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Drug eluting balloons and stents for symptomatic peripheral arterial disease

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Drug eluting balloons and stents for symptomatic peripheral arterial disease

[Läkemedelsavgivande ballonger och stentar vid behandling av symtomgivande benartärsjukdom]

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1. Abbreviations

Amp	=	Amputation
CT	=	Computed Tomography
BMS	=	Bare metal stent
DEB	=	Drug-eluting balloon
DES	=	Drug-eluting stent
LLL	=	Late lumen loss
Mort	=	Mortality
MRI	=	Magnetic resonance imaging
P1	=	Patients with intermittent claudication
P2	=	Patients with critical ischemia
P3	=	Patients belonging to either P1 or P2 (not separated)
PAD	=	Peripheral artery disease
PP	=	Primary patency (most common definition: patent reconstruction [i.e. not thrombosed] without any reintervention. In some included studies, differently defined as: freedom from $\geq 50\%$ restenosis)
PTA	=	Percutaneous transluminal angioplasty
QoL	=	Quality of life
RCT	=	Randomized controlled trial
Rest	=	Restenosis (measured as: binary patency late lumen loss, primary patency, target lesion revascularization)
Ruth	=	Rutherford symptom score
UCB	=	Uncoated balloon
TLR	=	Target lesion revascularisation (most common definition: reintervention for $\geq 50\%$ restenosis within ± 5 mm proximal and/or distal to the target lesion in patients with recurrent symptoms)
TVR	=	Target vessel revascularisation
Wd	=	Walking distance

2. Summary of the Health Technology Assessment

Abstract

Background: Endovascular treatment of atherosclerotic disease of the extremities is increasingly used as an alternative to open surgery, with an expectation of benefits in form of shorter convalescence and less invasive surgery. However, there is a risk of restenosis mainly due to intimal hyperplasia after balloon dilatation related intimal injury. Special dilatation balloons and endovascular stents containing anti-proliferative agents have been designed in an attempt to reduce this risk. The results with these devices are however poorly documented.

Objective: The aim of the current HTA was to compare the effectiveness and risks of endovascular stents and balloons with or without anti-proliferative agents, in the treatment of atherosclerotic disease of the lower extremities.

Search methods and study selection: Systematic literature searches were conducted in PubMed, Embase, the Cochrane Library and a number of HTA-databases. Systematic reviews, controlled studies and case-series (on adverse events) were considered for inclusion.

Literature: We identified 17 randomized controlled studies (RCT), four cohort studies and 13 case series. Eight RCTs and four cohort studies compared drug eluting stents (DES) with bare metal stents (BMS), and nine RCTs compared drug eluting balloons (DEB) with uncoated balloons (UCB). There was a great heterogeneity in terms of included patient groups (intermittent claudication and/or critical ischemia, above- or below the knee, or mixed), substance used (everolimus, paclitaxel or sirolimus), device tested (stent or balloon), and studied outcomes (Table 1). Most studies were available for sirolimus containing stents in below-the knee location in patients with critical ischemia (3 RCTs and 3 cohorts), and for balloon intervention in the mixed patient population, using the agent paclitaxel (7 RCTs).

Conclusions: Despite almost 3,000 studied patients, no positive effects on patient-related outcomes have consistently been observed with drug eluting stents or balloons in the treatment of atherosclerotic disease of the lower extremities, compared with uncoated stents or balloons.

Mortality rate within 12 months was reported to be between zero and 18 %, probably mainly related to the underlying general atherosclerotic disease. Commonly encountered SAEs are mortality, amputations, pseudo aneurysms and thrombosis.

For patients with intermittent claudication (P1) due to below the knee lesions, it is uncertain whether there is little or no difference regarding mortality, restenosis or symptom severity with DES (sirolimus) compared with BMS. Very low certainty of evidence (GRADE ⊕○○○).

In patients with critical ischemia (P2) and lesions below the knee, DES (everolimus) may reduce restenosis compared with BMS. In the same patient group, DEB with paclitaxel compared with UCB may slightly reduce symptom severity (Rutherford score). Low certainty of evidence (GRADE ⊕⊕○○).

Importantly, for patients with critical ischemia below the knee, in one RCT comparing DEB (paclitaxel) with UCB, a significant increase in amputation rate (not reported in the RCT) was detected in the DEB group when all amputated patients from the study flowchart were included in the analysis. There was also a non-significant but numerically higher mortality in the DEB (paclitaxel) group compared with the UCB group.

In a mixed population (P3) (i.e. intermittent claudication or critical ischemia patients) with lesions above the knee, DES (paclitaxel) compared with BMS may reduce restenosis. DES (sirolimus) compared with BMS in lesions below the knee, may reduce restenosis and may slightly reduce symptom severity. In the mixed population, with lesions above and/or below the knee, restenosis may be reduced with DEB (paclitaxel) compared with UCB. In all cases low certainty of evidence (GRADE ⊕⊕○○).

In the studied patient populations (P1-P3), the effect estimates for all other studied outcomes were uncertain, non-significant or inconclusive.

Very low-, or low certainty of evidence (GRADE ⊕○○○ or ⊕⊕○○).

3. Svensk sammanfattning

Svensk sammanfattning

Bakgrund: Endovaskulär behandling av symtomgivande perifer kärlsjukdom i benen används i ökande grad som alternativ till öppen kirurgi, med förväntade fördelar i form av kortare konvalescenstid och minskat behov av öppen kirurgi. Det finns emellertid en hög risk för återfall, framför allt på grund av så kallad intima hyperplasi efter ballongvidgning. Särskilda ballonger och stentar med proliferationshämmande läkemedel har utvecklats i syfte att minska denna risk. Effektiviteten och säkerheten av dessa läkemedelsavgivande ballonger/stentar är dock bristfälligt dokumenterad.

Syfte: Att jämföra effektivitet och risker med endovaskulära stentar och ballonger med respektive utan proliferationshämmande läkemedel, för behandling av symtomgivande perifer kärlsjukdom i benen.

Litteratursökning och studieurval: Systematisk litteratursökning gjordes i PubMed, Embase, Cochrane Library och ett antal olika HTA-databaser, i syfte att identifiera relevanta systematiska översikter, kontrollerade studier och fallserier (avseende biverkningar).

Litteratur: Litteratursökningen identifierade 17 randomiserade kontrollerade studier (RCT), fyra kohortstudier och 13 fallserier. Det förelåg en stor heterogenitet avseende studerade patientgrupper (claudicatio intermittens och/eller kritisk ischemi, lesioner över- eller under knäet, eller blandade populationer), läkemedel (everolimus, paclitaxel eller sirolimus), produkt (stent eller ballong), samt studerade utfall (Table 1). Det största antalet studier avsåg sirolimusavgivande stentar vid lesioner under knäet hos patienter med kritisk ischemi (3 RCTs och 3 kohortstudier), samt paclitaxelavgivande ballonger i en blandpopulation (claudicatio intermittens eller kritisk ischemi) (7 RCT).

Sammanfattande slutsatser: Trots att nästan 3 000 patienter studerats saknas genomgående stöd för fördelaktiga resultat avseende patientnära utfallsmått, vad gäller effekten av läkemedelsavgivande stentar eller ballonger för behandling av symtomgivande perifer kärlsjukdom i benen, jämfört med icke-läkemedelsavgivande stentar eller ballonger. Mortalitet inom ett år rapporteras förekomma efter 0-18 % av ingreppen, sannolikt främst relaterat till bakomliggande generell ateroskleros. Vanligt förekommande allvarliga biverkningar är mortalitet, amputationer, pseudoaneurysm och trombosier.

Hos patienter med claudicatio intermittens (P1) på grund av lesioner under knäet är det osäkert huruvida det finns någon skillnad avseende mortalitet, förekomst av restenos eller förändring i symptom (enl. Rutherford) med läkemedelsavgivande stent med sirolimus jämfört med konventionell stent (utan läkemedel). Otillräckligt vetenskapligt underlag (GRADE ⊕○○○).

