in both groups.

In a subgroup analysis, the authors concluded that the use of nitinol stents resulted in higher technical success and a non significant trend for lower TVR and no difference in re-stenosis rates. Palmaz stent resulted in a trend for higher TVR though not statistically significant. The effect of the use of stent graft on TVR was neutral.

## Cochrane Systematic Review: Endovascular Stents for Intermittent Claudication

Bachoo and colleagues (38) searched the Cochrane Central Register of Controlled Trials (last searched August 2009). This Specialized Register is maintained by the trial coordinator through weekly electronic searches of Medline, EMBASE, CINAHL, AMED, conference proceedings and hand searching of relevant journals. The search included all RCTs comparing angioplasty alone compared with angioplasty in addition to stent as treatments for intermittent claudication of the lower extremities in adults of proven diagnosis with aorto-iliac or femoro-popliteal lesions on angiography. Two RCTs (24;28) were included. Methodological qualities of trials were assessed by two independent reviewers and disagreements were resolved by consensus. Emphasis on methodological quality was placed on allocation concealment, sequence generation, blinding , incomplete data assessment and selective outcome reporting and scored as 'yes', 'no' or 'unclear'. The outcome assessed included technical failure, re-stenosis / re-occlusion, post intervention morbidity, re-intervention, and ABPI. The results of the methodological quality and pooled estimates of the outcomes assessed are shown in Table 12.

**Table 12: Assessment of Risk of Bias and Pooled Outcome Estimates for Re-stenosis, Re-intervention, Technical Failures, Ankle Brachial Pressure index, Treadmill Walking, Complications and Symptomatic Deterioration- Stent vs PTA***

| Outcome | No. of studies | No. of Patients | Pooled Estimates | Assessment of Risk of Bias |
|---|---|---|---|---|
| Re-stenosis | 2 | 104 | OR: 2.37, 95%CI 0.99 to 5.71. | Sequence generation: Unclear<br>Allocation concealment: Unclear<br>Blinding: No<br>Incomplete outcome data: Unclear<br>Free of provisional reporting : Yes |
| Treadmill Walking Distance (m) | 1 | 53 | MD: -83.2, 95%CI -290.22 to 123.82. | |
| Embolic events: | 1 | 51 | OR: 3.51, 95%CI 0.14 to 90.33 | |
| Early Thrombosis | 1 | 51 | OR: 0.36, 95%CI 0.01 to 9.27. | |
| Re-intervention | 1 | 53 | OR: 0.78, 95%CI 0.25 to 2.41 | |
| Symptom deterioration | 1 | 51 | OR: 1.43, 95%CI 0.44 to 4.58. | |
| ABPI | 2 | 104 | MD: 0.01, 95%CI -0.06 to 0.08. | |
| Technical failures | 2 | 104 | OR: 1.6, 95%CI 0.32 to 8.01 | |

*Source: Bachoo P, Thorpe PA, Maxwell H, Welch K. Endovascular stents for intermittent claudication. Cochrane Database of Systematic Reviews 2010;(1):CD003228.*

The authors concluded that the results of this review failed to provide robust evidence in favour of either PTA + stent or PTA alone for all outcomes assessed. They also concluded that methodological weakness in the included studies, such as short follow-up period, failure to blind outcome assessors, and no prior power calculation compromised the value of the results. The authors also recommended that future systematic reviews should combine both intermittent claudication and critical limb ischemia.

## Cochrane Systematic Review: Angioplasty versus Stenting for Superficial Femoral Artery Lesions

Twine and colleagues (39) searched Cochrane Central Register of Controlled Trials (last searched February 2009). The Peripheral Vascular Disease Group Register has been compiled from searching Medline (1950 to date), EMBASE Classic (1947 to 1979), EMBASE (1980 to date), CINAHL (1982 to date) and LILACS (last searched July 2008, the index to UK Thesis (searched May 2006) and the United States Department of Health & Human Services Agency for Health Care Research and Quality Technology Assessment (AHRQ) and hand searching of journals and conference proceedings. The search included all RCTs comparing PTA alone compared with PTA in addition to stent as treatments for intermittent claudication or critical limb ischemia (Fontaine stages II to IV) (53). Patients with TASC A and B with SFA lesions were considered. Eight RCTs (21;22;24-26;28;29;46) were included. Methodological quality of trials were assessed by two independent reviewers and confirmed by the third author. Emphasis was placed on allocation concealment. Each trial was scored as A (clearly concealed), B (unclear if concealed) or C (not concealed) and also a summary score of A (low risk), B (moderate risk), C (high risk). Discrepancies between reviewers were discussed and consensus reached. Trials that score a C were excluded. Those that scored a B were discussed and consensus reached. The primary outcome included re-stenosis (trials with at least 6 months follow up using angiography or duplex ultrasound). Secondary outcomes included improvement in ABI, walking distance and QoL scores. The authors noted that analysis was based on endpoint data from individual trials "which all quoted intention- to treat principle". The results of the assessment of methodological quality showed the risk of bias for allocation

concealment as low and unclear for other potential biases. Pooled estimates of the outcomes assessed are summarized in Table 13.

**Table 13: Pooled Estimates for Patency, Treadmill Walking, Quality of Life and Ankle Brachial Index- Stent vs PTA***

| Outcome | No. of studies | No. of patients | Pooled Estimates |
|---|---|---|---|
| Patency: 6 Months | | | |
| Duplex | 4 | 325 | OR: 1.71, 95%CI 1.03 to 2.85 |
| Angiography | 3 | 261 | OR: 2.06, 95%CI 1.15 to 3.72 |
| Patency:12 Months | | | |
| Duplex | 6 | 520 | OR: 1.41, 95%CI 0.97 to 2.04 |
| Angiography | 5 | 384 | OR: 1.31, 95%CI 0.84 to 2.03 |
| Patency: 24 Months | | | |
| Duplex | 3 | 192 | OR: 1.78, 95%CI 0.98 to 3.24 |
| Angiography | 2 | 74 | OR: 0.70, 95%CI 0.28 to 1.76 |
| ABPI | | | |
| 6 months | 1 | 104 | MD: 0.07, 95%CI 0.04 to 0.10 |
| 12 months | 3 | 291 | MD: 0.07, 95%CI 0.05 to 0.09 |
| 24 months | 1 | 98 | MD: 0.03, 95%CI -0.04 to 0.10 |
| Treadmill Walking | | | |
| 6 months | 1 | 104 | MD: 88.00, 95%CI 74.54 to 101.46 |
| 12 months | 2 | 240 | MD: 62.52, 95%CI 48.36, 76.68 |
| 24 months | 1 | 98 | MD: 17.00, 95%CI -123.23, 157.23 |
| Quality of Life | | | |
| 6 months | | | |
| Physical | 1 | 104 | MD: -4.00, 95%CI -9.40, 1.40 |
| Mental | 1 | 104 | MD: 2.00, 95%CI -3.64, 7.64 |
| 12 months | | | |
| Physical | 1 | 104 | MD: -2.0, 95%CI -7.59, 3.59 |
| Mental | 1 | 104 | MD: 3.00, 95%CI -1.65, 7.65 |

*Source: Twine CP, Coulston J, Shandall A, McLain AD. Angioplasty versus stenting for superficial femoral artery lesions. Cochrane Database of Systematic Reviews 2009 ;( 2):CD006767.*

The authors concluded that primary stent has a small but statistically significant short term improvement in primary patency over lesions treated with PTA alone. The effect was prominent at 6 months but the benefits of stenting diminished with time. A similar but lesser effect was seen for ankle brachial pressure index (ABPI), while a more pronounced improvement in treadmill walking distance was observed in the group receiving PTA in addition to stent at 6 and 12 months but not at 24 months. The authors stated that the results are heavily weighted on one trial (26). No significant differences in the QOL between the two groups were observed. The authors also concluded that while a large number of patients were available overall, some analyses contained small number of studies and should be interpreted with caution. Combining the overall completeness, acceptability and quality of evidence, the authors concluded that it cannot be accepted that the small differences found between the two groups are of actual significance and thus routine stenting following PTA cannot be recommended.

# MAS Evidence Based Analysis:

## Primary Stenting vs PTA in Superficial Femoral Popliteal Artery Stenosis or Occlusive Disease

A total of 7 studies were identified that compared the effectiveness of primary stenting with PTA in patients with superficial femoral artery disease (SFPA). Five of the seven included studies that used balloon expandable stent (21;22;24;28;29) while the other two used self expandable stent. (25;26) Post-operatively, in studies using self expandable stent patients were managed pharmacologically with clopidogrel and ASA while those using balloon expandable stent were mostly managed with ASA only, with exception of one study that used anticoagulant therapy coumadin in addition to ASA. Doses of ASA varied between studies. In the two studies that used clopidogrel, dose and duration of therapy varied between the two studies. According to the reported study methods of 5 studies, patients randomized to PTA received stent if the results from angioplasty were suboptimal. (21;22;24-26) In one study, four obese patients crossed over from stent to PTA (28). In another study, no cross over treatment occurred.(29) Patients crossed over remained in the group to which they were assigned but were considered secondarily patent. Study follow up ranged from 6 months to 39 months.

## Primary Outcome: Primary Patency

Definition of patency varied between studies; defined as less than 30% stenosis or peak systolic velocity (PSV) ratio $\leq 2.5$ in three studies, (22;25;28) less than 50% stenosis in three other studies (21;26;29) and in one study (24) significant stenosis was defined as increased systolic velocity within the vessel 1.5 times higher than in normal regions of the artery. Patency was determined using angiography only in one study, (29) computer tomographic angioplasty / digital subtraction angiography in one study (26) duplex ultrasound in two (25;28) and in three studies, results of the duplex ultrasound were confirmed with angiography (21;22;24).
Results of the pooled estimates for patency analysed using ITT and per protocol approach as well as subgroup analyses by stent type and time of outcome assessment are shown in Figure 3-10.

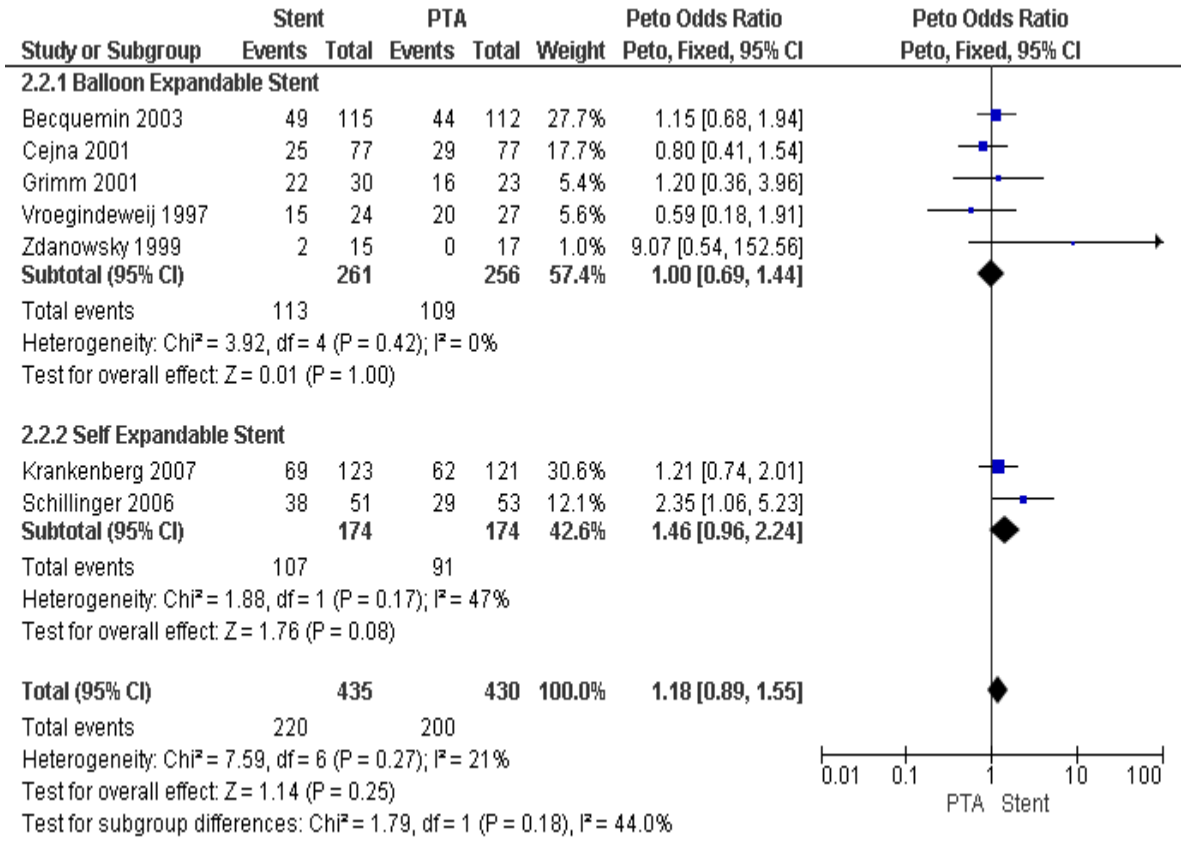



*Figure 3: Primary Patency at Study Endpoint Using Intention to Treat Principle- Stent vs PTA*

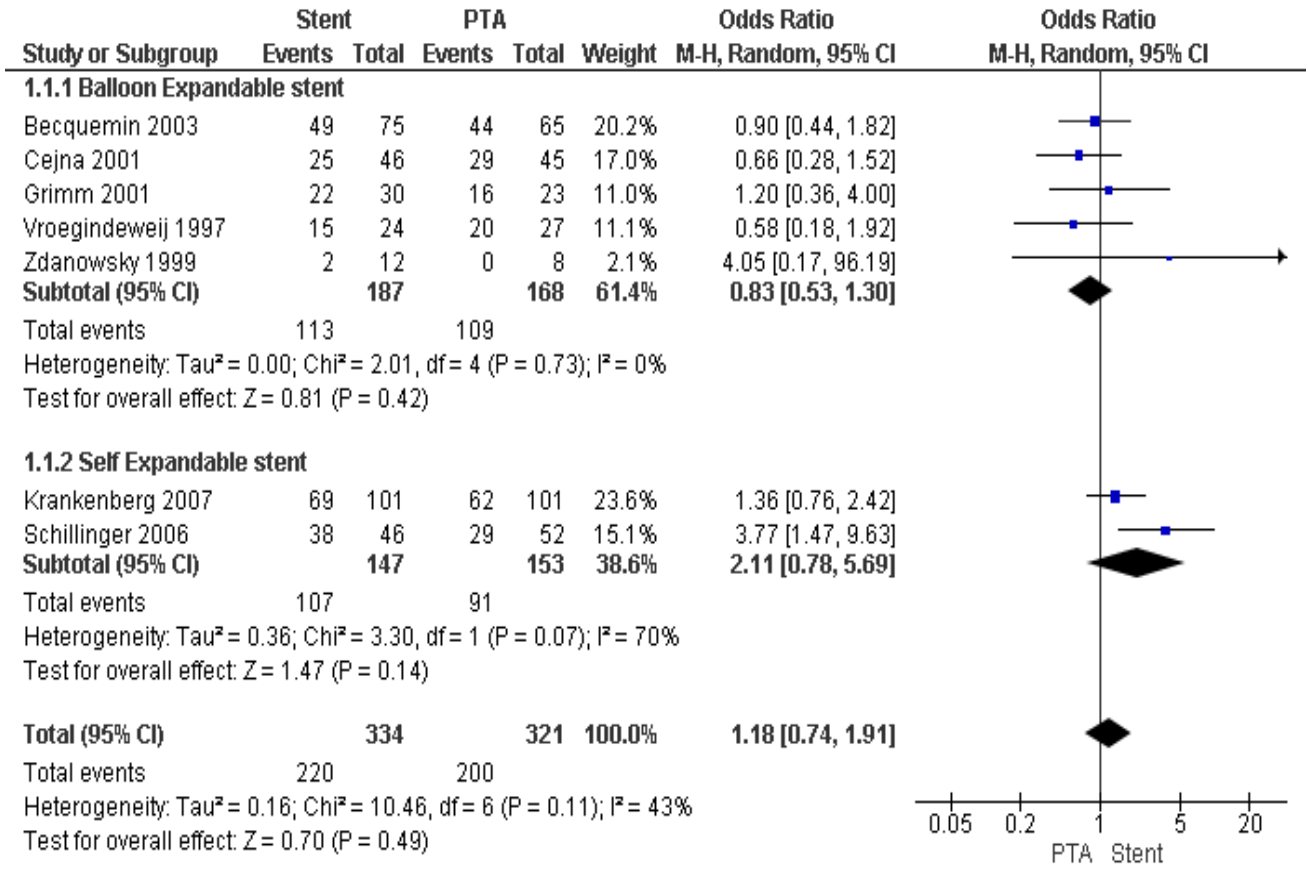



*Figure 4: Primary Patency at Study Endpoint Using Per Protocol Approach- Stent vs PTA*