Hos patienter med kritisk ischemi (P2) och lesioner under knäet, kan läkemedelsavgivande stent med everolimus minska förekomsten av restenos något jämfört med konventionell metallstent. I samma patientgrupp kan läkemedelsavgivande ballong med paclitaxel minska symptomgrad (enl. Rutherford) något jämfört med konventionell (icke-läkemedelsavgivande) ballong. Begränsat vetenskapligt underlag (GRADE ⊕⊕○○).

Hos patienter med kritisk ischemi på grund av lesioner under knäet, sågs i en RCT (ref) som jämförde läkemedelsavgivande ballong (paclitaxel) med konventionell ballong signifikant fler amputationer, när samtliga patienter från studiens flödesschema inkluderades i analysen (rapporterades dock inte så i studien). I samma studie sågs även en numerärt högre (ej statistiskt signifikant) mortalitet med läkemedelsavgivande ballong (paclitaxel) jämfört med konventionell ballong.

I en blandad population (P3) (dvs. claudicatio intermittens eller kritisk ischemi patienter) med lesioner över knäet kan läkemedelsavgivande stent med paclitaxel minska förekomsten av restenos jämfört med konventionell metallstent. Vid lesioner under knäet kan läkemedelsavgivande stent med sirolimus jämfört med konventionell metallstent minska förekomsten av restenos och minska symptom något. I en blandad population (dvs. claudicatio intermittens eller kritisk ischemi patienter) med lesioner över och/eller under knäet, kan läkemedelsavgivande ballong med paclitaxel minska risken för restenos jämfört med konventionell ballong. Begränsat vetenskapligt underlag (GRADE ⊕⊕○○).

Avseende de studerade patientgrupperna (P1-P3) är samtliga övriga effektuppskattningar osäkra eller uppmätta skillnader icke signifikanta och slutsatser därmed icke konklusiva. Otillräckligt- eller begränsat vetenskapligt underlag (GRADE ⊕○○○ eller ⊕⊕○○).

The above summaries were written by HTA-centrum and approved by the Regional board for quality assurance of activity-based HTA. The Regional Health Technology Assessment Centre (HTA-centrum) Region Västra Götaland, Sweden has the task to make statements on HTA reports carried out in VGR. The English summary is a concise summary of similar outline as the summaries in the Cochrane systematic reviews. The Swedish summary addresses the question at issue, results and quality of evidence regarding efficacy and risks, and economical and ethical aspects of the particular health technology that has been assessed in the report, and is ended with a final statement/concluding remark from HTA-centrum.

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4. Summary of Findings (SoF-table)

Outcome variable	Design and number of studies	Relative effect	Absolute effect	Quality of evidence GRADE
PICO 1: Intermittent claudication Drug eluting stent (sirolimus) vs bare metal stent – below the knee				
Mortality	RCT 1	I=12.5% C=6.5% n.s.	I=5/40 C=3/46 n.s.	⊕○○○ Very low
Restenosis ¹	RCT 1	PP: I=85.3% C=55.0% p=0.006 TLR: I=5.9% C=20% n.s.	Not calculated	⊕○○○ Very low
Rutherford score (symptom severity)	RCT 1	Not calculated	median ΔRuth: I= -1.5 (-3 to -1) C= -1 (-2 to 0) p=0.01	⊕○○○ Very low

PICO 2: Critical ischemia Drug eluting stent (everolimus) vs bare metal stent – below the knee				
Mortality	RCT 1 Cohort 1	I=18.1% C=15.8% n.s.	I=19/74 C=15/66 n.s.	⊕⊕○○ Low
Amputation	RCT 1 Cohort 1	I=1.4% C=3.0% n.s.	I= 1/74 C= 2/66 n.s.	⊕○○○ Very low
Restenosis ¹	RCT 1	Not calculated	LLL: I= 21% C=47% PP: I=85%, C=54% TLR: I=9%, C=34% (p=0.001 for all)	⊕⊕○○ Low
Rutherford score (symptom severity)	RCT 1	Not calculated	ΔRuth >2: I=60%, C=56% (n.s.)	⊕⊕○○ Low

Outcome variable	Design and number of studies	Relative effect	Absolute effect	Quality of evidence GRADE
PICO 2: Critical ischemia Drug eluting stent (sirolimus) vs bare metal stent – below the knee				
Mortality	RCT 1 Cohort 2	Inconsistent data	Inconsistent data	⊕○○○ Very low
Amputation	RCT 1 Cohort 2	Inconsistent data	Inconsistent data	⊕○○○ Very low
Restenosis ¹	RCT 1 Cohort 2	Inconsistent data	Inconsistent data	⊕○○○ Very low
Rutherford score (symptom severity)	RCT 1	Not calculated	ΔRuth: DES -3, BMS -2 n.s	⊕○○○ Very low

PICO 2: Critical ischemia Drug eluting balloon (paclitaxel) vs uncoated balloon – below the knee				
Mortality	RCT 2	Not calculated	Study 1: I = 7.7%, C = 4.4%, n.s. Study 2: * I =9.6%, C = 7.6%, n.s.	⊕⊕○○ Low
Amputation	RCT 2	Not calculated	Study 1: I=0/239 (0.0%) C=1/119 (0.8%), n.s. Study 2: † I=20/227 (8.8%) C=4/111 (3.6%), p=0.08	⊕○○○ Very low
Restenosis ¹	RCT 2	Not calculated	Study 1: BR: I=27%, C=74% TLR: I=10%, C=20% p=0.02 or less Study 2: BR: I=41%, C=36% TLR: I=11.9%, C=13.5% n.s.	⊕○○○ Very low
Rutherford score (symptom severity)	RCT 1	Not calculated	ΔRuth: DCB 4.3, UCB 3.1 p=0.004	⊕⊕○○ Low

* Drug eluting balloon 18% vs. uncoated balloon 15% (n.s.) mortality according to trial flowchart.

† Drug eluting balloon 15% vs. uncoated balloon 7% (p=0.0181) amputations according to trial flowchart.

Outcome variable	Design and number of studies	Relative effect	Absolute effect	Quality of evidence GRADE
PICO 3: Mixed population (critical ischemia and intermittent claudication) Drug eluting stent (paclitaxel) vs bare metal stent – above the knee				
Mortality	RCT 1	Not calculated	I=9/241 (3.7%) C=4/238 (1.7%) n.s.	⊕⊕○○ Low
Amputation	RCT 1	Not calculated	I=1/241 (0.5%) C=0/238 (0.0%) n.s.	⊕⊕○○ Low
Restenosis ¹	RCT 1	Not calculated	PP: I=83%, C= 33% TLR: I=10%, C=18% p=0.01 or less.	⊕⊕○○ Low
Rutherford score (symptom severity)	RCT 1	Not calculated	ΔRuth data not shown n.s.	⊕○○○ Very low

PICO 3: Mixed population (critical ischemia and intermittent claudication) Drug eluting stent (sirolimus) vs bare metal stent – below the knee				
Mortality	RCT 1	Not calculated	I=14/84 (17%) C=11/79 (14%) n.s.	⊕⊕○○ Low
Amputation	RCT 1	Not calculated	I=2/82 (3.2%) C=4/79 (6.4%) n.s.	⊕⊕○○ Low
Restenosis ¹	RCT 1	Not calculated	PP: I=81% C=56%, p=0.04 TLR: I=10%, C=18%, n.s.	⊕⊕○○ Low
Rutherford score (symptom severity)	RCT 1	Not calculated	ΔRuth from baseline: I=-2 (-3 to -1) C= -1 (-2 to 9) p=0.004	⊕⊕○○ Low