**Sensitivity Analysis- Primary Patency by Time of Assessment**

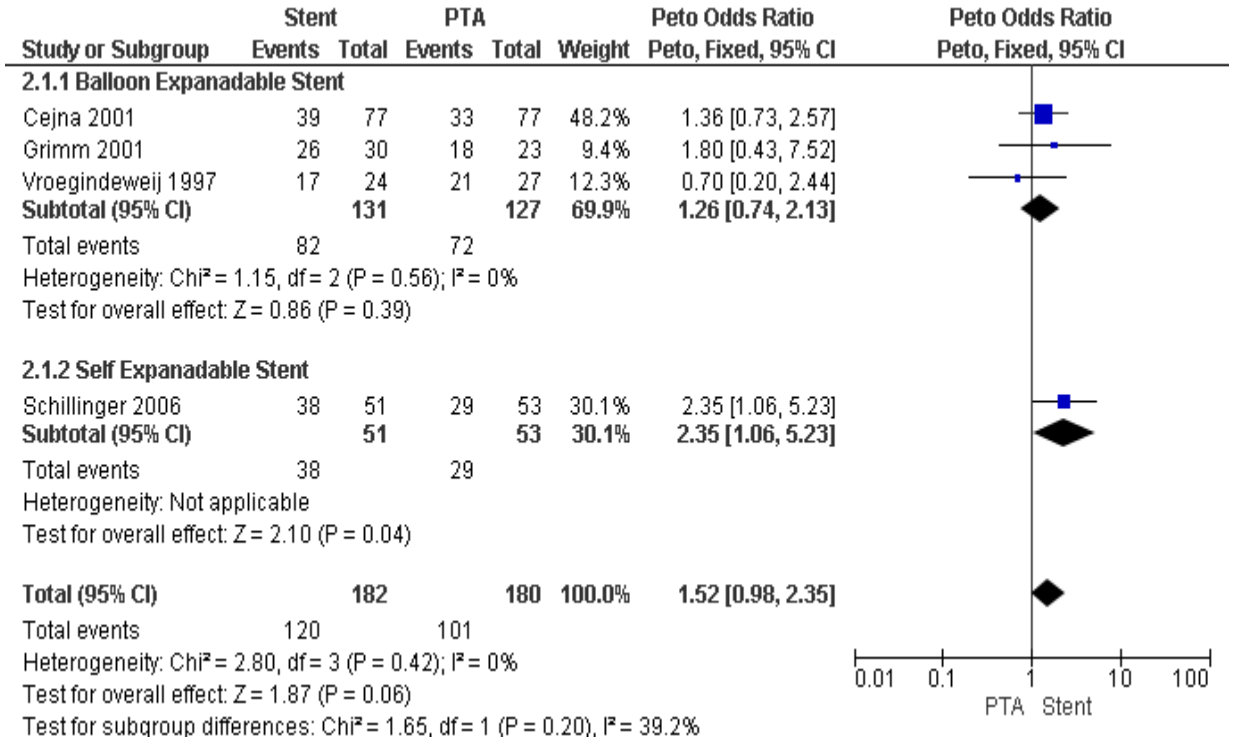



*Figure 5: Six Months Patency using Intention to Treat Principle- Stent vs PTA*

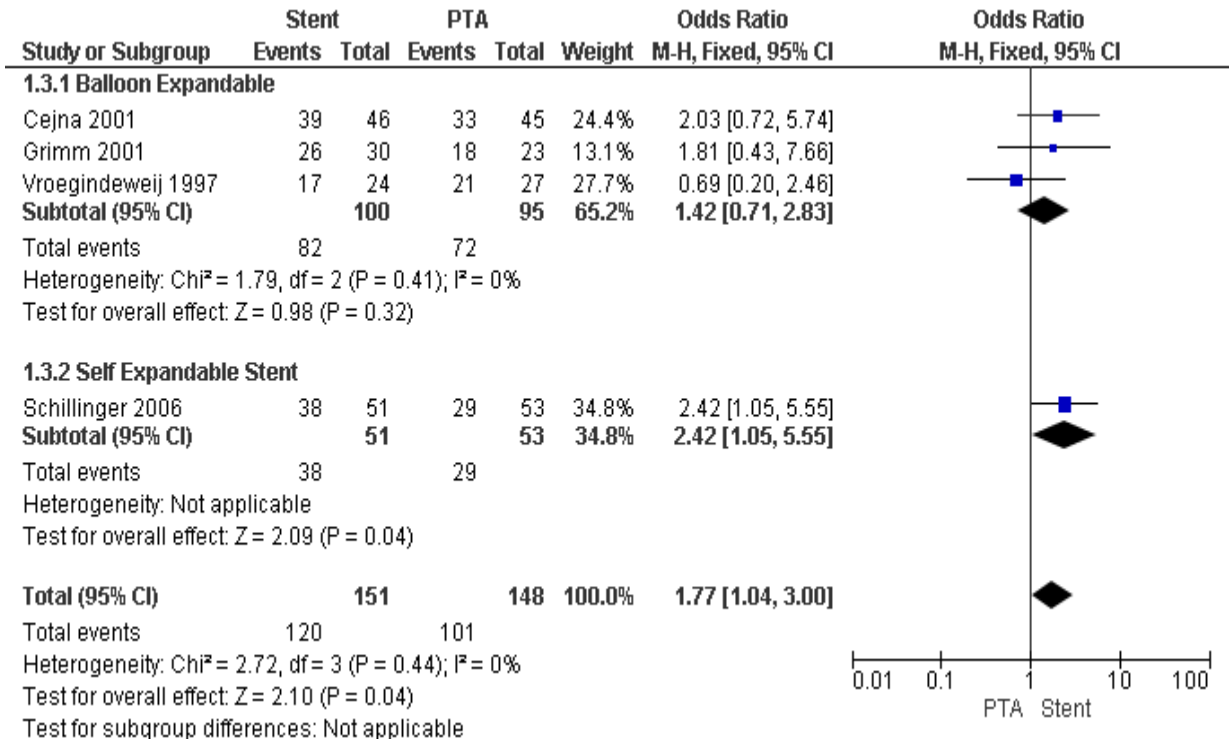



*Figure 6: Six Months Patency using Per Protocol Approach- Stent vs PTA*

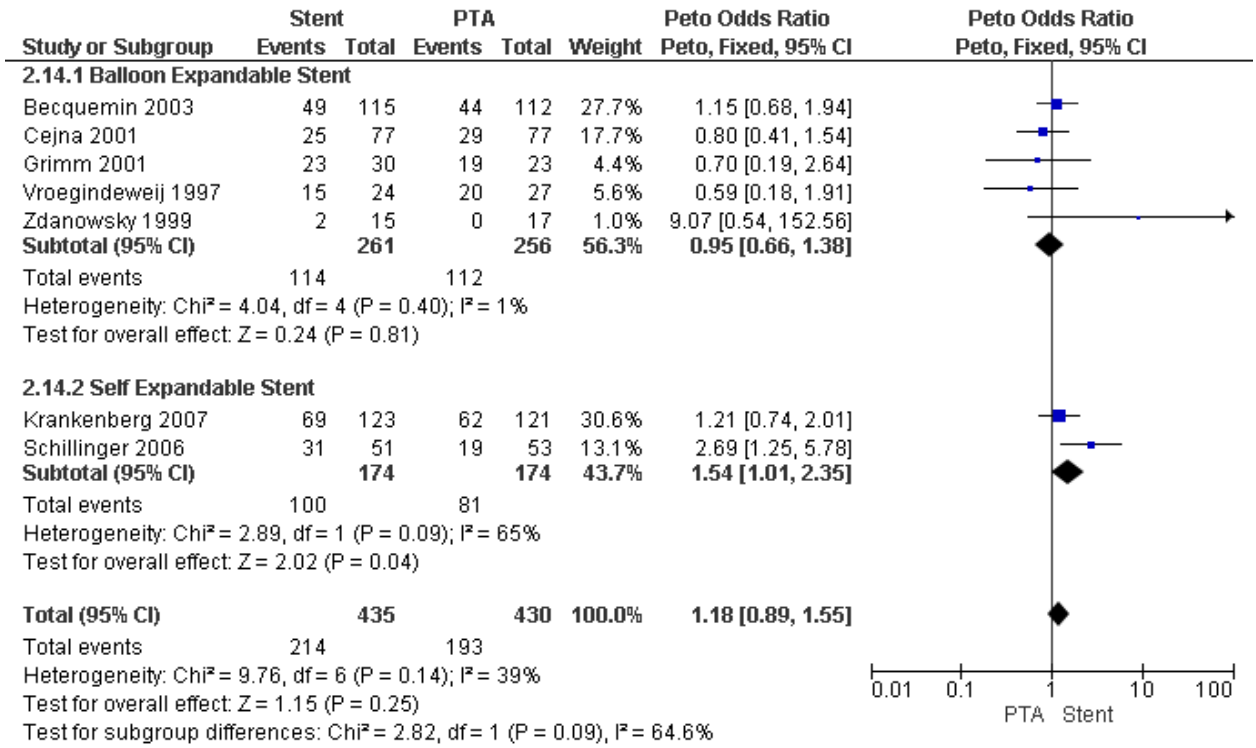



*Figure 7: Twelve Months Patency using Intention to Treat Approach- Stent vs PTA*

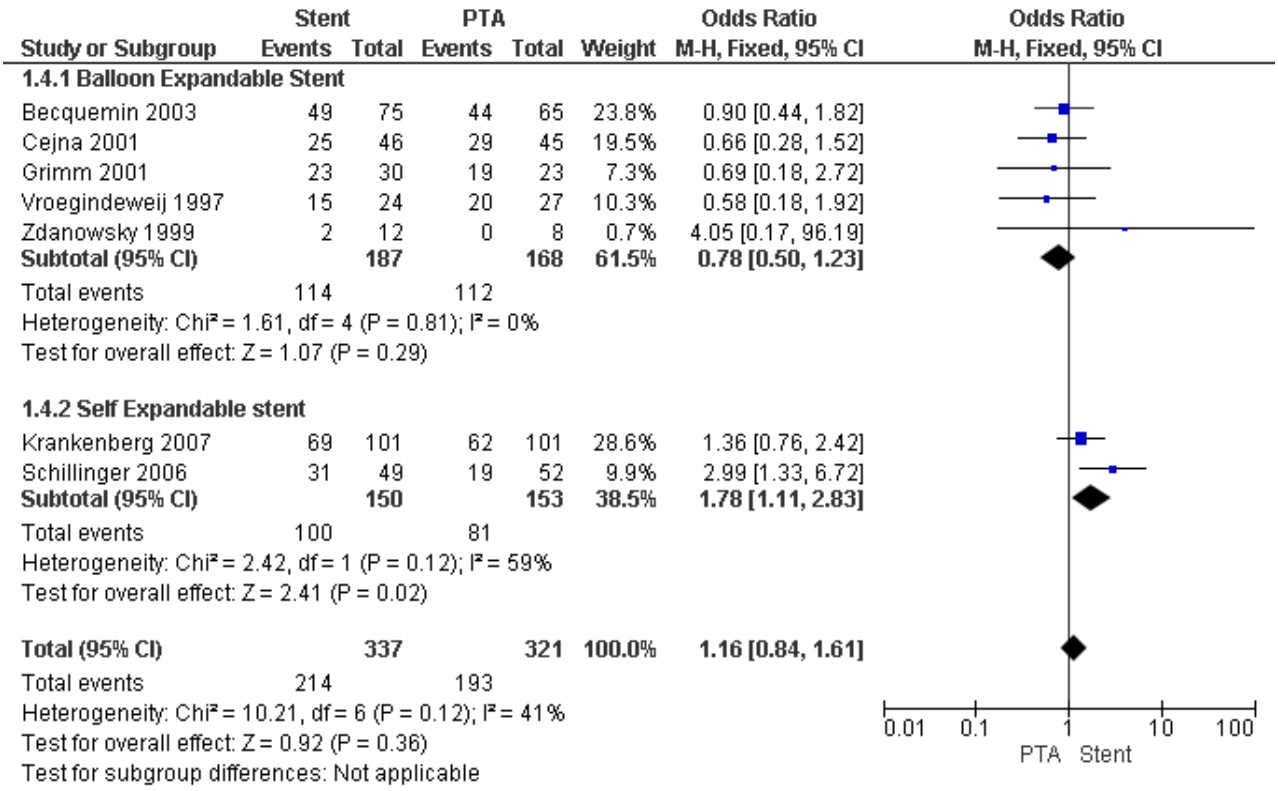



*Figure 8: Twelve Months Patency using Per Protocol Approach- Stent vs PTA*

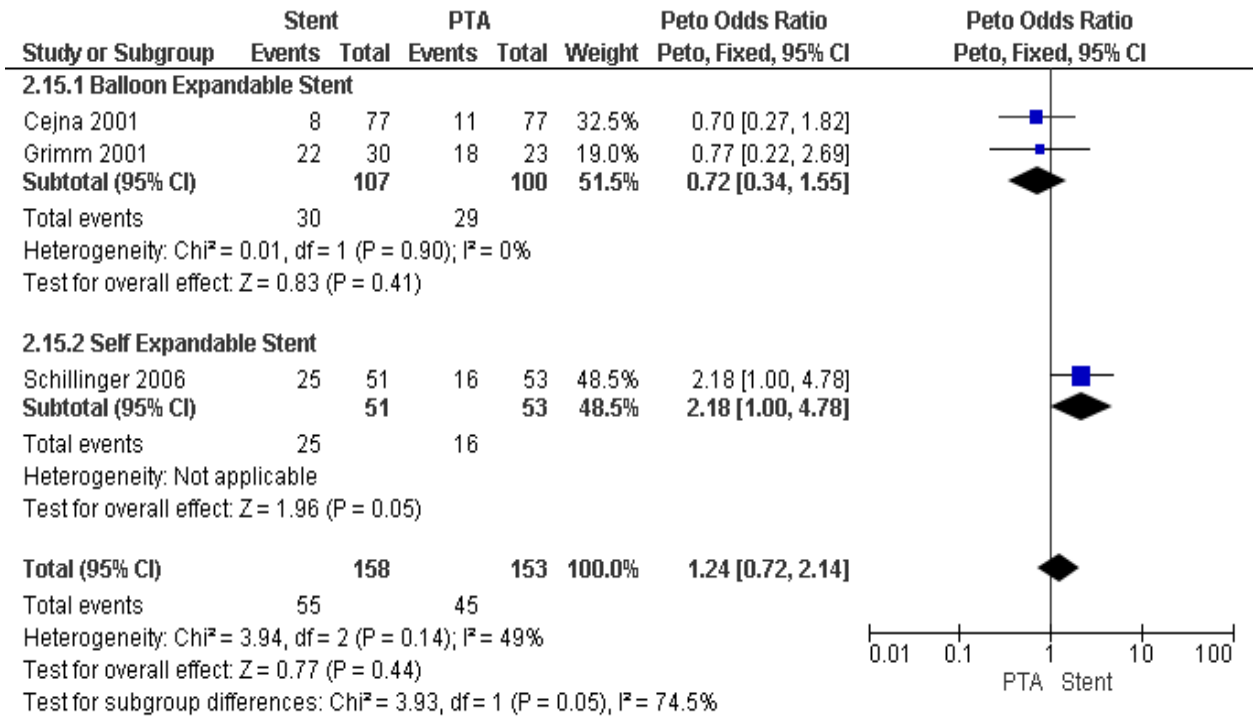



*Figure 9: Twenty Four Months Patency Using Intention to Treat Approach- Stent vs PTA*

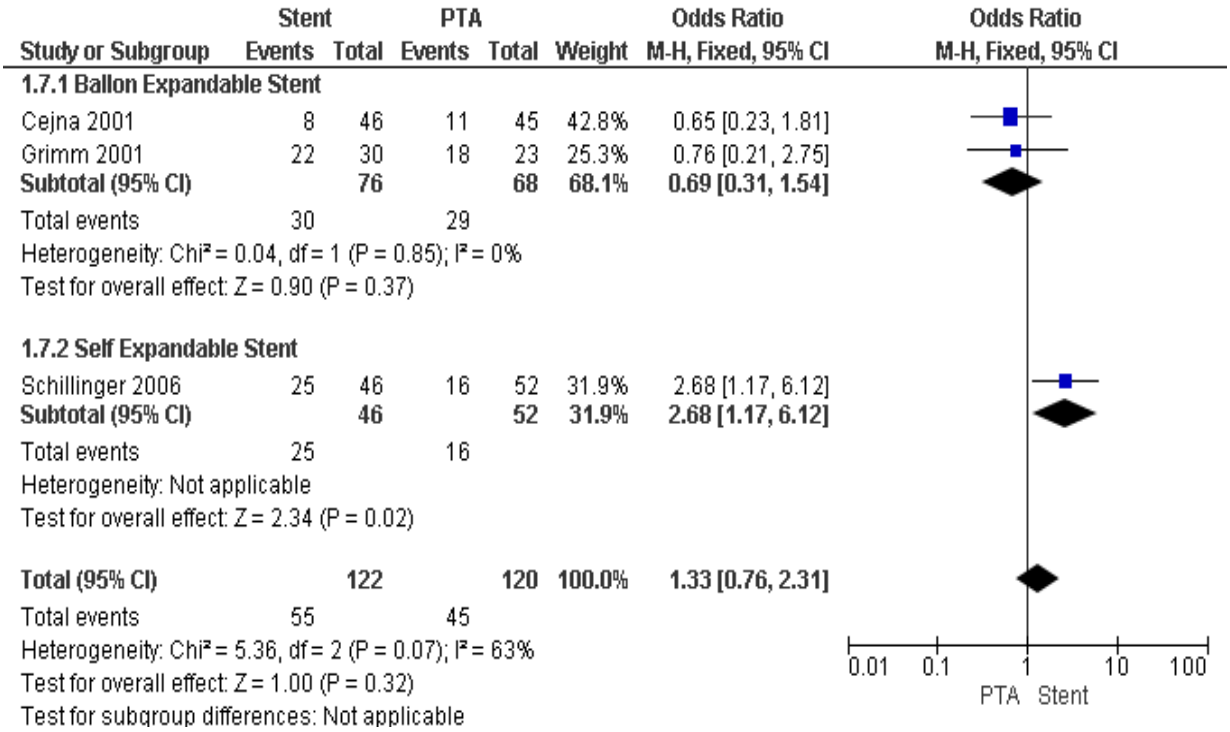



*Figure 10: Twenty Four Months Patency Using Per Protocol-Stent vs PTA*

**Conclusion:**

**Balloon Expandable Stent vs PTA**

Based on the pooled estimates above, there is no statistically significant difference in patency rates between the balloon expandable stents and PTA at all time points using both ITT and per protocol analysis.

**Self Expandable Stent vs PTA**

Based on the pooled estimates above, there is statistically significant difference in patency rates between the two treatment groups at all time points using both ITT and per protocol analysis.

## Secondary Outcomes:

### Immediate Technical Success

In all seven studies comparing primary stenting with PTA, immediate technical success was defined as residual stenosis less than 30%. In some studies, direct stent implantation was performed without predilation of the lesion, (25;26;28) while in others predilation was performed before stent placement especially in patients with heavily calcified lesions. (21;22) The results of the pooled estimates shown in Figure 11 demonstrate that primary stenting using self expandable stent provide immediate technical success compared to PTA alone. Bailout stenting was performed in 15% of the patients randomized to PTA alone.

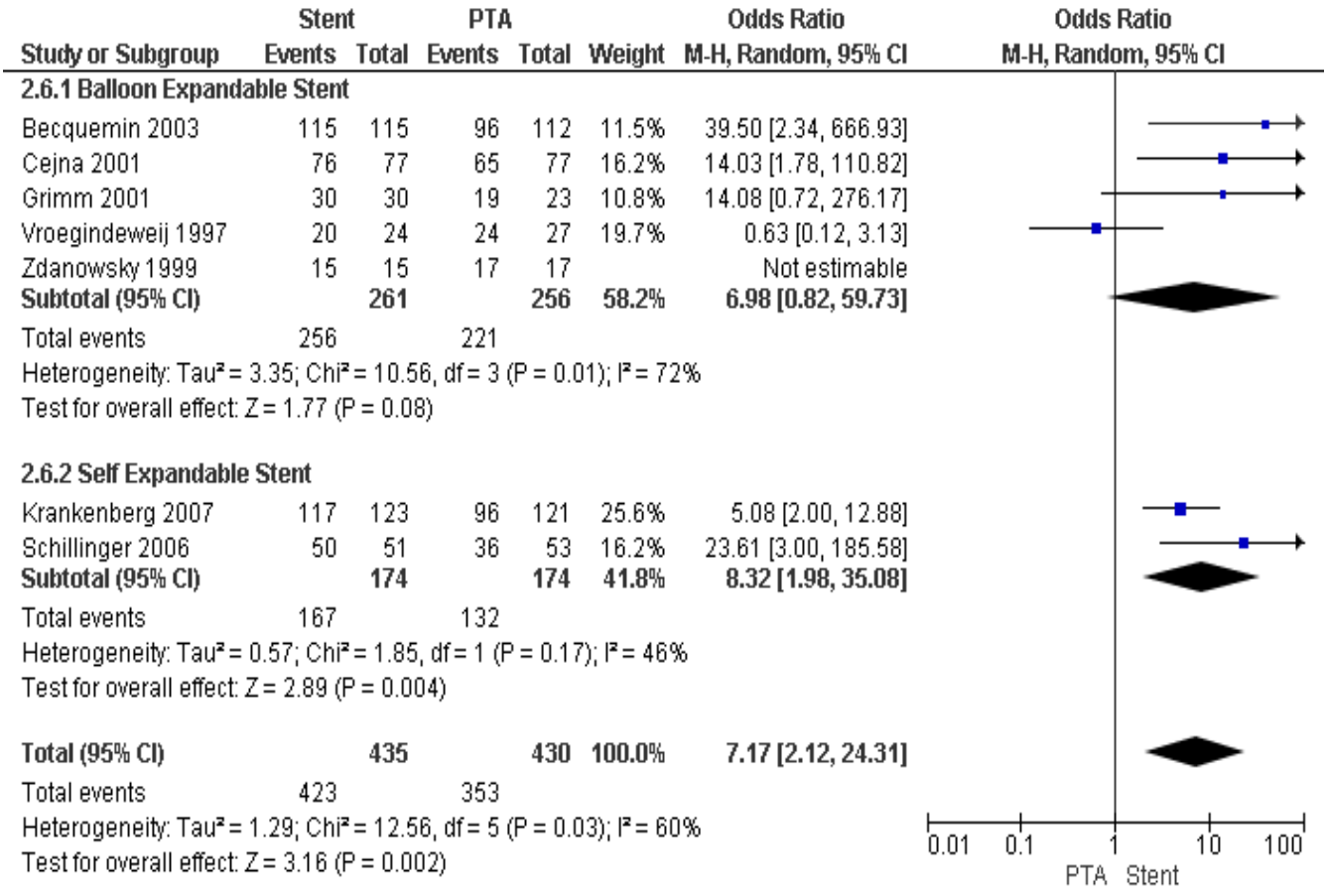



*Figure 11: Immediate Technical Success- Stent vs PTA in Superficial Femoral Artery Disease*

## Re-intervention

Six studies reported re-interventions rates during the course of the study follow-up. The types of re-interventions performed between studies included angioplasty procedures, stent implantations and bypass grafting. The mean time to re-intervention varied between patients, treatment groups and between studies. The results of the pooled estimates shown in Figure 12 demonstrate no significant difference in re-intervention rates between the two groups regardless of the type of stent.

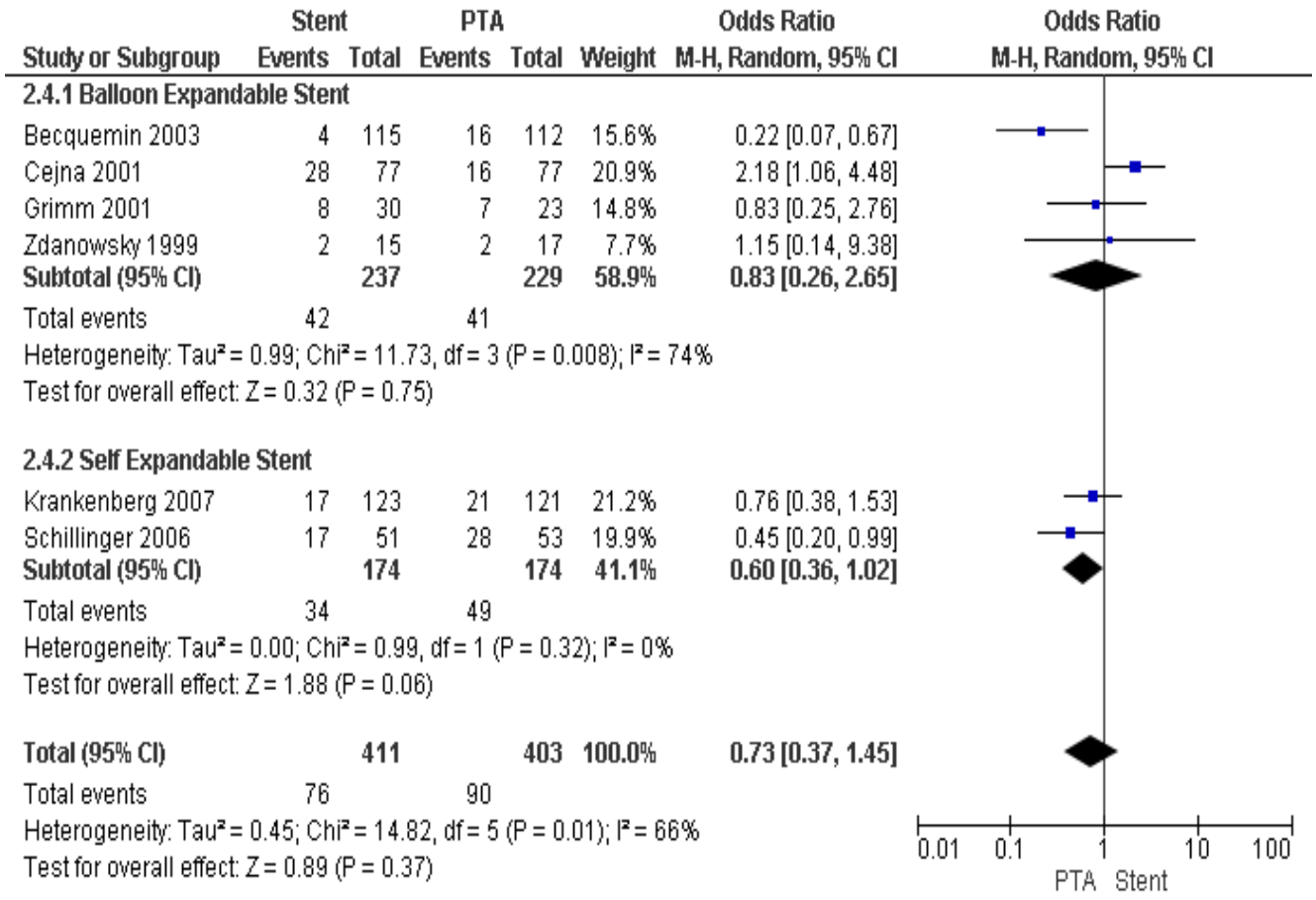



*Figure 12: Re-intervention- Stent vs PTA in Superficial Femoral Artery Disease*

## Perioperative and Less Than one Month Postoperative Complications

Six studies reported procedural and post-operative complications rates less than 30 days after the procedure. The most commonly reported complications included thrombosis, embolism, bleeding or hematoma, MI, arterial rupture or dissection and amputation. The results of the pooled estimates shown in Figure 13 demonstrate no statistically significant difference in complication rates between the two treatment groups regardless of the type of stent.

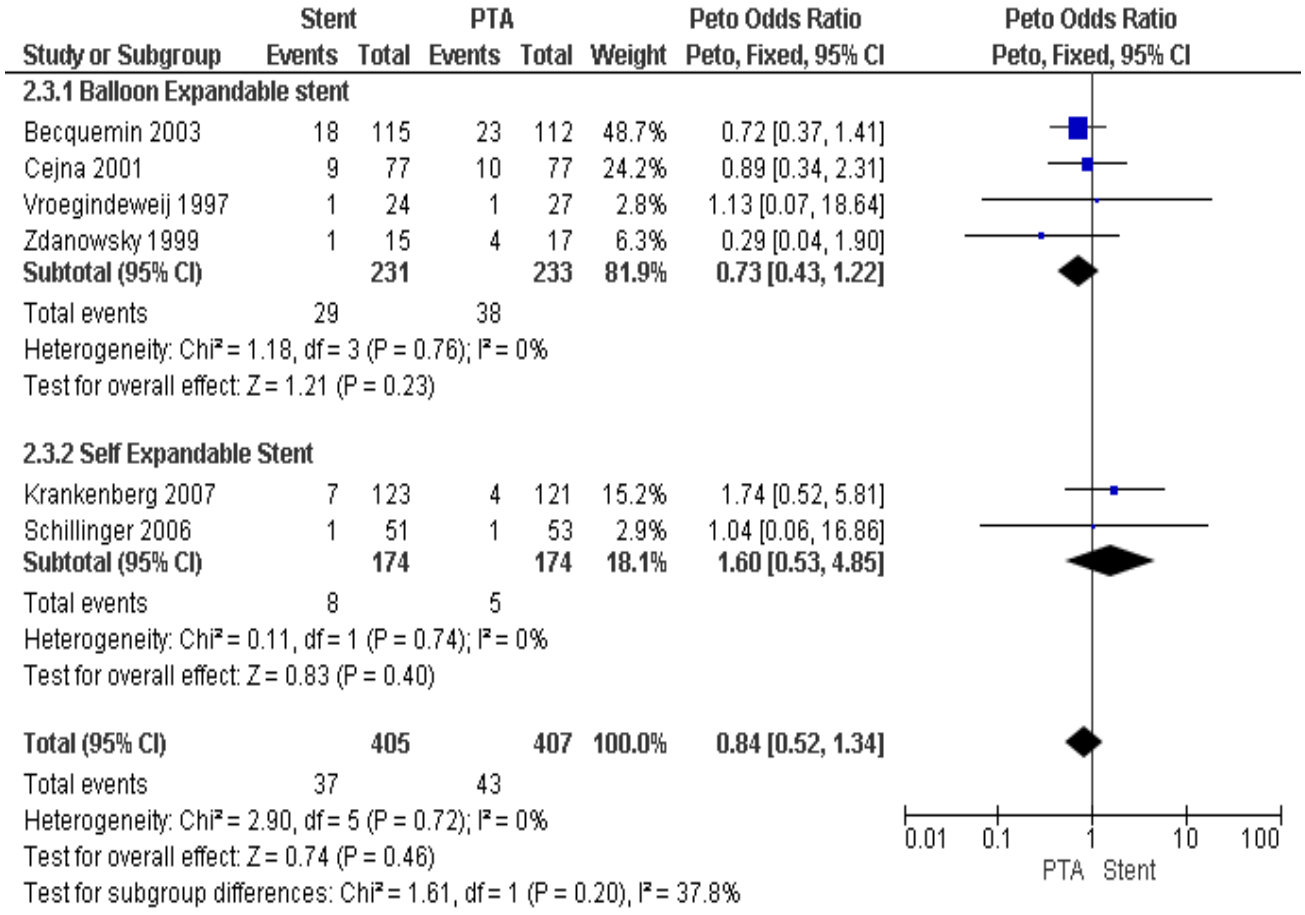



*Figure 13: Perioperative and less than one Month Postoperative Complications- Stent vs PTA in Superficial Femoral Artery Disease*

## All Cause Mortality

All cause mortality during study follow-ups were reported in four studies. The results of the pooled estimates shown in Figure 14 show no statistically significant difference between the two treatment groups.

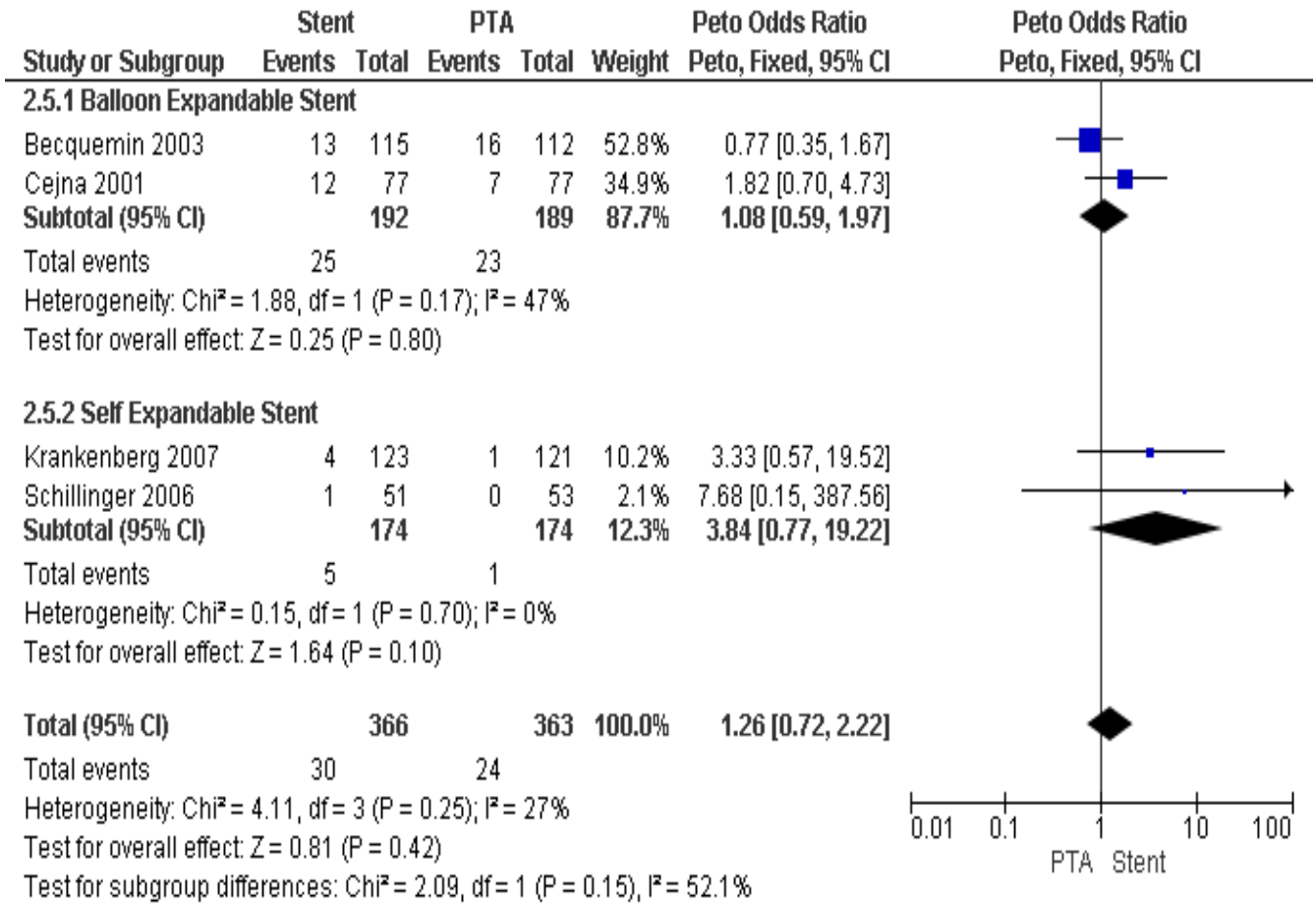



*Figure 14: All Cause Mortality- Stent vs PTA in Superficial Femoral Artery Disease*

## Amputation

A total of four studies reported amputation rates. Amputations were described as either major or minor or both. In two studies, amputations were reported less than 30 days following the procedure. (21;22) In two other studies amputations were reported at 12 and 24 months. (25;34) Based on the results of the pooled estimates in Figure 15, there is no statistically significant difference in amputation rates between the two groups regardless of the type of stent.