Outcome variable	Design and number of studies	Relative effect	Absolute effect	Quality of evidence GRADE
PICO 3: Mixed population (critical ischemia and intermittent claudication) Drug eluting balloon (paclitaxel) vs uncoated balloon – above and/or below the knee				
Mortality	RCT 3	Not calculated	I=0-4.1% C=0-7.5% n.s.	⊕⊕○○ Low
Amputation	RCT 3	Not calculated	I=0-4.0% C=0-12.0% n.s.	⊕⊕○○ Low
Restenosis ¹	RCT 4	Not calculated	LLL: I=0.64 (SD 0.9), C=1.81 (SD 0.1) p=0.01 PP: I=67-76%, C=40-55% p from 0.04 to n.s. TLR: I=7.7-29%, C=25-48% p from 0.02 to n.s.	⊕⊕○○ Low
Rutherford score (symptom severity)	RCT 1	Not calculated	ΔRuth from baseline: I=1.6 (SD 1.3) C=2.1 (SD 1.3) p not stated	⊕○○○ Very low

5. Participants

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Conflicts of interest for the proposer or any of the participants

Mårten Falkenberg has assignments as proctor and lecturer for the companies COOK, Cordis, Gore, Medtronic, and Johnson & Johnson, that have products within this area. Mårten Falkenberg is principal investigator for Swedish Drug Elution Trial in Peripheral Arterial Disease (SWEDEPAD), granted by Vetenskapsrådet and The Swedish Heart-Lung Foundation (Hjärt-Lungfonden), and supported through reduced costs for endovascular appliances by the companies: Bard, COOK, Meliora Medtech, Boston Scientific, and Vascular EPS.

Project time

HTA was accomplished during the period of 2013-05-01 - 2015-04-29

Last up-date of the literature searches was made in November 2014.

6. Peripheral artery disease – Background and Treatment

Peripheral artery disease and its degree of severity

Symptomatic peripheral artery disease due to atherosclerosis (PAD) is the most common indication for vascular surgical interventions in Sweden. PAD causes, to various degrees, a reduction in the blood flow through the arteries transporting blood to the lower limbs resulting in tissue hypoxia. When symptoms occur they may vary from pain during exercise or walking (i.e. intermittent claudication) to severe blockage of the arteries in the lower extremities (i.e. critical ischemia). Patients with intermittent claudication can walk varying distances before onset of pain, which in the more serious cases may impair their quality of life. Those with critical ischemia suffer from chronic at-rest pain, ulcers, or gangrene, and have a markedly elevated risk for amputation.

- ☒ Risk of premature death.
- ☒ Risk of permanent illness or damage, or reduced quality of life.
- ☒ Risk of disability and health-related quality of life.

Prevalence and incidence of peripheral artery disease

Based on the population and age distribution in Region Västra Götaland and national prevalence data on PAD, there are approximately 4,400 individuals with critical ischemia, and 25000 individuals with intermittent claudication in the region (Sigvant *et al.*, 2007)

According to data from the National Registry of Vascular Surgery (SWEDVASC), in the year 2012 approximately 4,900 patients in Sweden had an invasive intervention for PAD in a lower extremity. Barely 2/3 of these patients had critical ischemia, and slightly over 1/3 had intermittent claudication. The number of invasive interventions for lower extremity PAD has, according to SWEDVASC, increased in number every year during the last five years. In year 2012, in Sweden, the proportion of patients that were treated with minimally invasive procedures (endovascular intervention) in the iliac arteries was approximately 80 % versus 70 % for the infrainguinal arteries.

Present treatment of peripheral artery disease

Chronic PAD in the lower extremities is diagnosed and treated both within primary care and inpatient care. In primary care the diagnosis can be verified by clinical assessment and peripheral blood pressure measurements. Risk factors such as smoking, heredity and metabolic disturbances should be identified and corrected if possible. Patients with severely decreased peripheral blood pressure and at-rest pain, ulcerations or gangrene, meet the diagnostic criteria for critical ischemia and are at risk for amputation. These patients should immediately be referred to a vascular surgery clinic for consideration of invasive intervention.

Patients with intermittent claudication have a milder form of PAD and should primarily be treated with life-style changing approaches (e.g. smoking cessation and exercise), platelet inhibitors (mainly aspirin) and, when needed, treatment of hypertension, blood lipids, and diabetes. If these measures do not alleviate the symptoms within a 6-12 month period and the patient still has a PAD related reduction in walking capacity, the patient should be referred to a vascular surgery clinic for consideration of invasive treatment.

Invasive treatment of PAD is often conducted in out-patient care. However, at Sahlgrenska University hospital, these treatments are conducted in inpatient care, and may be performed with either open surgery or endovascularly. In open surgery, the obstructive lesions in the vessel are either removed (thrombendarterectomy) or bypassed. Endovascular intervention is guided on the basis of X-ray with a contrast agent to visualize the blood vessels.

For endovascular intervention against infrainguinal claudication, when indicated, critical ischemia in the lower extremity, access to the blood vessel is made through the groin, and the narrowed or occluded section is passed with a thin metal guide-wire. When the conductor has passed the narrow section the vessel is dilated from the inside with a 'balloon' (percutaneous transluminal angioplasty, PTA). The balloon causes intentional damage to the thickened and calcified vessel wall by increasing its inner diameter, thereby allowing passage of sufficient blood flow to the affected limb. Sometimes the balloon angioplasty is supplemented with a stabilizing stent consisting of a tubular metal grid.

In recent years, the endovascular interventions have become increasingly common while the open surgical procedures have decreased in number. One reason for this is that an endovascular intervention is less demanding for the patient and can be performed under local anaesthesia through a small puncture in the groin. Open surgery involves a greater risk for cardiovascular complications and requires long incisions to expose the arteries, leading to longer hospital stays and longer convalescence periods. However, the endovascular technique bears a major problem compared to open surgery. An initial success with improved blood flow is in some cases followed by so-called restenosis, or re-narrowing of the arteries. The mechanism is probably that the balloon-caused injury to the vessel wall induces a vigorous wound healing process, with cell proliferation and connective tissue formation, which narrows the vessel lumen again. If restenosis occurs, the blood flow decreases again and the symptoms return. Thus, restenosis remains a significant problem after endovascular interventions.

Number of patients per year who are treated for peripheral arterial disease

In Sweden (SWEDVASC) during year 2012, approximately 4,900 patients were invasively treated for PAS in the lower limbs, of which 3,550 were treated endovascularly and 1,350 with open surgery. The corresponding numbers, in 2012, for Region Västra Götaland (Sahlgrenska University Hospital, Södra Älvsborg Hospital, Norra Älvsborg Hospital, and Skövde Hospital) were approximately 760 invasively treated patients, of which 530 (70 %) were treated endovascularly.

The normal pathway of a patient through the health care system

Typically, patients with critical ischemia and some patients with more severe intermittent claudication are referred from primary care to the vascular surgery clinics. If invasive intervention is warranted it is carried out at a vascular surgery department. It is particularly important that patients with critical limb ischemia get a rapid handling in order to minimize suffering and risk for gangrene and amputation. For endovascular interventions, the length of the hospital stay is normally about 24 hours. In some cases the intervention can also be carried out in the outpatient setting. The hospital stay may however be prolonged if additional care is needed, such as advanced pain relief, treatment of ulcers, or if reoperation of wound infections or hospital based rehabilitation is required. Sometimes patients (mostly with critical ischemia) contact the vascular surgery department directly, or get referred from the emergency care unit with particularly severe symptoms, intolerable pain and/or progressive ulceration.

Current waiting time in days for medical assessment

For patients with critical ischemia, the waiting time must not exceed 2-3 weeks and if the symptoms are particularly severe, more rapid or even emergency care is required. Preoperative assessment with non-invasive imaging with ultrasound, CT or MRI, is preferred before invasive procedures are started, and should be initiated as soon as possible.