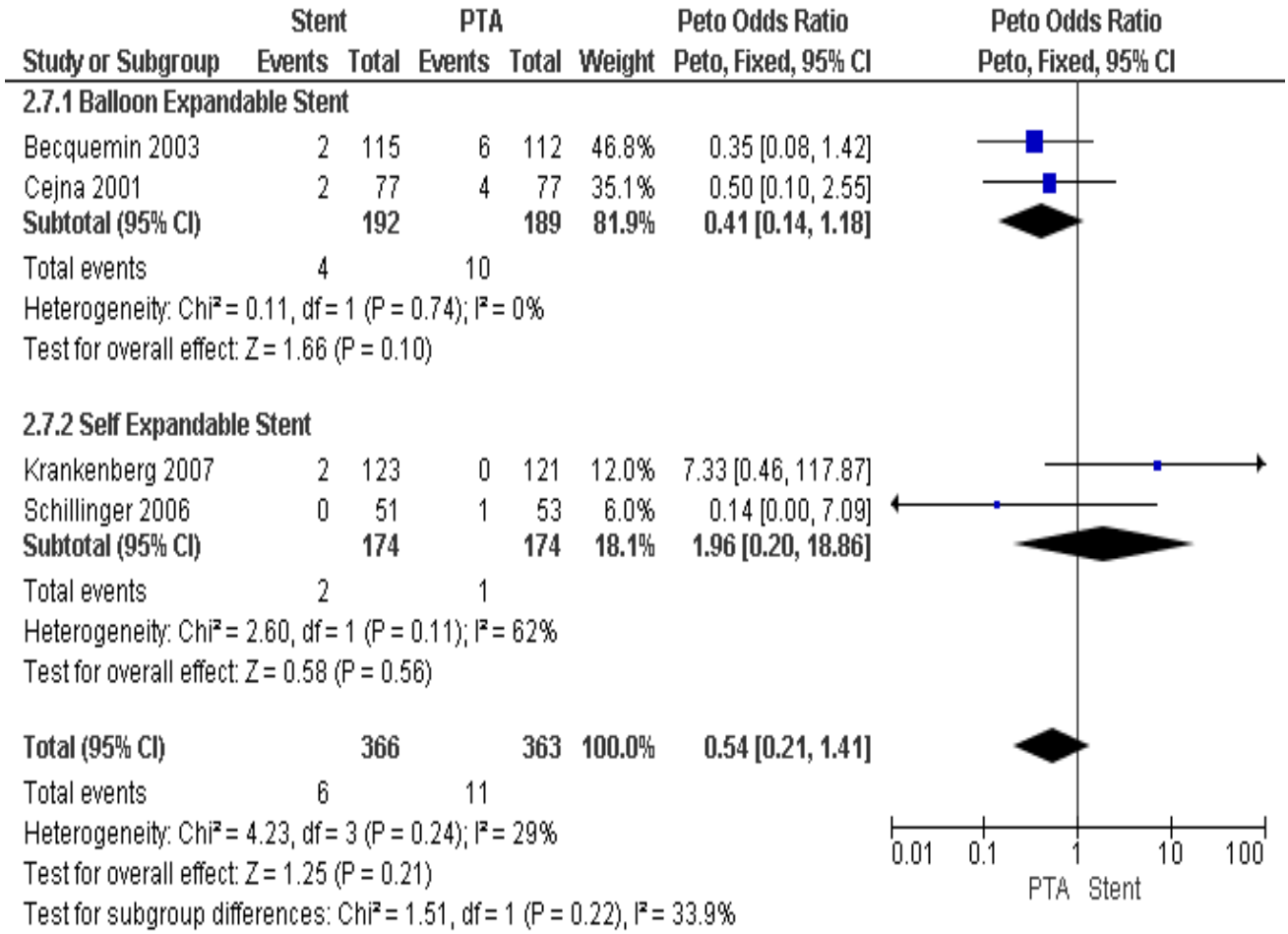



*Figure 15: Amputations- Stent vs PTA in Superficial Femoral Artery in Superficial Femoral Artery Disease*

## Ankle Brachial Index at Rest Less Than one Month Post Procedure

A total of five studies reported mean ankle brachial index less than a month following treatment procedure. Based on the results of the pooled estimates shown in Figure16, there is no statistically significant difference in the mean ankle brachial index in the two treatment groups regardless of the type of stent.

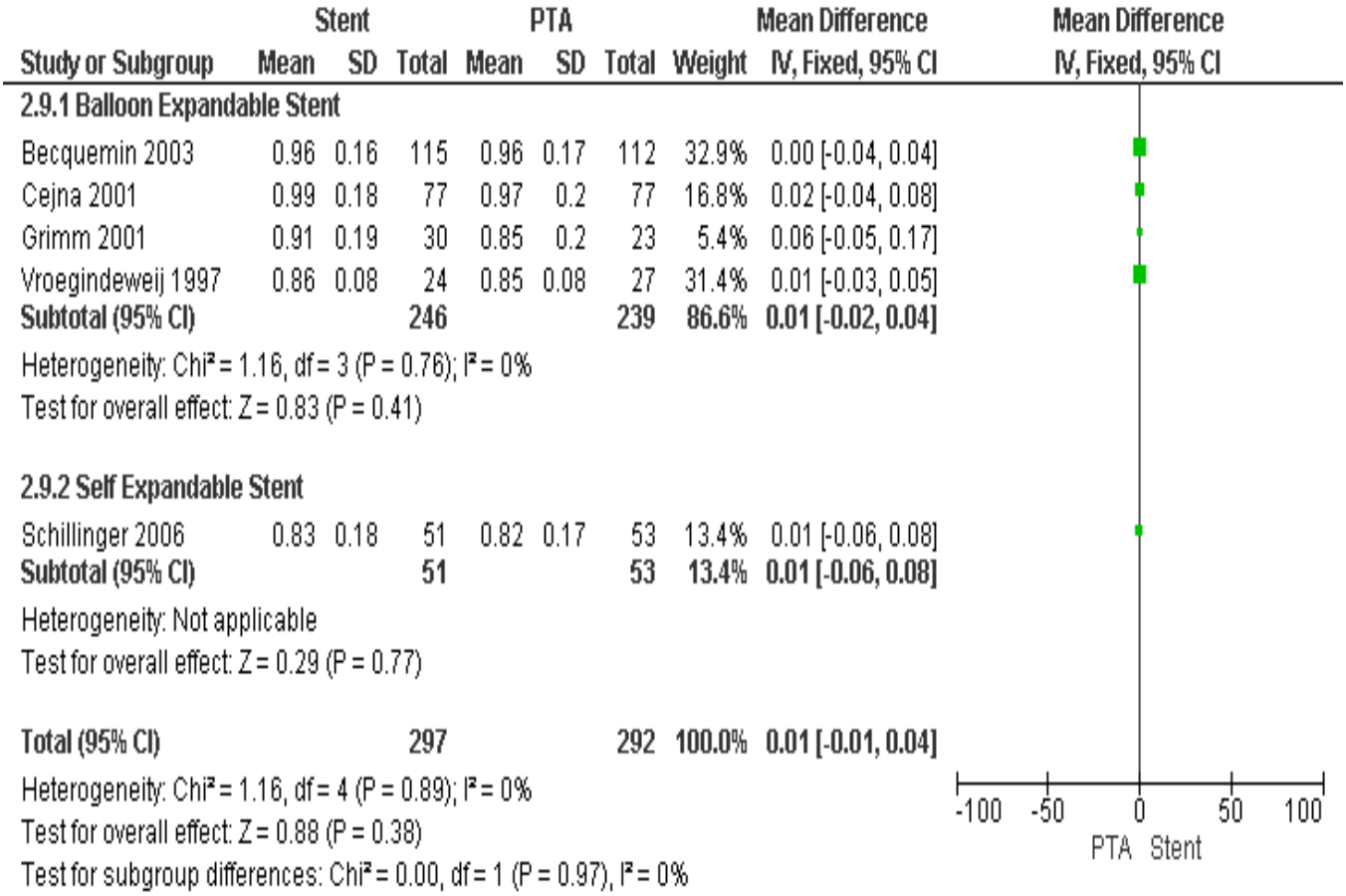



*Figure 16: Ankle Brachial Index at Rest Less Than one Month Post Procedure- Stent vs PTA in Superficial Femoral Artery Disease*

## Treadmill Walking Distance (in metres)

Maximum walking distance was reported in three studies. (24-26) However, due to differences in statistical measures used in reporting the results, the results could not be pooled. The results of individual studies are summarized below.

In the study by Grimm et al, the mean walking distance after stenting was 383.5 ± 237.5 metres compared to 466.7 ± 461.9 metres in the PTA group (MD -83.2m, 95%CI -290.22, 123.82) which failed to reach statistical significance. In the study by Schillinger et al, the average distance walked six months post treatment was 363 metres in the stent group versus 270 metres in the PTA group. The authors concluded that patients in the stent group were able to walk significantly farther on a treadmill than those in the PTA

group. In the study by Krankenberg et al the treadmill median walking distance 12 months after treatment was 185 metres in the stent group compared with 150 metres for the PTA group, resulting in a statistically significant difference.

## Clinical Improvement

Clinical improvement at 12 months was reported in four studies. (22;25;28;29) Improvement was defined as a change of at least one category on Rutherford or SVS-ISCVS (Society of Vascular Surgery/International Society of Cardiovascular Surgery) scale. Appendix 6 shows categories of the scale. Based on the results of the pooled estimates shown in Figure 17, there was no statistically significant difference in clinical improvement between the two treatment groups regardless of the type of stent.

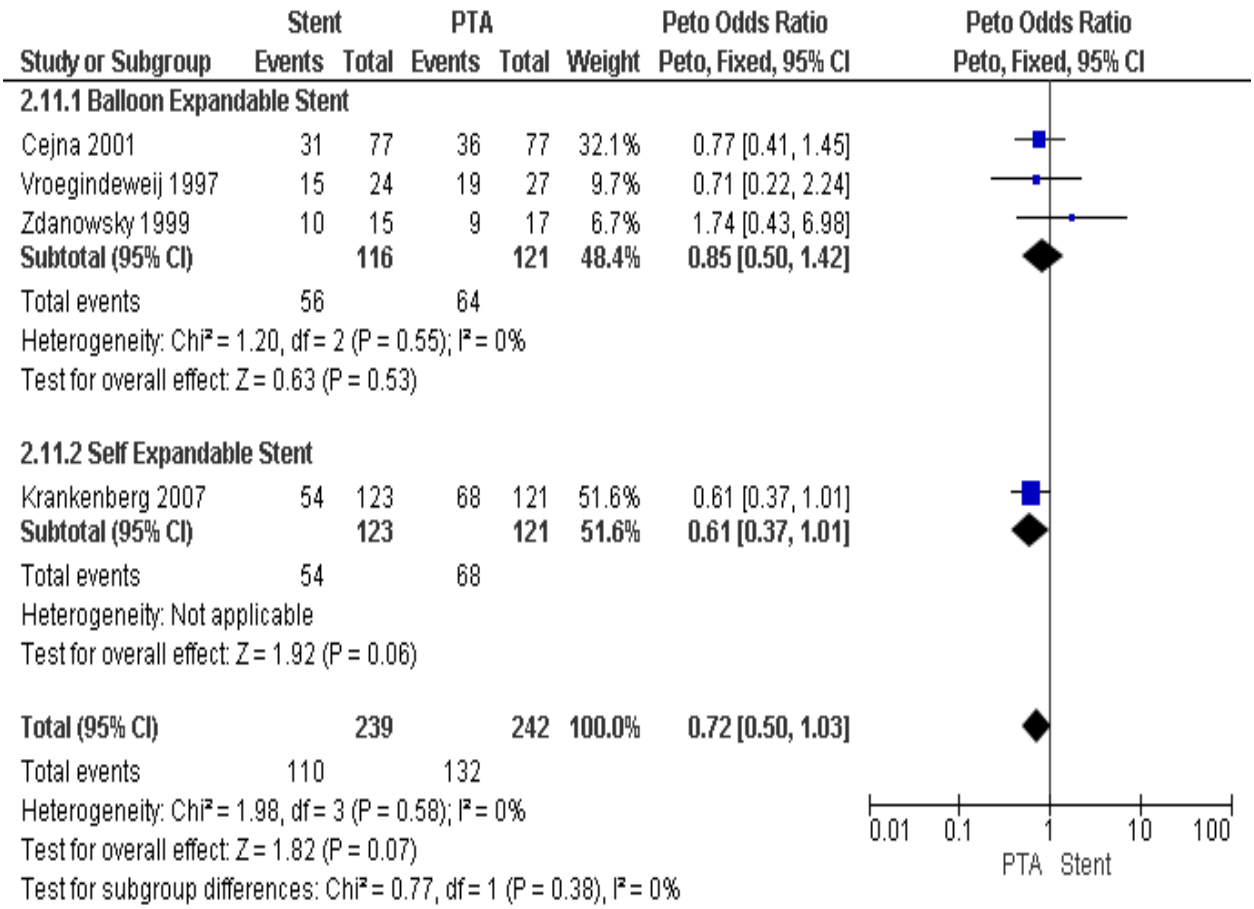



*Figure 17: Clinical Improvement - Stent vs PTA in Superficial Femoral Artery Disease*

## Assessment of Quality of Evidence: Stent Vs. PTA in Superficial Femoral Artery Disease

The quality of evidence for all outcomes was assessed by GRADE criteria. The quality of evidence was downgraded from High to Moderate due to inconsistency of results of balloon expandable vs self expandable on patency and lack of standardized definition of some outcomes between studies. Table 15 summarizes the results of the quality assessment.

**Table 15: Quality of Evidence: Stent Vs. PTA in Superficial Femoral Artery Disease**

Stent for PAD

Patient or population: [Patients with superficial femoral artery disease]
Intervention: Stent
Comparison: PTA

| Outcomes | Illustrative comparative risks* (95% CI) Assumed risk / Corresponding risk | | Relative effect (95% CI) | No of Participants (studies) | Quality of the evidence (GRADE) | Comments |
|---|---|---|---|---|---|---|
| | Control | Stent | | | | |
| Primary Patency | Study population | | OR 1.18 (0.89 to 1.55) | 865 (7 studies) | ⊕⊕⊕⊖ moderate [1,2,4, 6] | |
| | 465 per 1000 | 506 per 1000 (436 to 574) | | | | |
| | Medium risk population | | | | | |
| | 512 per 1000 | 553 per 1000 (483 to 619) | | | | |
| Overall Procedural Complications | Study population | | OR 0.84 (0.52 to 1.34) | 812 (6 studies) | ⊕⊕⊕⊖ moderate [1,4,5] | |
| | 106 per 1000 | 91 per 1000 (58 to 137) | | | | |
| | Medium risk population | | | | | |
| | 84 per 1000 | 72 per 1000 (46 to 109) | | | | |
| Re-intervention | Study population | | OR 0.73 (0.37 | 814 (6 studies) | ⊕⊕⊕⊖ moderate [1,7] | |
| | 223 per 1000 | 173 per 1000 (96 to 294) | | | | |

| | | | | |
|---|---|---|---|---|
| | Medium risk population<br>191 per 1000 147 per 1000 (80 to 255) | to 1.45) | | |
| Mortality | Study population<br>60 per 1000 74 per 1000 (44 to 124)<br>Medium risk population<br>4 per 1000 5 per 1000 (3 to 9) | OR 1.26 (0.72 to 2.22) | 729 (5 studies) | ⊕⊕⊕⊖ moderate[8] |
| Technical Success | Study population<br>821 per 1000 970 per 1000 (907 to 991)<br>Medium risk population<br>844 per 1000 975 per 1000 (920 to 992) | OR 7.17 (2.12 to 24.31) | 865 (7 studies) | ⊕⊕⊕⊖ moderate[1] |
| Amputation | Study population<br>29 per 1000 16 per 1000 (6 to 40)<br>Medium risk population<br>19 per 1000 10 per 1000 (4 to 27) | OR 0.54 (0.21 to 1.41) | 761 (5 studies) | ⊕⊕⊕⊖ moderate[9] |
| Ankle Brachial Index < less than a month after treatment | The mean Ankle Brachial Index < less than a month after treatment in the intervention groups was 0.01 higher (0.01 lower to 0.04 higher) | | 589 (5 studies) | ⊕⊕⊕⊖ moderate[10] |
| Clinical Improvement | Study population<br>545 per 1000 463 per 1000 (375 to 552)<br>Medium risk population<br>546 per 1000 464 per 1000 (376 to 553) | OR 0.72 (0.5 to 1.03) | 481 (4 studies) | ⊕⊕⊕⊖ moderate[11] |

*The basis for the assumed risk (e.g. the median control group risk across studies) is provided in footnotes. The corresponding risk (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

CI: Confidence interval; OR: Odds ratio;

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1] Inadequate blinding
[2] Inconsistency of results
[3] Discrepant prevalence of total occlusions between the two arms
[4] Definition of outcomes not standard across all studies
[5] Complications may not be due to treatment received making it difficult to differentiate the source
[6] Medication therapy post procedure. Some studies discharge patients on both clopidogrel and ASA while others place them on ASA only
[7] Type of re-intervention may differ between patients and across studies
[8] In some studies overall all cause mortality is reported while others report <30 days mortality or > 30 days mortality
[9] Some studies report overall amputations while others differentiate between major and minor amputations
[10] In some studies, it is not clear whether ABI measurements were taken at rest or after exercise
[11] Most studies define clinical improvement according to Rutherford or SVS-ISCVS scale with the exception of one study

## Drug Eluting Stents vs Bare Metal Stents in Crural Artery Disease

Two studies compared drug eluting stents with bare metal stent. One study (published in 3 papers) (43-45) evaluated its efficacy and safety in the superficial femoral artery and was excluded as it was a feasibility study. The other evaluated its effectiveness in patients with stenosis of the crural arteries (23) and was eligible for inclusion. The primary endpoint was re-stenosis rate and secondary outcomes included rate of revascularization, technical success, hemodynamic and clinical success. Patients were followed for six months. Details of study characteristics are provided in Appendix 8. Table 16 provides a summary of the study findings. The quality of evidence for this trial was rated as very low due to lack of allocation concealment, blinding, and small sample size and wide confidence intervals.

**Table 16: Summary of findings Drug Eluting Stent* vs Bare Stent in Crural Arteries.**

| | Number of Events | | |
|---|---|---|---|
| Outcome | DES (N=25) | Bare stents (N=25) | OR (95%CI) |
| Clinical Patency | 24 | 19 | Not significant |
| Re-stenosis | 4 | 19 | 0.09 (0.03, 0.28) |
| Target Lesion Revascularization | 3 | 14 | 0.15 (0.05, 0.47) |
| Technical success | 25 | 25 | |
| Complications | 2 | 2 | 1.00 (0.13, 7.56) |
| Late Lumen Loss | 0.46(0.72) | 1.70 (0.94) | MD: -1.24 (-1.70, -0.78) |
| Minimal Lumen Diameter | 2.25 (0.82) | 0.99(1.08) | MD: 1.26 (0.73, 1.79) |
| ABI (mean) | 0.70 | 0.61 | |

**Note that drug-eluting stents are not licensed by Health Canada for peripheral artery disease*

The authors concluded that based on the quantitative angiography variables used to assess re-stenosis, Sirolimus-eluting stent was superior 6 months after intervention. Sirolimus eluting stents decreased the risk of stenosis in comparison to standard stents.

## Iliac Artery Occlusive Disease

Only one study (Dutch Iliac Trial) evaluated effectiveness of direct stenting using balloon-expandable stents compared with PTA with subsequent stent placement in case of a residual mean pressure gradient greater than 10mm Hg across the treated site in patients with iliac artery occlusive disease. Patients were followed for up to 8 years. The follow-up results are published in five separate articles. (27;30-32;35) Details of the study characteristics are described in Appendix 8. Table 17 provides a summary of the study findings.

**Table 17: Summary Results of Dutch Iliac Trial**

| | Number of Events | | |
|---|---|---|---|
| **Outcome (time)** | **Bare Stent (N=187 limbs)** | **PTA (N=169 limbs)** | **OR (95%CI)** |
| Patency (24 months) | 133 | 118 | 1.06 (0.67, 1.68) |
| Clinical Improvement -at least 1 Rutherford category ( # of patients) | | | |
| 3 months | 103 (143) | 101(136) | 0.89(0.53, 1.52) |
| 12 months | 64 (143) | 62 (136) | 0.97 (0.60, 1.55) |
| 24 months | 29 (143) | 26 (136) | 1.08 (0.60,1.94) |
| Re-intervention | | | |
| 12 months | 5 | 4 | 1.13(0.30, 4.29) |
| 24 months | 6 | 10 | 0.53(0.19, 1.48) |
| 5-8 years (mean 5.6 years) | 33 | 33 | 0.88 (0.52, 1.51) |
| Technical success | 186 | 104 | 12.23 (7.17, 20.88) |
| Symptomatic success at 5-8 years ( %) | 31(34) | 38(49) | Significant in favour of PTA |
| Complications at 24 months ( # of patients) | 6(143) | 10(136) | 0.56 (0.20, 1.53) |
| Mortality at 5 years ( # of patients) | 21 (143) | 22 (136) | 0.89 (0.47, 1.71) |
| Amputation at 5 years | 3 (143) | 8 (136) | 0.37(0.11, 1.23) |
| ABI (mean±SD) | | | |
| 3 months | 0.96(0.18) | 0.96(0.21) | No significant |
| 12 months | 0.94(0.19) | 0.98(0.18) | No significant |
| 24 months | 0.91(0.21) | 1.0(0.19) | No significant |
| 5-6 years | 0.90(0.20 | 0.96(0.22) | No significant |
| Cardiovascular event at 5 years ( # of patients) | 18 (143) | 15 (136) | 1.16 (0.56, 2.40) |
| Treadmill Walking (mean±SD) in metres | | | |
| 3 months | 263(57) | 255(64) | MD: 8.00(-6.25, 22.25) |
| 12 months | 261(58) | 263(65) | MD: -2.00(-16.48, 12.48) |
| 24 months | 258(68) | 255(68) | MD:3.00(-12.96, 18.96) |
| QoL (RAND-36 Item Health Survey 5 year follow-up) | Not Significant | | |

The authors concluded that:
At 2 years following the procedure, there were no substantial differences in technical results and clinical outcomes of the two treatment strategies both at short term and long term follow-up. Since angioplasty followed by provisional stenting placement is less expensive than direct placement of a stent, the former seems to be a treatment of choice for life limiting intermittent claudication caused by iliac artery occlusive disease.
At 5 years following the procedure, no difference in the number of re-interventions between the two treatment groups. Patients with iliac disease are at high risk of cardiovascular morbidity and mortality.

At 6 to 8 years following the procedure, patients treated with PTA and selective stent placement had a better outcome for symptomatic success compared with patients treated with primary stent placement. The results of patency, ABI and quality of life did not support a difference between the groups. The two treatment strategies provided equal long-term clinical results.

Using on treatment analysis, the authors concluded that no significant difference with regard to symptomatic, hemodynamic success, patency, quality of life and re-interventions between patients treated with stent versus those treated with PTA alone.

As shown in the table below, the quality of evidence using GRADE for all outcomes assessed was rated as moderate.

## Assessment of Quality of Evidence: Stent versus PTA in Iliac Artery Occlusive Disease

The quality of evidence for all outcomes was assessed by GRADE criteria. The quality of evidence was downgraded from High to Moderate due to inadequate blinding. Table 18 summarizes the results of the quality assessment.

**Table 18: Quality of Evidence Using Grade for Stent versus PTA for Patients with Iliac Artery Occlusive Disease**

**Stent compared to PTA for Iliac artery occlusive disease**

**Patient or population:** patients with Iliac artery occlusive disease
**Settings:**
**Intervention:** Stent
**Comparison:** PTA

| Outcomes | Illustrative comparative risks* (95% CI) Assumed risk PTA | Corresponding risk Stent | Relative effect (95% CI) | No of Participants (studies) | Quality of the evidence (GRADE) | Comments |
|---|---|---|---|---|---|---|
| **Primary Patency (ITT)** | **Study population** | | **OR 1.03** (0.56 to 1.87) | 356 (1 study) | ⊕⊕⊕⊖ **moderate**[1] | |
| | **14 per 100** | **14 per 100** (8 to 23) | | | | |
| | **Medium risk population** | | | | | |
| | **14 per 100** | **14 per 100** (8 to 23) | | | | |
| **Re-Intervention** | **Study population** | | **OR 1.16** (0.71 to 1.9) | 356 (1 study) | ⊕⊕⊕⊖ **moderate**[1] | |
| | **22 per 100** | **25 per 100** (17 to 35) | | | | |
| | **Medium risk population** | | | | | |
| | **22 per 100** | **25 per 100** (17 to 35) | | | | |
| **Complications** | **Study population** | | **OR 0.56** (0.2 to 1.53) | 279 (1 study) | ⊕⊕⊕⊖ **moderate**[1] | |
| | **7 per 100** | **4 per 100** (2 to 11) | | | | |
| | **Medium risk population** | | | | | |
| | **7 per 100** | **4 per 100** (2 to 11) | | | | |
| **Amputation** | **Study population** | | **OR 0.37** (0.11 to 1.23) | 279 (1 study) | ⊕⊕⊕⊖ **moderate**[1] | |
| | **6 per 100** | **2 per 100** (1 to 7) | | | | |
| | **Medium risk population** | | | | | |
| | **6 per 100** | **2 per 100** | | | | |

| | | | | | |
|---|---|---|---|---|---|
| | | (1 to 7) | | | |
| **Ankle Brachial Index** | | The mean Ankle Brachial Index in the intervention groups was **0.08 lower** (0.14 to 0.02 lower) | | 279 (1 study) | ⊕⊕⊕⊖ **moderate**[1] |
| **Treadmill Walking Distance (in metres)** | | The mean Treadmill Walking Distance (in metres) in the intervention groups was **3 higher** (12.96 lower to 18.96 higher) | | 279 (1 study) | ⊕⊕⊕⊖ **moderate**[1] |
| **Clinical Improvement** | **Study population** | | **OR 1.08** (0.6 to 1.94) | 279 (1 study) | ⊕⊕⊕⊖ **moderate**[1] |
| | **19 per 100** | **20 per 100** (12 to 31) | | | |
| | **Medium risk population** | | | | |
| | **19 per 100** | **20 per 100** (12 to 31) | | | |
| **Primary Patency (Per Protocol)** | **Study population** | | **OR 1.03** (0.37 to 2.84) | 70 (1 study) | ⊕⊕⊕⊖ **moderate**[1] |
| | **70 per 100** | **70 per 100** (46 to 87) | | | |
| | **Medium risk population** | | | | |
| | **70 per 100** | **70 per 100** (46 to 87) | | | |
| **Cardiovascular event** | **Study population** | | **OR 1.16** (0.56 to 2.4) | 279 (1 study) | ⊕⊕⊕⊖ **moderate**[1] |
| | **11 per 100** | **13 per 100** (6 to 23) | | | |
| | **Medium risk population** | | | | |
| | **11 per 100** | **13 per 100** (6 to 23) | | | |
| **Quality of Life** | | The mean Quality of Life in the intervention groups was **3.93 lower** (5.77 to 2.08 lower) | | 2511 (1 study) | ⊕⊕⊕⊖ **moderate**[1] |
| **Quality of Life - Physical Functioning** | | The mean Quality of Life - Physical Functioning in the intervention groups was **10.2 lower** (16.47 to 3.93 lower) | | 279 (1 study) | ⊕⊕⊕⊖ **moderate**[1] |
| **Quality of Life - Physical Role Functioning** | | The mean Quality of Life - Physical Role Functioning in the intervention groups was **8.8 lower** (18.23 lower to 0.63 higher) | | 279 (1 study) | ⊕⊕⊕⊖ **moderate**[1] |
| **Quality of Life - Emotional Role Functioning** | | The mean Quality of Life - Emotional Role Functioning in the intervention groups was **5.7 lower** (13.18 lower to 1.78 higher) | | 279 (1 study) | ⊕⊕⊕⊖ **moderate**[1] |
| **Quality of Life - Social Functioning** | | The mean Quality of Life - Social Functioning in the intervention groups was | | 279 (1 study) | ⊕⊕⊕⊖ **moderate**[1] |

| | | | | | |
|---|---|---|---|---|---|
| | | **0.2 higher**<br>(5.51 lower to 5.91 higher) | | | |
| **Quality of Life - Bodily Pain** | | The mean Quality of Life - Bodily Pain in the intervention groups was<br>**9.7 lower**<br>(15.57 to 3.83 lower) | | 279<br>(1 study) | ⊕⊕⊕⊖<br>**moderate**[1] |
| **Quality of Life - General Health Perception** | | The mean Quality of Life - General Health Perception in the intervention groups was<br>**6 lower**<br>(11.36 to 0.64 lower) | | 279<br>(1 study) | ⊕⊕⊕⊖<br>**moderate**[1] |
| **Quality of Life - Mental Health** | | The mean Quality of Life - Mental Health in the intervention groups was<br>**1.5 lower**<br>(5.63 lower to 2.63 higher) | | 279<br>(1 study) | ⊕⊕⊕⊖<br>**moderate**[1] |
| **Quality of Life - Vitality** | | The mean Quality of Life - Vitality in the intervention groups was<br>**3.2 lower**<br>(8.04 lower to 1.64 higher) | | 279<br>(1 study) | ⊕⊕⊕⊖<br>**moderate**[1] |
| **Quality of Life - Health Change** | | The mean Quality of Life - Health Change in the intervention groups was<br>**0.4 higher**<br>(4.42 lower to 5.22 higher) | | 279<br>(1 study) | ⊕⊕⊕⊖<br>**moderate**[1] |
| **Mortality** | **Study population** | | **OR 0.89**<br>(0.47 to 1.71) | 279<br>(1 study) | ⊕⊕⊕⊖<br>**moderate**[1] |
| | **16 per 100** | **15 per 100**<br>(8 to 25) | | | |
| | **Medium risk population** | | | | |
| | **16 per 100** | **15 per 100**<br>(8 to 25) | | | |

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

**CI:** Confidence interval; **OR:** Odds ratio;

GRADE Working Group grades of evidence
**High quality:** Further research is very unlikely to change our confidence in the estimate of effect
**Moderate quality:** Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate
**Low quality:** Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate
**Very low quality:** We are very uncertain about the estimate

[1]inadequate blinding

## Conclusions from the Evidence Based Analysis.

**Balloon-expandable stent vs PTA in superficial femoral artery disease**

Based on a moderate quality of evidence, there is no significant difference in patency between primary stenting using balloon expandable bare stents and PTA at 6, 12 and 24 months in patients with superficial femoral artery. The pooled OR for patency and their corresponding 95% CI are: 6 months 1.26 (0.74, 2.13); 12 months 0.95 (0.66, 1.38); and 24 months 0.72 (0.34, 1.55).

There is no significant difference in clinical improvement, re-interventions, peri and post operative complications, mortality and amputations between primary stenting using balloon-expandable bare stents and PTA in patients with superficial femoral artery. The pooled OR and their corresponding 95% CI are clinical improvement 0.85 (0.50, 1.42); ankle brachial index 0.01 (-0.02, 0.04) re-intervention 0.83 (0.26, 2.65); complications 0.73 (0.43, 1.22); all cause mortality 1.08 (0.59, 1.97) and amputation rates 0.41 (0.14, 1.18).

**Self-expandable stent vs PTA in superficial femoral artery disease.**

Based on a moderate quality of evidence, primary stenting using self-expandable bare stents is associated with significant improvement in patency at 6, 12 and 24 months in patients with superficial femoral artery. The pooled OR for patency and their corresponding 95% CI are: 6 months 2.35 (1.06, 5.23); 12 months 1.54 (1.01, 2.35); and 24 months 2.18 (1.00. 4.78).

However, the benefit of primary stenting is not observed for clinical improvement, re-interventions, peri and post operative complications, mortality and amputation in patients with superficial femoral artery disease. The pooled OR and their corresponding 95% CI are clinical improvement 0.61 (0.37, 1.01); ankle brachial index 0.01 (-0.06, 0.08) re-intervention 0.60 (0.36, 1.02); complications 1.60 (0.53, 4.85); all cause mortality 3.84 (0.74, 19.22) and amputation rates 1.96 (0.20, 18.86).

**Balloon-expandable stent vs PTA in iliac artery occlusive disease**

Based on moderate quality of evidence, despite immediate technical success, 12.23 (7.17, 20.88), primary stenting is not associated with significant improvement in patency, clinical status, treadmill walking distance and reduction in re-intervention, complications, cardiovascular events, all cause mortality, QoL and amputation rates in patients with intermittent claudication caused by iliac artery occlusive disease. The pooled OR and their corresponding 95% CI are: patency 1.03 (0.56, 1.87); clinical improvement 1.08 (0.60, 1.94); walking distance 3.00 (12.96, 18.96); re-intervention 1.16 (0.71, 1.90); complications 0.56 (0.20, 1.53); all cause mortality 0.89 (0.47, 1.71); QoL 0.40 (-4.42, 5.52); cardiovascular event 1.16 (0.56, 2.40) and amputation rates 0.37 (0.11, 1.23). To date no RCTs are available evaluating self-expandable stents in the common or external iliac artery stenosis or occlusion.

**Drug-eluting stent vs balloon-expandable bare stent in crural arteries**

Based on a very low quality of evidence, at 6 months of follow-up, sirolimus drug-eluting stents are associated with a reduction in target vessel revascularization and re-stenosis rates in patients with atherosclerotic lesions of crural arteries compared with balloon expandable bare stent. The OR and their corresponding 95% CI are: re-stenosis 0.09 (0.03, 0.28) and TVR 0.15 (0.05, 0.47) in patients with atherosclerotic lesions of the crural arteries at 6 months follow-up. Both types of stents offer similar immediate success. Limitations of this study include: short follow-up period, small sample and no assessment of mortality as an outcome. Further research is needed to confirm its effect and assess its safety.

## Discussion

The key findings of the MAS analyses are: compared with PTA, primary stenting using self-expanding bare stents is associated with significant improvement in patency at 6, 12 and 24 months in patients with superficial femoral artery. However, no statistically significant differences between primary stenting and PTA on re-interventions, clinical improvement, complications, mortality, amputations and ABI were observed. Methodological differences between MAS review and the five published systematic reviews and meta-analysis of RCTs reports are summarized below.

AHRQ review (37):

- The AHRQ review did not assess patency or re-stenosis as an outcome.

Kasapis et al (40):

- Includes three trials that are excluded by MAS review for the following reasons: 1) two were results published by FDA as reports of summary of findings on safety and effectiveness, (51;52) 2) the other used stent graft which is currently not licensed by Health Canada for femoro-popliteal artery disease. (50) MAS inclusion criteria are based on published results and devices licensed by Health Canada. Furthermore, MAS analysis also includes sub group analysis by time of outcome assessment.

YaJun et al (41):

- Only included RCTs using balloon expandable stents. MAS analysis includes both balloon and self-expandable stents.
- Included one study that was not randomized. MAS analysis only included published results of randomized trials
- Analysis based on number of evaluable patients at the chosen endpoint during follow-up. MAS analysis is based on ITT.
- The conclusion of significant primary patency at 6 months are influenced by one trial (48) which was not included in the MAS review as it was a pilot trial. For MAS review, feasibility trials were excluded.