For intermittent claudication patients, rapid handling is not warranted to the same extent. The most important measures can be initiated already at the primary care level and when invasive treatment is considered necessary the treatment should normally be initiated within three months from the decision.

These stipulated lead times are normally held in the Västra Götaland region for patients with the highest priority. However, this is not always the case for patients with lower priority patients due to a limited capacity for endovascular interventions at the Sahlgrenska University Hospital.

7. Drug eluting balloons and stents in peripheral arterial disease

Background

As stated above, the major problem with endovascular treatment of PAD, as well as in coronary vessels (recently reviewed by SBU, 2014), is restenosis and this may occur after balloon treatment with or without subsequent stenting. In an attempt to reduce this risk, the balloon or stent is coated with a drug that inhibits cell proliferation. Inhibition of cell proliferation suppresses the healing process after vascular dilatation, and thereby reduces the renarrowing of the vessel, locally and without a systemic effect.

The antiproliferative drugs have their origins in treatment of malignant tumours. The most commonly used substance is paclitaxel, which is used for treatment of breast cancer. Paclitaxel is used in both balloons and stents. Other drugs used in balloons and stents are sirolimus and everolimus.

Drug eluting balloons and stents are used in a similar way as conventional, non-drug eluting devices. The drugs are released in a time-dependent manner from the coating and transferred into the vessel wall, whereafter the drug appears to be washed off into the bloodstream (Grenada et al., 2014; Zhao et al., 2012). The main technical differences consist in the need for a somewhat longer recommended insufflation time for the balloons, and a more active postoperative platelet inhibition treatment regimen.

The current HTA critically evaluates the effectiveness and risks of the novel technology with drug eluting balloons and stents regarding mortality, amputations, restenosis or clinical outcomes after treatment of PDA. Drug eluting devices are today used for the majority of patients undergoing a similar treatment in coronary arteries, but this is not the case for leg artery disease. Use of drug-eluting devices involves a major increase in costs as compared with conventional non-drug eluting devices.

The potential value of drug eluting balloons and stents in peripheral arterial disease

If effective, reduction of the risk for restenosis with the use of drug eluting balloons and stents may improve the benefit to the patient and might motivate the higher cost.

Diagnoses: I70.2 and I73.9B.

The central question for the current HTA project in one sentence

Do drug eluting balloons and stents improve the effectiveness and reduce the risks compared with uncoated balloons and stents in endovascular treatment of lower limb symptomatic peripheral arterial disease (PAD)?

PICO P= Patients, I= Intervention, C= Comparison, O=Outcome

P1 = Adults with intermittent claudication due to PAD in lower extremity

P2 = Adults with critical ischemia due to PAD in lower extremity

P3 = Mixed populations of P1 or P2

I= Endovascular treatment with drug (antiproliferative) eluting balloons or stents

C= Endovascular treatment with non-drug eluting balloons and stents

Critical for decision making

O1= Mortality (Mort)

O2= Amputation (Amp)

O3= Restenosis (rest) (measured as: binary patency late lumen loss, primary patency, target lesion revascularization (see also O6)

Important for decision making

O4 = Health related quality of life (HRQoL)

O5 = Walking distance (Wd), pain free

O6 = Reintervention (in the same vascular segment)

O7 = Rutherford score (Ruth), symptom severity (1-6)

Comments on patient populations and outcome variables:

Patient groups P1 and P2 are handled differently as detailed above and therefore need to be considered separately. However, this distinction is not made in several of the large trials and therefore we also decided to separately evaluate studies based on P3, i.e. the mixed population.

With regard to outcomes, O1, O2, O4, and O5 are clearly patient-related outcomes, while O6 is a mixed outcome determined by the physician. Since restenosis is the dominating mechanism behind poor results, there have been attempts to quantify the degree of restenosis using the outcome variables primary patency or binary restenosis and late lumen loss (for definitions, see under abbreviations). O7, the Rutherford score, is a mixed outcome measure including both patient related and surrogate variables.

8. Review of Evidence

Search strategy, study selection and references (Appendix 1)

Included studies – design and patient characteristics (Appendix 2)

Excluded articles – (Appendix 3)

Outcome tables – (Appendix 4)

Two of the authors (TS, JP) performed systematic searches in Medline, PubMed, Embase, the Cochrane Library and a number of HTA-databases in May 2013. Several updates of the searches were made, the last in November 2014. Reference lists of relevant articles were also scrutinised for additional references. Search strategies, eligibility criteria and a graphic presentation of the selection process are accounted for in Appendix 1. The same authors (TS, JP) conducted the literature searches, selected studies and independently assessed the obtained abstracts and a first selection of full-text articles for inclusion or exclusion. Any disagreements were resolved in consensus. The remaining articles were sent to all the authors, who read the articles independently and then decided in a consensus meeting which articles that should be included, except for the latest update (Nov 2014) when two of the authors (HS, PS) decided on inclusion of relevant articles.

The literature search identified a total of 965 articles (after removal of duplicates). Two authors (TS, JP) then excluded 871 articles after reading their abstracts. Another 28 articles were excluded by the same authors after reading the articles in full text. The remaining 66 articles were sent to all the authors, and 34 of them were finally included in the report. 17 were randomised controlled trials (RCT), four were cohort studies and fourteen case series. The RCTs and cohort studies have been critically appraised. The appraisal of articles is based on checklists from SBU (Swedish Council on Health Technology Assessment) regarding RCTs and cohort studies. Excluded articles are listed in Appendix 3.

The quality of evidence was rated according to the Grade system.

The present knowledge of drug eluting balloons and stents in peripheral arterial disease

General comment on heterogeneity

The material consisted of 17 RCTs, four cohort studies and 13 case series, each with more than 100 patients (our limitation level). In addition, we identified 11 systematic reviews/meta-analyses consistent with the PICO.

The case-series were only used to extract data on adverse events and complications. Since none of the identified systematic reviews (Antoniou *et al.*, 2013; Biondi-Zoccai *et al.*, 2013; Canaud *et al.*, 2014; Cassese *et al.*, 2012; Fusaro *et al.*, 2013a; 2013b; Jens *et al.*, 2014a, 2014b; Katsanos *et al.*, 2013b, 2014; Razavi *et al.*, 2014) covered the same amount of recent literature as the current report, only primary publications of controlled studies were considered for data extraction.

The data extraction was based on 17 RCTs and four cohort studies, reporting on 14 different patient materials with a follow up time from 6 to 36 months. The antiproliferative drug used was everolimus in two studies, paclitaxel in 11 studies, and sirolimus in eight studies. Eight RCTs and four cohort studies compared drug eluting stents (DES) with bare metal stents (BMS), and nine RCTs compared drug eluting balloons (DEB) with uncoated balloons (UCB).

Regarding *intermittent claudication* patients only (P1), separate data were only found as a subgroup analysis in one RCT (Rastan *et al.*, 2011).

Data on patient populations with indications for treatment h *critical ischemia* (P2), were presented in four RCTs (Bosiers *et al.*, 2012; Liistro *et al.*, 2013b; Rastan *et al.*, 2011 [subgroup analysis]; Zeller *et al.*, 2014b) and in (all identified) four cohort studies (Karnabatidis *et al.*, 2011, Siablis *et al.*, 2005, 2007, 2009).

In the cohort studies, the comparison was in all cases drug eluting stent (DES) vs. bare metal stent (BMS). In one study with 36 months follow-up, the drug was everolimus (Karnabatidis *et al.*, 2011), and in the remaining three studies (same material at 6, 12 and 36 months), it was sirolimus (Siablis *et al.*, 2005; 2007; 2009). Mortality, amputation rates and restenosis data were reported in all four cohort studies.

Data on mixed materials (P3) - *critical ischemia and intermittent claudication* patients - was reported in the 14 remaining studies, all RCTs. Seven RCTs compared DES vs BMS, and seven compared DEB vs uncoated balloon (UCB). Four of these studies had included above-knee lesions only, three had included below-knee lesions only, and seven had included mixed lesions, above and/or below the knee.

Among the 17 RCTs, four had a follow up time of 6 months, seven 12 months, one 18 months, five 24 months and one 36 months. The total number of studied participants was >2,000 (some studies report partly on the same material).

The choice of outcome variables varied markedly across the studies (Table 1). The most common patient-related outcome variables, also included in our PICO, were mortality (20 studies - in many cases considered and handled as an adverse event) and amputation rate (18 studies). Often various angiographic parameters were used to evaluate restenosis (20 studies - e.g. late lumen loss, primary patency). Reinterventions were measured as (need of) target lesion revascularization (20 studies), and changes in symptom severity were frequently measured with Rutherford score (12 studies). We found no study describing HRQoL-data or pain free walking distance.

Table 1. Included controlled studies with the studied interventions (I), comparisons (C), the active substances used, and follow-up periods (outcomes within parentheses) [PICO: P 1-3 within brackets]

Site	I/C	Everolimus	Paclitaxel	Sirolimus
Above the knee lesions	DES/BMS		[P3] RCT: Dake, 2011a 12 mo, (Mort , Amp, <u>Rest</u> , Ruth) [P3] RCT: Dake, 2013 24 mo, (Mort, Amp, Rest, Ruth)	[P3] RCT: Duda , 2005 6 mo, (Mort , Rest, Ruth) [P3] RCT: Duda , 2006 24 mo, (Mort , Amp, Rest, Ruth)
	DEB/UCB			
Below the knee lesions	DES/BMS	[P2] RCT: Bosiers, 2012 12 mo, (Mort, Amp, <u>Rest</u> , Ruth) [P2] Cohort; Karnabatidis, 2011 36 mo, (Mort, Amp, Rest)		[P3] RCT: Falkowski, 2009 6 mo, (Mort, Rest, Ruth) [P1, P2, P3] RCT: Rastan, 2011 12 mo, (Mort, Mort [P1], Amp, Rest, <u>Rest</u> [P3], Ruth, <u>Ruth</u> [P3]) [P3] RCT - Rastan, 2012 36 mo, (Mort, Amp, Rest, Ruth) [P2] Cohort: Siablis, 2005 6 mo, (Mort, Amp, Rest) [P2] Cohort: Siablis, 2007 12 mo, (Mort, Amp, Rest) [P2] Cohort: Siablis, 2009 36 mo, (Mort, Amp, Rest)
	DEB/UCB		[P2] RCT: Liistro, 2013b 12 mo, (Mort , Amp, Rest, <u>Ruth</u>) [P2] RCT: Zeller, 2014b 12 mo, (Mort , Amp , Rest)	
Above and/or below the knee lesions	DES/BMS			
	DEB/UCB		[P3] RCT: Fanelli, 2012 6 mo, (Mort, Amp, Rest) [P3] RCT: Fanelli, 2014b 12 mo, (Mort, Amp, <u>Rest</u>) [P3] RCT: Scheinert, 2014 24 mo, (Mort, Amp, Rest, Ruth) [P3] RCT: Tepe, 2008 24 mo, (Mort, Amp, Rest, Ruth) [P3] RCT: Tepe, 2013 * 24 mo, (Rest) [P3] RCT: Werk, 2008 18 mo, (Mort, Amp, Rest, Ruth) [P3] RCT: Werk, 2012 12 mo, (Mort, Amp, <u>Rest</u> , Ruth)	

Amp = Amputation, BMS = Bare metal stent, DEB = Drug-eluting balloon, DES = Drug-eluting stent, Mort = Mortality, P1 = Patients with intermittent claudication, P2 = Patients with critical ischemia, P3 = Mixed population with patients belonging to P1 and P2 (not separated), QoL = Quality of life, RCT = Randomized controlled trial, Rest = Restenosis (late lumen loss, primary patency, target lesion revascularization), Ruth = Rutherford symptom score, UCB = Uncoated balloon.

* Patients with non-flow-limiting dissections from the THUNDER study.

Underlining of an outcome indicates low certainty of evidence (GRADE ⊕⊕○○) for a positive effect favouring drug eluting stent or balloon, compared with uncoated stent or balloon. **Bold font** indicates a numerical (or significant) unfavourable effect for the outcome drug eluting stent or balloon, compared with uncoated stent or balloon.

P1: Patients with intermittent claudication

There were no studies with everolimus in this patient group.

Critical outcomes

Mortality (Appendix 2 and Appendix 4:1)

Drug eluting stent (DES) with sirolimus vs. bare metal stent (BMS) – Below the knee

This patient group was studied in one RCT (n=86), in a subgroup analysis (Rastan *et al.*, 2011). No flowchart was presented for the subgroup which generates concerns, both regarding directness and study limitations. Mortality at 12 months was 12% in the DES group and 6% in the BMS group (n.s.).

Conclusion: It is uncertain whether there is little or no difference in mortality comparing DES (sirolimus) with BMS below the knee, in patients with intermittent claudication.

Very low certainty of evidence (GRADE ⊕○○○).

Amputation

Was not studied in this patient group.

Restenosis (Appendix 2 and Appendix 4:1)

Drug eluting stent (DES) with sirolimus vs. bare metal stent (BMS) – Below the knee

Restenosis in this patient group studied in one RCT (n=86) reporting 12 month data, with similar limitations as for mortality (Rastan *et al.*, 2011).

Significant difference was only seen for PP with 85% for DES versus 55% for BMS (p=0.006). TLR was 6% for DES and 20% for BMS (n.s.) (Rastan *et al.*, 2011).

Conclusion: It is uncertain whether there is any difference in restenosis comparing DES (sirolimus) with BMS below the knee, in patients with intermittent claudication.

Very low certainty of evidence (GRADE ⊕○○○).

Rutherford score (symptom severity) (Appendix 2 and Appendix 4:1)

Drug eluting stent (DES) with sirolimus vs. bare metal stent (BMS) – Below the knee

Rutherford score was studied in one RCT (n=86) with 12 month data (Rastan *et al.*, 2011).

No significant difference between the study groups was seen regarding change in the Rutherford score (ΔRuth; -1.5 for DES and -1 for BMS, n.s.).

Conclusion: It is uncertain whether there is any difference in symptom severity measured with Rutherford score comparing DES (sirolimus) with BMS below the knee, in patients with intermittent claudication.

Very low certainty of evidence (GRADE ⊕○○○).

P2: Critical ischemia patients

Critical outcomes

Mortality (Appendix 2 and Appendix 4:2)

Drug eluting stent (DES) with everolimus vs. bare metal stent (BMS) – Below the knee

The effect of DES with everolimus vs. BMS on 12-month mortality was studied in one RCT (n=140) and one cohort study (n=81), in patients with below the knee disease (Bosiers *et al.*, 2012, Karnabatidis *et al.*, 2011).

The RCT reported 18% versus 16% (n.s.) mortality (Bosiers *et al.*, 2012), and the cohort study 5% versus 15% (n.s.) mortality in the DES and the BMS groups, respectively (Karnabatidis *et al.*, 2011).

Conclusion: DES (everolimus) compared with BMS below the knee, may result in little or no difference in mortality in patients with critical ischemia. Low certainty of evidence (GRADE ⊕⊕○○).

Drug eluting stent (DES) with sirolimus vs. bare metal stent (BMS) – Below the knee

The effect of DES with sirolimus vs. BMS on mortality, was studied in one RCT (n=75) (subgroup analysis, Rastan *et al.*, 2011) and three cohort studies based on the same material with 6, 12 and 36 months

follow up times (Siablis *et al.*, 2005, 2007, 2009). Only three of the studies reported mortality at 12-months (Rastan *et al.*, 2011; Siablis *et al.*, 2007, 2009).