Bachoo et al (38)

- Only included studies with patients with intermittent claudication. Only two studies were included and results could not be pooled for most outcomes. MAS analysis included studies with patients with intermittent claudication and critical ischemia.

Twine et al (39)

- "Analysis based on endpoint data from the individual clinical trials, which all quoted intention- to treat principle". This is not a true definition of ITT. A true definition of ITT analysed patients according to the treatment to which they were randomized. ITT is more pragmatic and preserve sample size. MAS analysis was based on a true definition of ITT.
- The analysis combined both balloon and self expanding stents. MAS analysis was performed according to a type of stent.
- The observed short term benefit of stenting was influenced by a trial using self expanding stent.

# Economic Analysis

**DISCLAIMER**: The Medical Advisory Secretariat uses a standardized costing method for its economic analyses of interventions. The main cost categories and the associated methods from the province's perspective are as follows:

**Hospital**: Ontario Case Costing Initiative cost data are used for in-hospital stay, emergency visit and day procedure costs for the designated International Classification of Diseases (ICD) diagnosis codes and Canadian Classification of Health Interventions procedure codes. Adjustments may be required to reflect accuracy in estimated costs of the diagnoses and procedures under consideration. Due to the difficulties of estimating indirect costs in hospitals associated with a particular diagnosis or procedure, the secretariat normally defaults to considering direct treatment costs only.

**Nonhospital**: These include physician services costs obtained from the Ontario Schedule of Benefits, laboratory fees from the Ontario Schedule of Laboratory Fees, drug costs from the Ontario Drug Benefit Formulary, and device costs from the perspective of local health care institutions whenever possible or its manufacturer.

**Discounting**: For cost-effectiveness analyses, a discount rate of 5% is applied as recommended by economic guidelines.

**Downstream costs**: All numbers reported are based on assumptions on population trends (i.e. incidence, prevalence and mortality rates), time horizon, resource utilization, patient compliance, healthcare patterns, market trends (i.e. rates of intervention uptake or trends in current programs in place in the Province), and estimates on funding and prices. These may or may not be realized by the system or individual institutions and are often based on evidence from the medical literature, standard listing references and educated hypotheses from expert panels. In cases where a deviation from this standard is used, an explanation is offered as to the reasons, the assumptions, and the revised approach. The economic analysis represents ***an estimate only***, based on the assumptions and costing methods that have been explicitly stated above. These estimates will change if different assumptions and costing methods are applied to the analysis.

## Study Question

The objective of this economic analysis was to report costs associated with percutaneous transluminal angioplasty (PTA) and selective stenting as a treatment management for peripheral artery disease (PAD) of the lower extremities.

## Economic Literature Review

A literature search was performed on February 8th, 2010 using OVID MEDLINE, MEDLINE In-Process and Other Non-Indexed Citations, OVID EMBASE, Wiley Cochrane, Centre for Reviews and Dissemination/International Agency for Health Technology Assessment, and EconLit for studies published from 1950 (MEDLINE) to week 04, 2010 (EMBASE, MEDLINE). Included studies were those with full economic evaluations describing both costs and consequences of PTA and stenting of the following vessels and arteries (lower extremities): femoral, iliac, popliteal, tibial, infra-popliteal, femoro-popliteal, infra-inguinal, infra-genicular, tibio-peroneal, or crural.

The primary outcome of interest for the present review was the incremental cost-effectiveness ratio (ICER) using quality-adjusted life years (QALYs). A secondary outcome was hospital and/or physician

costs for PTA and stent placement procedures related to PAD of the lower extremities.

## Search Strategy Results

There were six studies identified that compared either primary stent placement, or selective stenting following PTA revascularization.(54-59) PTA and stent placement procedures were compared for iliac arterial stenosis in two studies (54;55); two studies compared procedures for femoro-popliteal arteries (56-58); and one study compared procedures in a population containing patients with either iliac or femoro-popliteal arterial stenosis.(59) The results of these studies were reported in either United States dollars (USD) (54-58) or European Union euros (EUR).(59)

All of the six studies were cost-effectiveness analyses (CEAs) (54-56;58;59), except for one study which examined the in-hospital costs only of stent implantation versus PTA (balloon angioplasty) (57) There were four studies which used decision-analytic models for the CEAs (54-56;58) and one study which was based on the prospective economic analysis of a randomized control trial (59); all of these studies reported costs per QALY.

Comparators of the cost-effectiveness analyses varied among the studies identified above. Primary stent placement versus PTA was evaluated in two studies (54;57). PTA followed by selective stent placement when necessary, due to PTA procedural failure, was compared to the following: PTA alone or primary stent placement in one study (54); hospital-based exercise in two studies (56;59); and bypass surgery in two studies (56;58). Additional comparators were defined in terms of treatment strategies and therapy sequences in certain studies, where the second treatment was given only when the first therapy had failed. In Bosch et al. 2000 (55), the following strategies were compared to each other in the study: PTA followed by no revascularization (i.e. no additional PTA, selective stent placement, or bypass surgery); PTA with selective stent placement followed by no revascularization; PTA followed by a repeated PTA procedure; PTA followed by PTA with selective stenting; and PTA with selective stenting, followed by another PTA with selective stenting procedure. In Muradin et al. 2001 (58), the following strategies were compared: PTA with selective stent placement followed by bypass surgery; PTA alone followed by bypass surgery; and bypass surgery followed by surgical revision (another bypass surgery). In de Vries et al. 2002 (56), there were five strategies evaluated: 1) exercise as initial treatment followed by no treatment; 2) exercise followed by PTA with selective stent placement; 3) exercise followed by PTA with selective stenting or bypass surgery; 4) PTA with selective stenting or exercise, followed by PTA with selective stenting; 5) PTA with selective stenting or bypass surgery or exercise, followed by PTA with selective stenting or bypass surgery.

The ICERs, costs and QALYs gained when compared to reference (base) strategies are shown in Table 19. Note that the ICERs are presented for only the non-dominated strategies (i.e. strategies which showed higher or equivalent effectiveness for a lower cost, or greater effectiveness with a lower ICER). The study by Muradin et al. 2001 (58) did not evaluate PTA with a stenting procedure explicitly, rather a "hypothetical" endovascular device was used in their decision analytic model. Based on certain assumptions of device performance (patency, mortality rates), the study found that the use of an endovascular device would be cost-effective, as the range of device characteristics input in the model seemed to be plausible in real-world clinical settings.

The results of the CEAs were sensitive to certain factors used in the decision-analytic models. In general, PTA without stenting was favoured if the relative risk of long-term stent failure increased, or if the patency rate was similar between PTA and PTA with selective stenting procedures. Results were also sensitive to the following list of factors: large differences in health states values (utilities) associated with "severe claudication" versus "no or mild claudication" tended to decrease ICER values; comparisons with bypass surgery were sensitive to the quality of life (QoL) of patients with systemic complications (lower QoL tended to increase ICERs); higher costs of any revascularization procedure tended to decrease cost-

effectiveness; and increasing age or positive history of coronary artery disease tended to increase ICER values. Results of the CEAs were not sensitive to duration of revascularization procedure, distribution of one- or two-sided lesions, price of stent, discount rate; for comparisons with exercise, decreasing the survival benefit of the exercise program did not affect the results substantially.

## Conclusion of Literature Review

PTA with selective stent placement was often found to be cost-effective, with ICERs of less than $50,000 USD, when compared to other treatment strategies of PAD of the lower extremities (iliac or femoro-popliteal arteries). The cost of PTA with selective stent placement was higher than PTA alone, but less than the cost of bypass surgery. In terms of quality of life and QALYs gained, patients were shown consistently to benefit (greater QALYs gained) when PTA with selective stenting procedures were used when indicated; either as a primary procedure or as a secondary procedure upon failure of the first procedure. The only study showing PTA with selective stenting not to be economically attractive was performed by Spronk et al. 2008 (59), which was based on a randomized controlled trial showing no significant difference in effectiveness between PTA with selective stent placement and hospital-based exercise on patients with intermittent claudication.

**Table 19: Summary of ICERs and selected characteristics of studies evaluating PTA with stent, or without stent placement procedures**

| Study | Perspective | Time horizon | Comparator | Base strategy | ΔCost | ΔQALY | ICER |
|---|---|---|---|---|---|---|---|
| Bosch 1998 (54) | Societal | Lifetime | PTA with selective stent placement followed by no revascularization | No revascularization | $2,500 | 0.73 | 4,073 |
| | | | Initial and repeated (if necessary) PTA with selective stent placement | No revascularization | $4,438 | 1.31 | 4,519 |
| Bosch 2000 (55) | Societal | Lifetime | PTA with selective stent placement followed by no revascularization | No revascularization | $6,372 | 0.84 | 7,624 |
| | | | Initial and repeated (if necessary) PTA with selective stent placement | No revascularization | $8,627 | 1.10 | 8,519 |
| De Vries 2002 (56) | Societal | Lifetime | Exercise followed by PTA with selective stent placement or bypass surgery | Exercise | $25,833 | 0.17 | 359,948 |
| | | | PTA with selective stent placement or exercise, followed by repeated PTA with selective stent placement | Exercise | $3,750 | 0.10 | 36,360 |
| Greenberg 2004 (57) | Health system | 2 years | PTA with stent placement | PTA alone | $3,455 | NA | NA |
| Spronk 2008 (59) | Societal | 1 year | PTA with selective stent placement | Hospital-based exercise | € 2,318 | 0.01 | 231,800 |

Note: NA = Not applicable; All studies applied discounting to both costs and effects (QALYs), except for Spronk et al. 2008 (59) who applied discounting to costs only, and Greenberg et al. 2004 who did not discount costs of the 2-year randomized trial data.

## Ontario-Based Cost Impact Analysis

The annual volumes of PTA procedures of the lower limbs in Ontario, with or without stent placement, were obtained from the National Ambulatory Care Reporting System (NACRS) hospital day surgery database for fiscal years 2004 to 2008. Historical procedural volumes (shown in Table 20) were projected forward for the subsequent five years (2009-2013) based on average annual increases in the historical procedural time series (shown in Table 23). A list of 2009 Canadian Classification of Health Interventions (CCI) (60) procedure codes used to identify PTA procedures is shown in Table 21. Note that the primary analytic perspective of the cost impact analysis was that of the Ministry of Health and Long-Term Care (MOHLTC).

Total costs of PTA with selective stent placement were estimated using physician and hospital costs from the 2009 Ontario Health Insurance Schedule of Benefits and Fees (OHISBF) (61), and 2007 fiscal year data from the Ontario Case Costing Initiative (OCCI) (62) database, respectively. In the case of physician costs, two groups of codes were used to represent "high" and "low" estimates of PTA procedural costs with and without stenting, as coding variation existed in the remuneration of physicians for these procedures in Ontario. "PTA with stent placement" was defined using OHISBF codes J021, J022, R815, and J058 for the low cost estimate, and OHISBF code R875 for the high cost estimate (see Table 22); "PTA without stent" was defined using OHISBF codes J021, J022 and R815 for the low cost estimate, and OHISBF codes J021, J022 and R783 for the high cost estimate.

For hospital cost estimation of PTA with or without stent placement, the following two CCI codes were used: 1.KG.50.GQ-BD ("dilation, arteries of leg; using percutaneous transluminal approach and balloon dilator") and 1.KG.50.GQ-OA ("dilation, arteries of leg; using percutaneous transluminal approach and balloon dilator with endovascular stent insertion). The average total cost (direct and indirect costs) for PTA alone (without stent) was listed in the 2007 OCCI as $ 2,159 CAD, however, there was no corresponding procedural cost listed for PTA with stenting. To estimate this cost, the additional cost of the stent was imputed from the cost difference (ratio) of PTA performed on the abdominal arteries. The following two CCI codes were used to calculate a cost ratio associated with stent placement: 1.KE.50.GQ-BD ("dilation, abdominal arteries; using percutaneous transluminal approach and balloon dilator") and 1.KE.50.GQ-OA ("dilation, abdominal arteries; using percutaneous transluminal approach and balloon dilator with endovascular stent insertion"). The ratio of the cost of abdominal PTA with stent ($2,859 CAD) to abdominal PTA alone ($2,168 CAD) was calculated to be approximately 1.32. Noting that cost of the leg PTA procedure alone ($2,159) is similar to the cost of the corresponding abdominal procedure ($2,168), it was anticipated the average cost of the leg PTA with stent would be $2,847 CAD.

The average total cost of PTA was found to be between $2,868 and $ 3,413 CAD without stent placement, and between $ 3,636 and $ 4,178 CAD with stent placement. These average costs imply an incremental cost of stent placement for PTA procedures of between $223 to $1,310 CAD, or an average total incremental cost of about $770 CAD. Projected costs for fiscal years 2009-2013 is shown in Table 23 for PTA with selective stenting, where the proportion of PTA procedures with stent placement is shown at 60%, 75% and 90% of total procedural volume. The average annual cost for the years 2009-2013 of stent placement in 60% of PTA procedures is approximately $5.27 million CAD; stent placement in 75% of PTA procedures is $5.44 million CAD; and stent placement in 90% of PTA procedures is $5.61 million CAD.

**Table 20: Historical procedural volume of PTA day surgery visits in Ontario by fiscal year and stenting procedure of the lower limbs**

| PTA procedures | 2004 | | 2005 | | 2006 | | 2007 | | 2008 | |
|---|---|---|---|---|---|---|---|---|---|---|
| | N Visits | Col % | N Visits | Col % | N Visits | Col % | N Visits | Col % | N Visits | Col % |
| PTA with stent placement | 247 | 22.4 | 289 | 24.4 | 382 | 30.1 | 451 | 34.3 | 385 | 29.7 |
| PTA without stent | 854 | 77.6 | 898 | 75.7 | 889 | 69.9 | 863 | 65.7 | 910 | 70.3 |
| Total | 1,101 | 100.0 | 1,187 | 100.0 | 1,271 | 100.0 | 1,314 | 100.0 | 1,295 | 100.0 |

**Table 21: List of 2009 CCI procedure codes for PTA procedures with stent, or without stent placement**

| Code | Description |
|---|---|
| ***PTA procedure codes (Dilation, arteries of leg)*** | |
| 1.KG.50.GQ-xx | Using percutaneous transluminal approach - balloon, or laser, or endovascular stent |
| 1.KG.57.GQ-xx | Extraction, arteries of leg NEC - percutaneous transluminal approach |
| ***PTA procedure codes (Repair, arteries of leg)*** | |
| 1.KG.80.GQ-NR-N | Using percutaneous transluminal approach and endovascular stent with synthetic graft |

Note: In the above list, "xx" denotes all sub-category CCI codes found under the specified 7-digit heading.

**Table 22: List of 2009 OHISBF codes for PTA procedures with stent, or without stent placement**

| Code | Description | Cost |
|---|---|---|
| ***PTA-related fee codes*** | | |
| J021 | Insertion of catheter | $121.40 |
| J022 | Selective catheterization (x 1-4) | $60.15 |
| R783 | Aorto-Iliac repair - including common iliac repair | $1,012.00 |
| R791 | Femoro-popliteal - with saphenous vein | $857.35 |
| R815 | Abdominal - Arterioplasty with or without patch graft including | $527.75 |
| ***Additional fee codes for stenting*** | | |
| J058 | Vascular stenting | $79.75 |
| R875 | Endovascular aneurysm repair using stent grafting - All inclusive fee code | $1,330.40 |

**Table 23: Five-year projected procedural volume and cost of PTA day surgery visits and stenting procedure of the lower limbs**

| Projected procedural volume | 2009 | | 2010 | | 2011 | | 2012 | | 2013 | | 5-Year Average |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | 1,349 | | 1,404 | | 1,463 | | 1,523 | | 1,586 | | |
| **Cost of PTA with stents** | **Low** | **High** | **Low** | **High** | **Low** | **High** | **Low** | **High** | **Low** | **High** | **Annual** |
| 60% with stents | 4.49M | 5.22M | 4.68M | 5.44M | 4.87M | 5.66M | 5.07M | 5.90M | 5.28M | 6.14M | 5.27M |
| 75% with stents | 4.64M | 5.38M | 4.84M | 5.60M | 5.04M | 5.83M | 5.25M | 6.07M | 5.46M | 6.32M | 5.44M |
| 90% with stents | 4.80M | 5.53M | 5.00M | 5.76M | 5.21M | 6.00M | 5.42M | 6.25M | 5.65M | 6.50M | 5.61M |

Note: “M” in the above table refers to millions of CAD.