In the RCT there was 21% mortality in the DES groups versus 24% (n.s.) in the BMS group (Rastan *et al.*, 2011). The two cohort studies reported 14% (n=58) and 8% (n=103) mortality rates in the DES groups versus 10% and 12% in the BMS groups (both n.s.), respectively (Siablis *et al.*, 2007, 2009).

Conclusion: It is uncertain whether there is any difference in mortality comparing DES (sirolimus) with BMS below the knee, in patients with critical ischemia. Very low certainty of evidence (GRADE ⊕○○○).

Drug eluting balloon (DEB) with paclitaxel vs. uncoated balloon (UCB) – Below the knee

The effect of DEB with paclitaxel vs. UCB on 12-month mortality was studied in two RCTs (Liistro *et al.*, 2013; Zeller *et al.*, 2014b). In both RCTs there was a numerical but not significantly higher mortality in the DEB group.

Liistro *et al.* (2013) (n=132) reported 8% mortality in the DEB group versus 4% (n.s.) in the BMS group. In the other RCT by Zeller *et al.* (2014b) (n=358) a marked discrepancy in reported mortality was noted between the trial flowchart, with 18% mortality for DEB versus 15% for BMS (p=0.4631) and the data reported as trial results, with 10% mortality for DEB versus 8% for BMS (p=0.5626).

Meta-analyses of the combined effect estimates of the two RCTs, regarding the different scenarios according to the results section versus flowchart data from Zeller *et al.* (2014b) are shown in Figure 1 and Figure 2, respectively (Liistro *et al.*, 2013; Zeller *et al.*, 2014b).

Conclusion: DEB (paclitaxel) compared with UCB below the knee, may result in little or no difference in mortality in patients with critical ischemia in patients with critical ischemia.

Low certainty of evidence (GRADE ⊕⊕○○).

Figure 1.

Combined effect estimates of mortality in the two RCTs according to results in Zeller *et al.* (2014b).

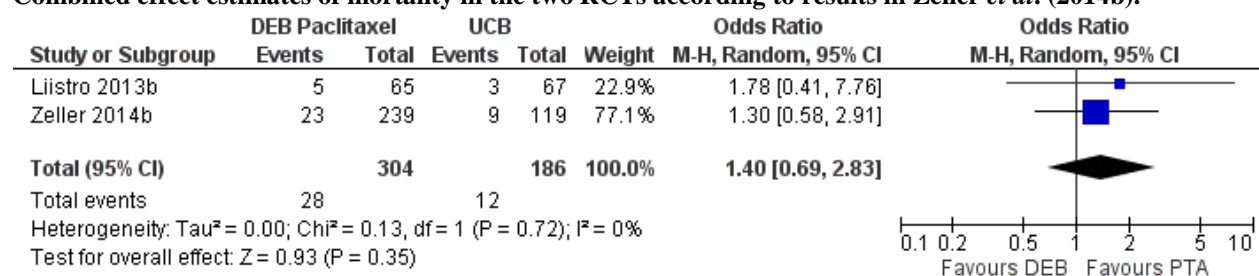
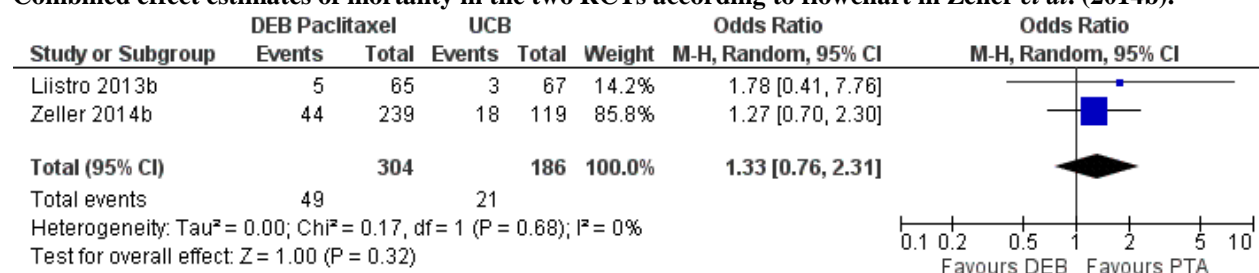


Figure 2.

Combined effect estimates of mortality in the two RCTs according to flowchart in Zeller *et al.* (2014b).



Amputation (Appendix 2 and Appendix 4:2)

Drug eluting stent (DES) with everolimus vs. bare metal stent (BMS) – Below the knee

One RCT (n=140) and one cohort study (n=81) compared the effect of DES with everolimus vs. BMS on amputation rate over 12-months (Bosiers *et al.*, 2012; Karnabatidis *et al.*, 2011).

The RCT reported one amputation in the DES group versus two amputations (n.s.) in the BMS group (Bosiers *et al.*, 2012). The cohort study reported 97% limb salvage in the DES groups versus 92% (n.s.) in the BMS group (Karnabatidis *et al.*, 2011).

Conclusion: It is uncertain whether there is any difference in amputation rate comparing DES (everolimus) with BMS below the knee, in patients with critical ischemia.

Very low certainty of evidence (GRADE ⊕○○○).

Drug eluting stent (DES) with sirolimus vs. bare metal stent (BMS) – Below the knee

The effect of DES with sirolimus vs. BMS on amputation rate at 12 months was studied in one RCT and two cohort studies (same material, different time points) (Rastan *et al.*, 2011; Siablis *et al.*, 2007, 2009). The RCT (n=75) reported 3% rate for both minor and major amputations in the DES group versus 4% minor and major amputation rates (both n.s.) in the BMS group (Rastan *et al.*, 2011). The cohort study by Siablis *et al.* (2007) (n=58) reported 10% minor and 3% major amputation rates, in the DES group, versus 17% and 0% (n.s.) in the BMS group. The limb salvage was 96% in the DES group and 100% (n.s.) in the BMS group (Siablis *et al.*, 2007). The other cohort study (n=103, same material, at 12-months) reported approx. 92% limb salvage rate in the DES group versus approx. 90% (n.s.) in the BMS group (Siablis *et al.*, 2009).

Conclusion: It is uncertain whether there is any difference in amputation rate comparing DES (sirolimus) with BMS below the knee, in patients with critical ischemia. Very low certainty of evidence (GRADE ⊕○○○).

Drug eluting balloon (DEB) with paclitaxel vs. uncoated balloon (UCB) – Below the knee

Two RCTs compared the effects of DEB with paclitaxel vs. UCB regarding 12-month amputation rate (Liistro *et al.*, 2013b; Zeller *et al.*, 2014b).

The RCT by Liistro *et al.* (2013b) (n=132) reported 0% amputations in the DEB group versus 2% (n.s.) in the UCB group. In the other RCT by Zeller *et al.* (2014b) (n=358) an important safety signal was detected. A major discrepancy in the number of amputations reported in the trial flowchart was noted, with 15% amputations for DEB versus 7% for UCB (p=0.0181), and the number of amputations reported in the results section, with 9% amputations for DEB versus 4% for UCB (p=0.080). Thus, according to the flowchart, but not according to the results section, there was a significantly higher rate of major amputations in the DEB group compared with the UCB group (Zeller *et al.*, 2014b).

Meta-analyses of the combined effect estimates of the two RCTs, regarding the different scenarios, according to the results section versus flowchart data from Zeller *et al.* (2014b) are shown in Figure 3 and Figure 4, respectively (Liistro *et al.*, 2013b; Zeller *et al.*, 2014b).

Conclusion: It is uncertain whether there is little or no difference in amputation rate comparing DEB (paclitaxel) with UCB below the knee, in patients with critical ischemia. Very low certainty of evidence (GRADE ⊕○○○).