# Appendices

## Appendix 1: Clinical Categories of Chronic Limb Ischemia

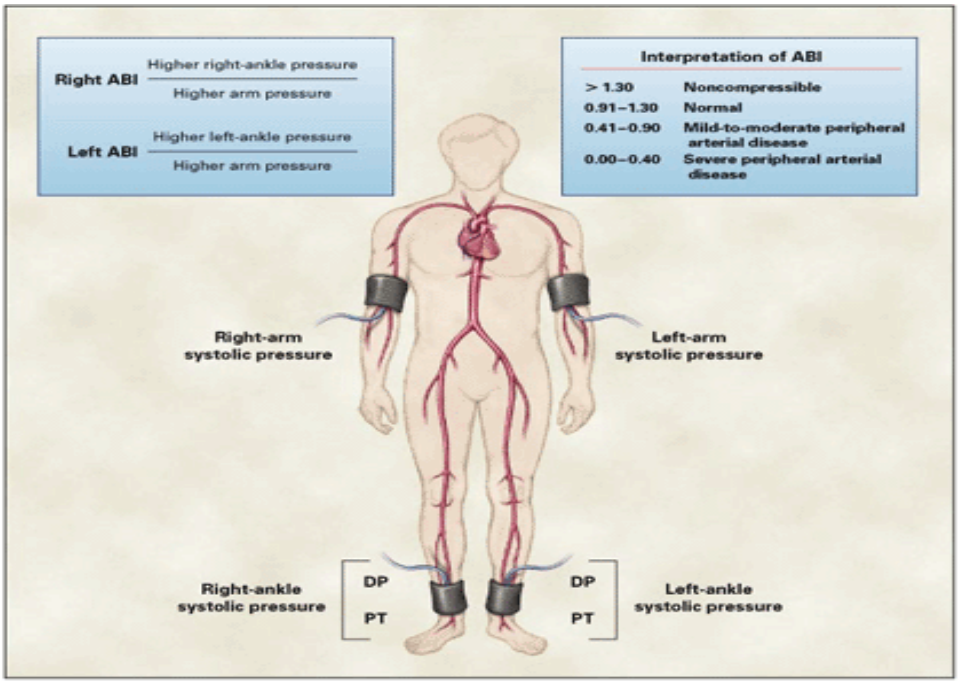
| Grade | Category | Clinical Description | Objective Criteria |
|---|---|---|---|
| 0 | 0 | Asymptomatic-no hemo-dynamically significant occlusive disease | Normal treadmill or reactive hyperaemia test |
| | 1 | Mild | Completes treadmill exercise; AP after exercise† >50mm Hg but at least 20 mm Hg lower than resting value |
| | 2 | Moderate claudication | Between category 1 and 3 |
| I | 3 | Severe claudication | Cannot complete standard treadmill exercise and AP after exercise<50mm Hg |
| II* | 4 | Ischemic rest pain | Resting AP < 40mmHg, flat or barely pulsatile ankle or metatarsal PVR;TP< 30mmHg |
| | 5 | Minor tissue loss-non-healing ulcer, focal gangrene with diffuse pedal ischemia | Resting AP < 60mmHg, ankle or metatarsal PVR flat or barely pulsatile;TP < 40mmHg |
| III* | 6 | Major tissue loss-extending above TM level, functional foot no longer salvageable | Same as category 5 |

AP-ankle pressure; PVR-pulse volume recording; TP-toe pressure, TM- transmetatarsal.

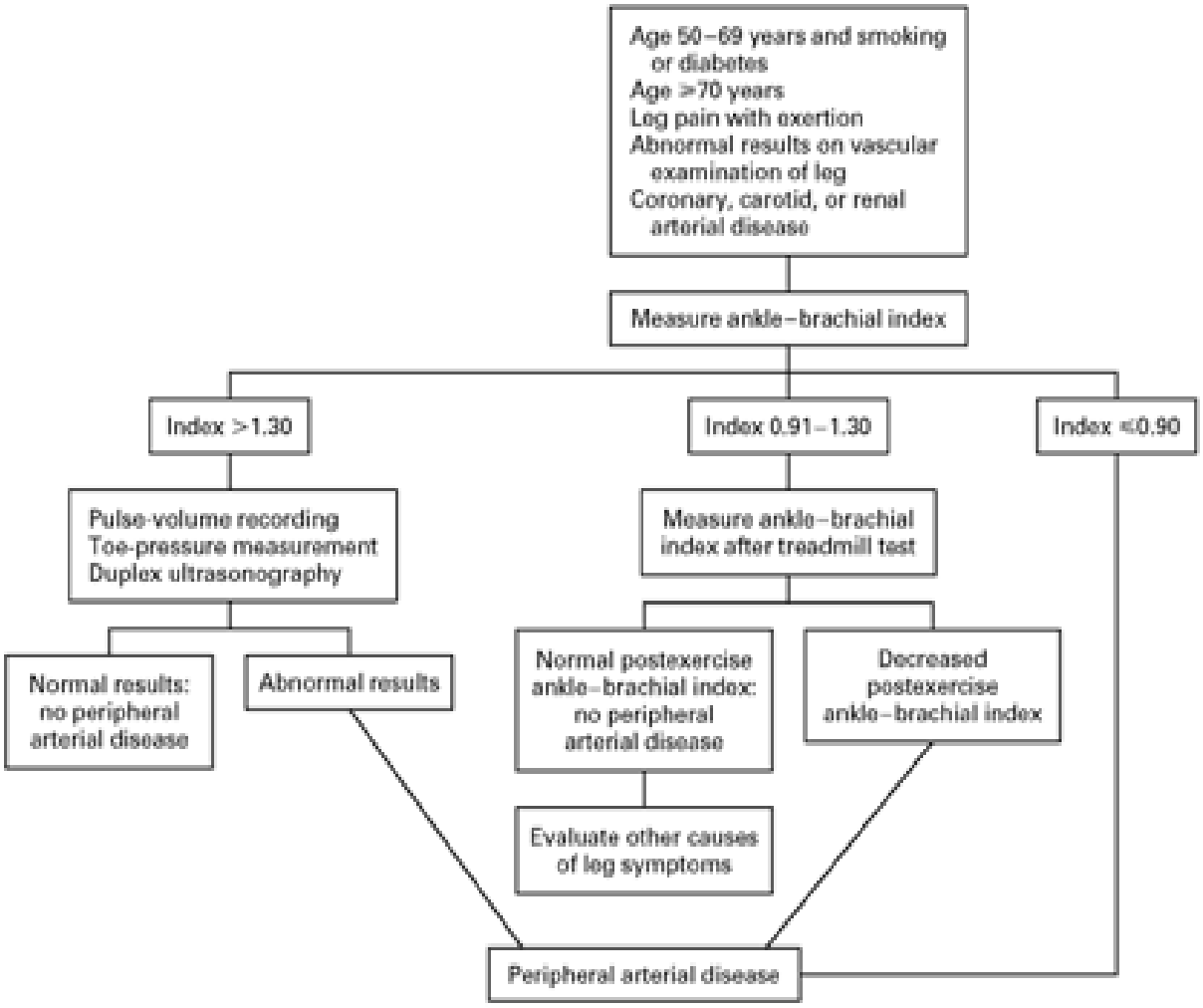
*Grades II and III-categories 4, 5 and 6 are embraced by the term chronic critical ischemia.
† Five minutes at 2mph on a 12% incline

*Source: Rutherford RB, Baker JD, Ernst C, Johnston KW, Porter JM, Ahn S et al. Recommended standards for reports dealing with lower extremity ischemia: revised version. J Vasc Surg 1997; 26(3):517-538.*

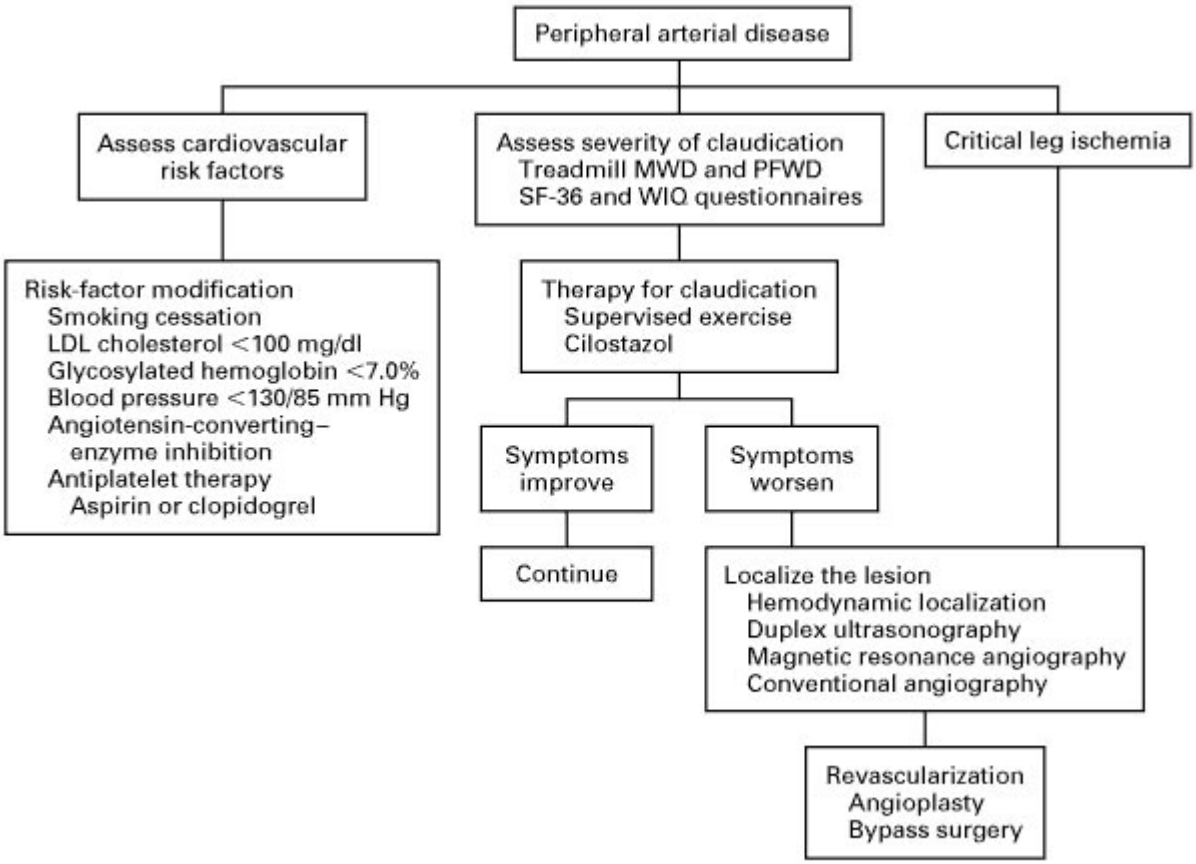
## Appendix 2: Measurement of the Ankle Brachial Index



## Appendix 3: Overall Strategy in Evaluating Patients in Whom PAD is Suspected



## Appendix 4: Evaluation and Treatment Strategies for Patients with Proved PAD



# Appendix 5: Fontaine Classification of PAD Symptoms

| Fontaine Stage | Definition of Clinical Manifestation |
|---|---|
| I | No symptoms |
| II | Intermittent claudication |
| III | Pain at rest |
| IV | Critical ischemia, ulceration, or gangrene |

# Appendix 6: Recommended Scale for Gauging Changes in Clinical Status (19)

| | |
|---|---|
| +3 | *Markedly improved:* No ischemic symptoms, and any foot lesions completely healed; ABI essentially "normalized" (increased to more than 0.90) |
| +2 | *Moderately improved:* No open foot lesions; still symptomatic but only with exercise and improved by at least one category*; ABI not normalized but improved by more than 0.10. |
| +1 | *Minimally improved:* greater than 0.10 increase in ABI† but no categorical improvement or vice versa (i.e. upward categorical shift without an increase in ABI of more than 0.10) |
| 0 | *No change:* No categorical shift and less than 0.10 change in ABI |
| -1 | *Mildly worse:* No categorical change but ABI decreased more than 0.10, or downward categorical shift with ABI decrease less than0.10 |
| -2 | *Moderately worse:* One category worse or unexpected minor amputation |
| -3 | *Markedly worse:* More than one category worse or unexpected major amputations |

*Categories refer to clinical classification
† In cases where the ABI cannot be accurately measured, an index based on the toe pressure, or any measurable pressure distal to the site of revascularization, may be substituted.

## Appendix 7: Literature Search Strategy

Search date: February 2, 2010
Databases searched: OVID MEDLINE, MEDLINE In-Process and Other Non-Indexed Citations, OVID EMBASE, Wiley Cochrane, Centre for Reviews and Dissemination/International Agency for Health Technology Assessment
Database: Ovid MEDLINE(R) <1950 to January Week 3 2010>
Search Strategy:

---

1 exp femoral artery/ or exp iliac artery/ or exp popliteal artery/ or exp tibial arteries/ (32107)
2 ((femoral or iliac or popliteal or tibial or infra-popliteal or infrapopliteal or femoropopliteal or femoro-popliteal or infrainguinal or infragenicular or tibioperoneal or tibio-peroneal or crural) adj2 (vessel* or arter*)).ti,ab. (26847)
3 1 or 2 (44206)
4 exp Peripheral Vascular Diseases/ (38657)
5 3 and 4 (1446)
6 (peripheral adj (arter* or vascular) adj (disease* or stenos* or angiopath* or lesion*)).ti,ab. (10504)
7 exp Intermittent Claudication/ (6126)
8 (leg* adj2 isch?emi*).mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier] (876)
9 5 or 6 or 7 or 8 (17385)
10 exp Stents/ (35816)
11 stent*.mp. (47105)
12 10 or 11 (47105)
13 9 and 12 (782)
14 limit 13 to (english language and humans) (695)
15 limit 14 to (controlled clinical trial or randomized controlled trial) (41)
16 exp Technology Assessment, Biomedical/ or exp Evidence-based Medicine/ (43565)
17 (health technology adj2 assess$).mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier] (882)
18 (meta analy$ or metaanaly$ or pooled analysis or (systematic$ adj2 review$)).mp. or (published studies or published literature or medline or embase or data synthesis or data extraction or cochrane).ab. (87331)
19 exp Random Allocation/ or random$.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier] (603641)
20 exp Double-Blind Method/ (103116)
21 exp Control Groups/ (1187)
22 exp Placebos/ (28235)
23 (RCT or placebo? or sham?).mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier] (177532)
24 or/15-23 (786687)
25 14 and 24 (113)

Database: EMBASE <1980 to 2010 Week 04>
Search Strategy:

---

1 exp leg artery/ (18789)
2 ((femoral or iliac or popliteal or tibial or tibioperoneal or tibio-peroneal or infra-popliteal or infrapopliteal or femoropopliteal or femoro-popliteal or infrainguinal or infragenicular or crural) adj2 (vessel* or arter*)).ti,ab. (22661)
3 1 or 2 (28926)
4 exp peripheral vascular disease/ (650785)

5 3 and 4 (12890)
6 (peripheral adj (arter* or vascular) adj (disease* or stenos* or angiopath* or lesion*)).ti,ab. (9345)
7 exp leg ischemia/ or exp intermittent claudication/ (7104)
8 or/5-7 (26087)
9 exp stent/ (43687)
10 stent*.ti,ab. (40614)
11 9 or 10 (51429)
12 8 and 11 (2493)
13 limit 12 to (human and english language) (1929)
14 Randomized Controlled Trial/ (179868)
15 exp Randomization/ (27412)
16 exp RANDOM SAMPLE/ (1751)
17 exp Biomedical Technology Assessment/ or exp Evidence Based Medicine/ (321229)
18 (health technology adj2 assess$).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name] (777)
19 (meta analy$ or metaanaly$ or pooled analysis or (systematic$ adj2 review$) or published studies or published literature or medline or embase or data synthesis or data extraction or cochrane).ti,ab. (74255)
20 Double Blind Procedure/ (75799)
21 exp Triple Blind Procedure/ (14)
22 exp Control Group/ (5479)
23 exp PLACEBO/ or placebo$.mp. or sham$.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name] (231323)
24 (random$ or RCT).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name] (466933)
25 (control$ adj2 clinical trial$).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name] (303171)
26 or/14-25 (859619)
27 13 and 26 (334)