Figure 3.

Combined effect estimates of amputations in the two RCTs according to results in Zeller *et al.* (2014b).

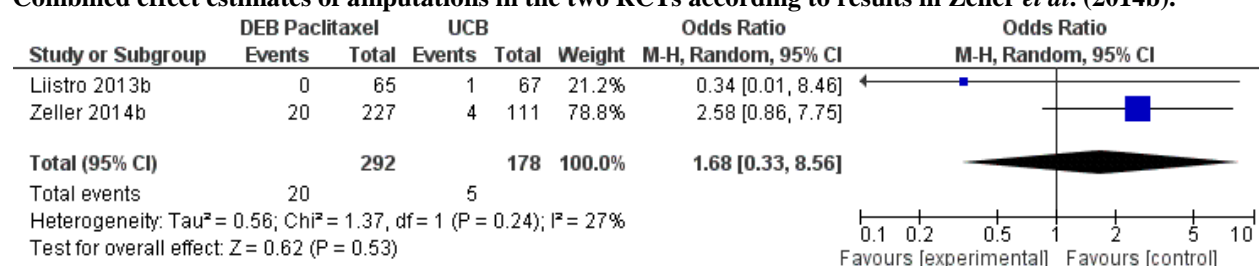
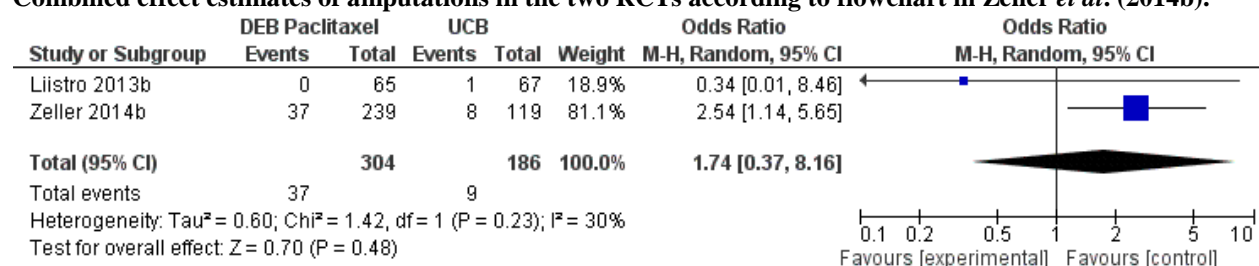


Figure 4.

Combined effect estimates of amputations in the two RCTs according to flowchart in Zeller *et al.* (2014b).



Restenosis (Appendix 2 and Appendix 4:2)

Drug eluting stent (DES) with everolimus vs. bare metal stent (BMS) – Below the knee

The effect of DES with everolimus vs. BMS on restenosis at 12 months was studied in one RCT and in one cohort study (Bosiers *et al.*, 2012; Karnabatidis *et al.*, 2011).

The RCT (n=140) reported significant improvements for the DES group compared with the BMS group, regarding LLL (DES 21%, BMS 47%, $p<0.0001$), PP (DES 85%, BMS 54%, $p=0.001$), and TLR (DES 9%, BMS 34%, $p=0.001$) (Bosiers *et al.*, 2012). The cohort study (n=81) reported approx. 87% primary patency in the DES group versus approx. 59% in the BMS group (p value not shown) (Karnabatidis *et al.*, 2011).

Conclusion: DES (everolimus) compared with BMS below the knee in patients with critical ischemia, may reduce restenosis as measured by angiographic outcomes and need for reintervention.

Low certainty of evidence (GRADE $\oplus\oplus\circ\circ$).

Drug eluting stent (DES) with sirolimus vs. bare metal stent (BMS) – Below the knee

The effect of DES with sirolimus vs. BMS on restenosis at 12 months was studied in one RCT (n=75) (subgroup analysis) and one cohort study (n=58) (Rastan *et al.*, 2011; Siablis *et al.*, 2007).

The findings were inconsistent. In the RCT, the PP (DES 75%, BMS 56%), TLR rates (DES 14%, BMS 13%) did not differ significantly between the groups (Rastan *et al.*, 2011), whereas the cohort study reported significant differences in PP (DES 87%, BMS 41%, $p<0.001$) and need for TLR (DES 9.1%, BMS 26%, $p=0.02$) (Siablis *et al.*, 2007).

Conclusion: It is uncertain whether there is any difference in restenosis rate comparing DES (sirolimus) with BMS below the knee, in patients with critical ischemia.

Very low certainty of evidence (GRADE $\oplus\circ\circ\circ$).

Drug eluting balloon (DEB) with paclitaxel vs. uncoated balloon (UCB) – Below the knee

DCB was compared with UCB in two RCTs using paclitaxel (Liistro *et al.*, 2013b; Zeller *et al.*, 2014b).

One RCT (n=132) showed significant difference in favour for DCB regarding binary restenosis (DEB 27%, UCB 74%, $p<0.001$), TLR (DCB 10%, UCB 20%, $p=0.02$) (Liistro *et al.*, 2013b), whereas in the other RCT (n=358) there were no significant differences between the DCB and UCB groups, with binary restenosis at 41% versus 36%, LLL at 0.60 versus 0.62, and TLR at 12% versus 14%, respectively (Zeller *et al.*, 2014b).

Conclusion: It is uncertain whether there is little or no difference in restenosis rate comparing DEB (paclitaxel) with UCB below the knee, in patients with critical ischemia.

Very low certainty of evidence (GRADE $\oplus\circ\circ\circ$).

Rutherford score (symptom severity) (Appendix 2 and Appendix 4:2)

Drug eluting stent (DES) with everolimus vs. bare metal stent (BMS) – Below the knee

The effect of DES with everolimus vs. BMS on Rutherford symptom score at 12 months was reported in one RCT (n=140), with no Rutherford symptom score improvement (one or more classes), with DES group 60%, and BMS at 56% (n.s.) (Bosiers *et al.*, 2012).

Conclusion: DES (everolimus) compared with BMS below the knee may result in little or no difference in symptom severity as measured by Rutherford score, in patients with critical ischemia.

Low certainty of evidence (GRADE $\oplus\oplus\circ\circ$).

Drug eluting stent (DES) with sirolimus vs. bare metal stent (BMS) – Below the knee

The effect of DES with sirolimus vs. BMS was studied in one RCT (n=75) (subgroup analysis) at 12 months (Rastan *et al.*, 2011).

The Rutherford symptom score change did differ over time between the groups (Δ Ruth: DES -3, BMS -2, n.s.) (Rastan *et al.*, 2011).

Conclusion: It is uncertain whether there is any difference in symptom severity as measured by Rutherford score comparing DES (sirolimus) with BMS below the knee, in patients with critical ischemia.

Very low certainty of evidence (GRADE $\oplus\circ\circ\circ$).

Drug eluting balloon (DEB) with paclitaxel vs. uncoated balloon (UCB) – Below the knee

DCB was compared with UCB in one RCT (n=132) using paclitaxel (Liistro *et al.*, 2013b).

The RCT showed significant difference in favour for DCB regarding change in Rutherford symptom score (Δ Ruth: DCB 4.3, UCB 3.1, $p=0.004$) (Liistro *et al.*, 2013b).

Conclusion: DEB (paclitaxel) compared with UCB below the knee may slightly reduce symptom severity as measured by Rutherford score, in patients with critical ischemia.
Low certainty of evidence (GRADE ⊕⊕○○).

P3: Mixed population (critical ischemia and intermittent claudication patients)

There were no studies with everolimus in this patient group.

Mortality (Appendix 2 and Appendix 4:3)

Drug eluting stent (DES) with paclitaxel vs. bare metal stent (BMS) – Above the knee

DES with paclitaxel vs. BMS in the above the knee lesion group was compared in two RCTs stating mortality data (Dake *et al.*, 2011a, 2013).