# Appendix 8: Characteristics of Included Studies

| Author, Year | Patients | Comparison | Outcomes Definitions | Follow-up in months | Authors conclusion | Notes |
|---|---|---|---|---|---|---|
| **Superficial Femoral Artery Disease** | | | | | | |
| Vroegindeweij, 1997 | Age: 41-82 with femoro-popliteal obstructive disease.<br>Male: n=36<br>Female: n=15<br>Disease Extent: ≤5 lesion length. Mild to moderate intermittent claudication according to SVS-ISCVS (class I)<br>Mild –Moderate claudication: n=42<br>Severe claudication : n=9<br>Coronary heart disease: n=15<br>Diabetes: n=6<br>Smoking: n=32<br>Hypertension: n=9<br>Hypercholesterolemia: n=16<br><br>Degree of stenosis:<br>50-69%: n=9<br>70-99%: n=33<br>Occlusion : n=9 | Balloon expandable Palmaz stent by Johnson and Johnson Interventional System, NJ) Vs balloon angioplasty | *Technical success*: ≤ 30% residual stenosis on arteriogram.<br><br>*Clinical/ hemodynamic success*: according to SVS-ISCVS.<br>*Primary Patency:* determined by duplex surveillance.<br><br>*Re-stenosis:* PSV ≥2.5<br>The location of stenotic sites at follow-up was compared with pre-intervention arteriograms to enable differentiation between re-stenosis and new stenosis.<br><br>*Re-intervention:* based on duplex US criterion(63) | 3, 6, 9, 12, 18, 24 | Stenting does not improve clinical and hemodynamic outcome. Thus use of primary stenting for femoro-popliteal artery stenosis / occlusion is not justified. However stenting has a supplemental value in complicated procedures to prevent occlusion due to major dissections after balloon angioplasty | - Early technical failures and attempted but abandoned procedures were considered endpoints of patency.<br>- Patients with crossover treatments remained assigned to the treatment group of randomization.<br>-Patients crossed over from stent to PTA: n=4<br>- Lesions not predilated before stenting.<br>- Patients continued with heparin for 24hrs following the procedure or until anticoagulant was within the therapeutic level according to international normalized ratio. After which, all patients received Coumadin. Anticoagulation treatment continued for 3 months where after treatment was changed to aspirin 80mg/day indefinitely.<br>- Data analyzed according to intention to treat principle. |

| Author, Year | Patients | Comparison | Outcomes Definitions | Follow-up in months | Authors conclusion | Notes |
|---|---|---|---|---|---|---|
| Zdanowski, 1999 | Patients with chronic limb ischemia aged 41-86 with femoral popliteal artery occlusion.<br>Diabetes n=10<br>Ulceration/gangrene n=21<br>Rest pain n=6<br>Claudication n=5<br><br>Disease extent: Occlusion length 2-20cm.<br>ABPI ranged 0.13-0.79 | Ballon expandable Strecker stent by Meditech, Boston Scientific Corporation, USA) vs PTA alone | Failures and complications were analyzed according to SVS-ISCVS:<br><br>*Technical success:* recanalisation with residual stenosis <30% and antegrade flow at occlusion of the procedure.<br><br>*Primary patency:* Single angioplasty treatment session.<br>*Secondary patency:* Further site procedures.<br><br>*Re-stenosis:* >50% from immediately after stenting.<br>*ABPI improvement:* Increase >0.10.<br><br>*Angiographic patency:* open artery at site of intervention<br>*Clinical improvement:* ≥50% cluadication distance improvement and resolution of rest pain and healing ulcers.<br><br>*Major complications:* Concern of either patient's general health or local complication. | 12 | Stenting does not significantly improve clinical state or angiographic patency. Stent implantation can only be recommended for complications such as dissection, intimal tearing or immediate re-occlusion after PTA. The results do not justify any routine placement of stent following PTA in the successfully recanalized femoro-popliteal arteries. | - No crossovers.<br>- All patients received Aspirin 160mg daily post operatively. |

| Author, Year | Patients | Comparison | Outcomes Definitions | Follow-up in months | Authors conclusion | Notes |
|---|---|---|---|---|---|---|
| Cejna, 2001 | Age 39-87 with femoropopliteal artery obstruction.<br>Male: n=95<br>Female: n=59<br>Disease Extent: ≤5 lesion length and at least one patent runoff vessel. Intermittent claudication SVS-ISCVS categories 1-3 or chronic critical limb ischemia SVS-ISCVS category 4 or minor tissue loss category 5.<br><br>SVS-ISCVS categories:<br>Mild to moderate: n=24<br>Severe claudication: n=84<br>Ischemic rest pain: n=18<br>Minor tissue loss: n=28<br>Diabetes: n=63<br>History of smoking: n=92<br>Hypercholesterolemia: n=69<br>Hypertony: n=67<br>Adipositas: n=42 | Balloon expandable Palmaz stent by Johnson and Johnson Interventional System, NJ) Vs balloon angioplasty | *Technical success:* ≤ 30% residual stenosis on bi plane angiography confirmed by color duplex sonography and measurement of ABI 24-48 hours post procedure.<br><br>*Primary Patency:* determined by duplex surveillance.<br><br>*Re-stenosis:* ≥ 70% on angiography or PVS>2.5.<br><br>*Hemodynamic success:* Improvement of ABI by 0.10.<br><br>*Hemodynamic/ clinical re-obstructions:* decrease of 0.10 ABI/decrease of one SVS-ISCVS category.<br><br>*Clinical success :* improvement according to SVS-ISCVS.<br><br>*Major complication:* Change in the level of care, surgery or prolonged hospital stay or death. Complications within 30 days were considered procedure related. | 3, 6, 12 | Primary technical success rate is significantly higher after stent placement than PTA. Patency, clinical and hemodynamic success rates were not improved after 1 year. Stent implantation with Palmaz stents can be advocated as a selective procedure after failed PTA. | - Trial performed on intention to treat principle considering early technical failures as endpoint of patency.<br>- Patients with crossover treatments remained assigned to the treatment group of randomization but considered secondarily patent (i.e. primary failures as endpoint of patency).<br>- Limbs crossed over to receive stent n=10<br>-Limbs were predilated before stent implantation.<br>- Postoperatively, patients were placed on acetylsalicylic acid 100mg/day indefinitely. |

| Author, Year | Patients | Comparison | Outcomes Definitions | Follow-up in months | Authors conclusion | Notes |
|---|---|---|---|---|---|---|
| Grimm, 2001 | Mean age: 69.3<br>Male: n=32<br>Female: n=21<br>Patients with single stenosis / occlusion of the superficial femoral artery including popliteal lesion (stages 1-3 on Rutherford scale) located 1cm from SFA bifurcation.<br>Category 1: n=10<br>Category 2: n=19<br>Category 3: n=23<br>Occlusion: n=16<br>Disease Extent: Lesion length < 5cm, ≥ 70% stenosis with at least 2 patent vessels for runoff | Balloon expandable Palmaz stent by Cordis, Netherlands) Vs PTA | *Technical success:* according to SCVIR (Society of Cardiovascular and Interventional Radiology), ≤ 20% residual stenosis, significant hemodynamic improvement and no major morbidity.<br><br>*Clinical success:* complete / substantial relief of symptoms. Long term clinical success defined as ABI >0.75, a patent vessel on angiography.<br><br>*Re-stenosis:* an increased systolic flow velocity at least < 1.5 times higher than normal<br>*Major complications:* prolonged hospital stay > 24hrs, unplanned increase in the level of care, death or permanent sequalae. | 6, 12, 24, 39 | PTA with stent in the femoro-popliteal artery did not produce better results than PTA alone although it provided better luminal gain after angioplasty. Therefore the use of stents in the femoro-popliteal vessel should be reassessed. | - If two stents had to be implanted the distal one was placed first.<br><br>- PTA patient crossed over to receive stent n=4.<br>- All patients received intravenous heparin for 24hrs after the procedure and thereafter received aspirin for remainder of their lives. |
| Becquemin, 2003 | Mean age 66. Patients with single stenosis / occlusion of the superficial femoral artery lesion located 1cm from SFA origin.<br>Severe claudication / limb threatening ischemia SVS-ISCVS stages IIb , III or IV.<br>Disease Extent: Lesion length 1-7cm with at least 1 patent leg artery.<br>Male : 142<br>Female : n=85<br>Heart disease : n=59<br>Previous stroke : 16<br>Diabètes: n=27<br>Hypertension: n=118<br>Dyslipidemia: n=91<br>Smoking: n=139<br>Previous vascular surgery: n=60 | Balloon expandable Palmaz Stent by Cordis or Johnson and Johnson interventional systems, NJ) vs PTA | *Re-stenosis:* >50% stenosis on angiography 1 year post procedure.<br><br>*Complications:* MI, stroke, death, deep venous thrombosis, pulmonary embolism, renal and life threatening complications | 1,3, 6, 12, 18,24, 36, 48 | Systematic stenting of short stenosis or occlusions of the superficial femoral artery is not justified. Palmaz stent should be reserved for suboptimal results of balloon angioplasty | - For sub-optimal results i.e. > 30% residual stenosis after repeat angioplasty, physician had the choice of retracting the balloon without any further intervention or of placing a stent.<br>- PTA patient crossed over to receive stent n=15.<br>In the primary stent group, stenting was placed before or after lesion predilation.<br>- Post operatively patients were given heparin for 24 hrs after the procedure and then placed on aspirin 300mg/day or ticlopidine indefinitely.<br>- Analysis performed on intention to treat principle. |

| Author, Year | Patients | Comparison | Outcomes Definitions | Follow-up in months | Authors conclusion | Notes |
|---|---|---|---|---|---|---|
| Schillinger, 2006; 2007, Sabeti 2007 | Patients with SFA (claudication / CLI)<br>Mean age: 66.5 years<br>Male: 55<br>Female: 49<br>Disease Extent: Rutherford stage 3-5<br>Category 3: n=91<br>Category 4: n=3<br>Category 5: n=10<br><br>> 50% stenosis or occlusion on DSA (digital subtraction angiography),<br>Lesion length > 30mm.<br>Diabètes: n=39<br>Hyperlipidemia: n=93<br>Hypertension: n=95<br>Smoking: n=46<br>Coronary artery disease: n=74<br>History of MI: n=14<br>History of stroke: n=7 | Self expanding nitinol stents by Dynalink or Absolute Guidant ) vs PTA | *Re-stenosis:* > 50% (PVR>2.4) at 6 months on CTA (computer tomographic angiography) or DSA and the occurrence of stent fractures on radiography.<br><br>*Other outcomes:*<br>Resting ABI,<br>Walking distance, amputation, death and re-intervention at 2 years. | 3, 6, 12, 24 | Primary implantation for self expanding nitinol stents for the treatment of lesions of SFA was associated with superior anatomical and intermediate term (6 and 12 months) compared to currently recommended approach of angioplasty with optional secondary stenting.<br>At 2 years stenting with self expanding nitinol stents yielded a sustained morphological benefit and a trend toward clinical benefit compared with balloon angioplasty with optional stenting | - In PTA group, if results were sub-optimal i.e. > 30% residual stenosis after repeat angioplasty stent was implanted.<br>- PTA patient crossed over to receive stent n=17.<br>- Patients in the stenting group received stenting without predilation with the exception of those with tight or heavily calcified lesions.<br>- Post-operatively, all patients received aspirin 100mg/day and clopidogrel 75mg/day for three months.<br>- Analysis of the primary and secondary endpoints was performed according to intention to treat principle. Secondary analysis according to treatment actually received. |

| Author, Year | Patients | Comparison | Outcomes Definitions | Follow-up in months | Authors conclusion | Notes |
|---|---|---|---|---|---|---|
| Krankenberg, 2007 | >21 years of age and had de novo SFA located 1cm from SFA origin.<br>Disease extent:<br>CLI of at least category 2 (moderate claudication) on Rutherford scale. 1-10cm lesion length, ≥70% stenosis.<br>Male:n=168<br>Female: n=76<br>Diabetes: n=81<br>Smoking: n=172<br>Hyperlipidemia n=148<br>Hypertension n=202<br>Prior peripheral artery disease intervention: n=91<br>History of stroke/TIA: n=20<br>History of coronary artery disease: n=90<br>Renal insufficiency: n=25<br><br>Rutherford category:<br>Asymptomatic n=2<br>Mild/Moderate claudication: n=71<br>Severe claudication: n=153<br>Ischemic pain at rest: n=4<br>Minor tissue damage: n=3 | Stent (Bard Luminexx 3 Vascular self expandable nitinol stent )by C.R. Bard Inc, Murray Hill , NJ) Vs PTA | *Technical success:*<br>PTA group: on site < 50% residual stenosis by ultrasound.<br>Stent group: on site < 30% residual stenosis by visual estimate.<br><br>*Re-stenosis:* PVR ≥2.4 on duplex ultrasound.<br><br>*Other Outcomes*: Target lesion revascularization, absolute walking distance at 2mph on a 12% incline, improvement in Rutherford category by at least 1 category, ABI at rest and major adverse events including stent integrity and death. | 12 | No statistically significant difference between the two treatment modalities on all outcomes with the exception of absolute walking distance.<br>Study limitations:<br>Study was powered to detect an absolute difference of 20% but not less than 20%. | - If technical failure persisted after repeat angioplasty, stent was implanted.<br>PTA patients crossed over to receive stent n=13.<br>- Direct stent implantation without predilation. In cases of tight stenosis and occlusions that precluded stent advancement, angioplasty was done to enable stent placement.<br>- Patients receiving stent were given 300mg clopidogrel within one hour of DSA and discharged on 75mg/day for 4 weeks. All patients discharged on aspirin 100mg/day indefinitely.<br>-Target lesion revascularization performed only if recurrent claudication and target lesion re-stenosis on onsite duplex ultrasound.<br>-Data analyzed according to intention to treat principle. |

| Author, Year | Patients | Comparison | Outcomes Definitions | Follow-up in months | Authors conclusion | Notes |
|---|---|---|---|---|---|---|
| **Iliac Artery Occlusive Disease** | | | | | | |
| (Dutch Iliac Stent Trial ) Tetteroo, 1996; Tetteroo, 1998; Bosch, 1999; Klein, 2004; Klein, 2006. | Patients with iliac (common and external) artery occlusive disease with pain localized in the buttock, upper leg, or calf, reduced pulsation of the femoral artery and reduced ABI.<br>Disease Extent:<br>≥ 50% reduction in arterial diameter.<br>Stenosis ≤10cm in length in the common or external iliac artery or occlusion <5cm<br><br>Male: n=201<br>Female: n=78<br>Tobacco use: n=252<br>Hypertension: n=77<br><br>Clinical grade (SVS/ISCVS classification)<br>Category 1: n=72<br>Category 2: n=146<br>Category 3: n=41<br>Category 4: n=18<br>Category 5: n=2<br>Former Recanalisation of same arterial segment:<br>PTA : n=24<br>Vascular surgery: n=7 | Balloon expandable Palmaz Stent by Cordis or Johnson and Johnson interventional systems) vs PTA | According to SVS-ISCVS:<br><br>*Technical success:* pressure gradient across the treated site ≤10mm Hg after procedure and pharmacologically induced visodalition.<br><br>*Clinical Success:* improvement of at least 1 Fontaine grade.<br><br>*Hemodynamic success:* improvement of ABI by 0.10 or more or no more than 0.15 deterioration from the first post procedural measurement.<br><br>*Re-stenosis:* PSV >2.5 on duplex ultrasonography.<br>*Quality of Life:* according to RAND-36.<br>*Re-intervention:* Whole common or external iliac artery that was treated.<br>*Other outcomes:* ABI, walking distance, complication, cardio vascular events, mortality, intra-arterial pressure gradients. | Within 24hrs 3, 12 and 24 months, 5-8 years after treatment | There was no short term or long term substantial differences in technical results and clinical outcomes of the two strategies. | - Some patients had multiple lesions. All lesions in a particular patient were treated by intervention group to which they were assigned.<br>- For PTA group, if suboptimal results after initial angioplasty, larger balloon were applied. If unsuccessful i.e. gradient >10mm Hg stent was placed. |

| Author, Year | Patients | Comparison | Outcomes Definitions | Follow-up in months | Authors conclusion | Notes |
|---|---|---|---|---|---|---|
| **Crural Artery Stenosis** | | | | | | |
| Falkowski 2009 | Patients at least 30 years of age with manifested symptoms of ischemia, Rutherford stage 3-5. They had to have primary stenosis in at least one of the crural arteries.<br>Length: minimum 60%<br>Vessel diameter: 2.0-3.5mm<br>Diabetes: n=20<br>Hypertension: n=31<br>Hyperlipidemia: n=18<br>Cardiac disease: n=21 | Sirolimus Eluting stent (Cypher Cordis Europa N.V.) vs Balloon expandable bare stent (uncoated non-drug eluting coronary stents by Sonic Cordis, Europa N.V.) | *Re-stenosis*: % with angiographic re-stenosis.<br><br>*Revascularization:* repeated procedures conducted after a period of 6 months on the basis of clinically and angiographically diagnosed re-stenosis either inside or on the edges of stent (TLR).<br><br>*Technical success:* < successful implantation <30% base on angiography.<br><br>*Hemodynamic success:* ABI improvement ≥0.1 at time of discharge.<br><br>*Hemodynamic success:* lack of deterioration of ABI>0.15 from baseline.<br><br>*Complications:* events leading to death, life-threatening, causing disability requiring longer hospitalization or a procedure. | 24hrs, 6 | Quantitative angiography demonstrated that all variables used to assess re-stenosis were superior for Sirolimus-eluting stent 6 months after intervention. Results of this study reveal that the use of Sirolimus eluting stents decreased the risk of stenosis in comparison to standard stents. | - Open RCT.<br>- All patients were recommended to undergo antiplatelet and thrombotic therapy before and after procedure. Three days before the procedure, patients received oral acetylsalicylic acid 100mg/day and or clopidogrel 75mg/day. These treatments continued for the whole follow-up.<br>- Angioplasty was performed first in cases of narrowed stenosis |

# Appendix 9: Characteristics of Excluded Studies

| Author, Year | Comparison | Reason for Exclusion |
|---|---|---|
| Spronk, 2009 | PTA + selective stent vs Hospital based exercise | Stent not a primary intervention |
| Bosiers, 2009 | Absorbable metal Stent vs PTA | Absorbable stents not licensed by Health Canada + feasibility study |
| Saxon 2008 | Polytetrafluorethylene stent graft vs PTA. | Trial stopped early because 1) there was a need to move the manufacturing site of the device and to make delivery system modifications; 2) The initial study design was flawed primarily due to endpoint definition of primary patency. 3) The delivery system had an olive on the front end and that was occasionally difficult to remove after deployment. At the time the study was stopped only 50% of the patients were enrolled. It was also recognized that requiring ABI improvement of 0.15 over baseline to maintain primary patency could not be met. Many patients did not comply or have exercise ABI's obtained at follow-up. |
| McQuade 2008 | ePTFE stent graft vs By-pass (24 months results of Kendora 2007) | Not licensed by Health Canada for Femoral popliteal artery |
| Kendora 2007 | ePTFE Stentgraft vs bypass Stent graft in SFA patients. | Not licensed by Health Canada for Femoral popliteal artery |
| Ansel, 2006 | Stent + Abciximab (glycoprotein IIb/IIa inhibition) vs Stent | Adjunct therapy to stent. |
| Rand 2005 | PTA vs Carbon film coated stents | Pilot study |
| Schillinger 2004 | PTA + Brachytherapy vs. PTA + selective stent +Brachytherapy | Stent not a primary intervention |
| Ponec 2004 | Wall stent vs Smart stent. | Equivalent study not objective of the review |
| Bonvini 2003 | Selective Stent with Brachytherapy vs. Stent | Stent not a primary intervention + Interim analysis |
| Saxon 2003 | ePTFE Stentgraft vs PTA | ePTFE Stentgraft not licensed by Health Canada for femoral popliteal artery |
| Duda 2002;2005;2006 | Sirolimus drug eluting stent and bare stent. | Feasibility study. Drug eluting stents not licensed by Health Canada for peripheral artery disease. |
| Krajcer 1997 | Bare stent (Wallstent Endoprosphesis) vs Covered stent (Wallgraft Endoprosphesis) | Feasibility study |

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