One of the RCTs (n=479) reported 4% mortality in the DES group versus 2% (n.s.) in the BMS group at 12-months follow-up (Dake *et al.*, 2011a).

Conclusion: It is uncertain whether there is little or no difference in mortality comparing DES (paclitaxel) with BMS above the knee, in a mixed patient population with critical ischemia and intermittent claudication. Low certainty of evidence (GRADE ⊕⊕○○).

Drug eluting stent (DES) with sirolimus vs. bare metal stent (BMS) – Above the knee

Mortality data comparing DES with sirolimus with BMS above the knee in this population was studied in two RCTs, reporting on same material after 6 and 24 months (Duda *et al.*, 2005, 2006). There was 7% mortality in DES group versus 4% (n.s.) BMS group at 6 months. At 24 months, there was 15% mortality in the DES group versus 4% (n.s.) in BMS group. Since 12-month data on mortality was not reported, the outcome was not graded for certainty of evidence.

Drug eluting stent (DES) with sirolimus vs. bare metal stent (BMS) – Below the knee

DES with sirolimus vs. BMS in the below the knee lesion population was compared in three RCTs (Falkowski *et al.*, 2009; Rastan *et al.*, 2011; Rastan *et al.*, 2012), two reporting data from the same material at 12 and 36 months. Mortality rate at 12 months in Rastan *et al.* (2011) (n=161) was 17% in the DES group and 14% (n.s.) in the BMS group.

Conclusion: DES (sirolimus) compared with BMS below the knee may result in little or no difference in mortality, in a mixed patient population with critical ischemia and intermittent claudication. Low certainty of evidence (GRADE ⊕⊕○○).

Drug eluting balloon (DEB) with paclitaxel vs. uncoated balloon (UCB) – Above and/or below the knee

Mortality data comparing DEB with paclitaxel vs. UCB in the mixed population with lesions above and/or below the knee was reported in six RCTs (Fanelli *et al.*, 2012, 2014b; Scheinert *et al.*, 2014; Tepe *et al.*, 2008; Werk *et al.*, 2008, 2012).

Three of the studies, Fanelli *et al.* (2014b) (n=50), Scheinert *et al.* (2014) n=101, and Werk *et al.* (2012) (n=85), reported 12 month data, with mortality ranging between 0-4% in the DEB groups versus 0-8% (all n.s.) in the UCB groups.

Conclusion: DEB (paclitaxel) compared with UCB above and/or below the knee may result in little or no difference in mortality, in a mixed patient population with critical ischemia and intermittent claudication. Low certainty of evidence (GRADE ⊕⊕○○).

Amputation (Appendix 2 and Appendix 4:4)

Drug eluting stent (DES) with paclitaxel vs. bare metal stent (BMS) – Above the knee

DES with paclitaxel vs. BMS, above the knee in this population was studied in two RCTs (Dake *et al.*, 2011a, 2013), but only Dake *et al.* (2011a) (n=479) reported 12-months data, with 0.5% amputations in the DES group versus 0% (n.s.) in the BMS group.

Conclusion: DES (paclitaxel) compared with BMS above the knee may result in little or no difference in amputation rate, in a mixed patient population with critical ischemia and intermittent claudication. Low certainty of evidence (GRADE ⊕⊕○○).

Drug eluting stent (DES) with sirolimus vs. bare metal stent (BMS) – Above the knee

Absence of amputations, as complication to the stent procedure, was reported in one RCT comparing DES with sirolimus with BMS in the above the knee lesion group at 24 months (Duda *et al.*, 2006). Since twelve-month data on amputations were not reported, the outcome was not graded for certainty of evidence.

Drug eluting stent (DES) with sirolimus vs. bare metal stent (BMS) – Below the knee

DES with sirolimus vs. BMS in the below the knee group was studied in one RCT (n=161) regarding amputation rate over 12 months (Rastan *et al.*, 2011).

There were 3% amputations in the DES group versus 6% (n.s.) in the BMS group (Rastan *et al.*, 2011).

Conclusion: DES (sirolimus) compared with BMS below the knee may result in little or no difference in amputation rate, in a mixed patient population with critical ischemia and intermittent claudication.

Low certainty of evidence (GRADE ⊕⊕○○).

Drug eluting balloon (DEB) with paclitaxel vs. uncoated balloon (UCB) – Above and/or below the knee

Amputation rates comparing DEB with paclitaxel vs. UCB in the above and/or below the knee lesion group was reported in six RCTs (Fanelli *et al.*, 2012, 2014b; Scheinert *et al.*, 2014; Tepe *et al.*, 2008; Werk *et al.*, 2008, 2012).

Three of the studies, Fanelli *et al.* (2014b) (n=50), Scheinert *et al.* (2014) n=101, and Werk *et al.* (2012) (n=85), reported 12 month data, with amputations ranging between 0-4% in the DEB groups versus 0-12% (all n.s.) in the BMS groups.

Conclusion: DEB (paclitaxel) compared with UCB above and/or below the knee may result in little or no difference in amputation rate, in a mixed patient population with critical ischemia and intermittent claudication. Low certainty of evidence (GRADE ⊕⊕○○).

Restenosis (Appendix 2 and Appendix 4:5)

Drug eluting stent (DES) with paclitaxel vs. bare metal stent (BMS) – Above the knee

DES with paclitaxel vs. BMS (above the knee) was compared in two RCTs with outcome restenosis (12 and 24 month follow-up) (Dake *et al.*, 2011a, 2013).

At 12 months, Dake *et al.* (2011a) (n=479) reported significant improvements regarding PP (DES 83%, BMS 33%, p<0.001), and TLR (DES 10%, BMS 18%, p=0.01).

Conclusion: DES (paclitaxel) compared with BMS above the knee, in a mixed patient population with critical ischemia and intermittent claudication, may reduce restenosis measured by angiographic outcomes.

Low certainty of evidence (GRADE ⊕⊕○○).

Drug eluting stent (DES) with sirolimus vs. bare metal stent (BMS) – Above the knee

DES with sirolimus vs. BMS above the knee was studied in two RCTs, one at 6 months and one at 24 months (same material) (Duda *et al.*, 2005, 2006). The trials did not report 12-month data and the outcome was not graded for certainty of evidence.

Drug eluting stent (DES) with sirolimus vs. bare metal stent (BMS) – Below the knee

DES with sirolimus vs. BMS in below the knee lesions regarding restenosis was compared in three RCTs at 6, 12, and 36 months, respectively (Falkowski *et al.*, 2009; Rastan *et al.*, 2011, 2012).

At 12 months, Rastan *et al.* (2011) (n=161) reported significant improvements regarding PP (DES 81%, BMS 56%, p=0.004), but not regarding TLR (DES 10%, BMS 18%, n.s.).

Conclusion: DES (sirolimus) compared with BMS below the knee, in a mixed patient population with critical ischemia and intermittent claudication, may reduce restenosis measured by angiographic outcomes.

Low certainty of evidence (GRADE ⊕⊕○○).

Drug eluting balloon (DEB) with paclitaxel vs. uncoated balloon (UCB) – Above and/or below the knee

Restenosis comparing DEB with paclitaxel vs. UCB above and/or below the knee was reported in seven RCTs, with follow-up periods from 6 to 24 months (Fanelli *et al.*, 2012, 2014b; Scheinert *et al.*, 2014; Tepe *et al.*, 2008, 2013; Werk *et al.*, 2008, 2012).

Four RCTs reported data at 12 months follow-up (Fanelli *et al.*, 2014b; Scheinert *et al.*, 2014; Tepe *et al.*, 2008; Werk *et al.*, 2012). Fanelli *et al.* (2014) (n=50) reported significant difference in LLL (DEB 0.64, UCB 1.81, p=0.01), PP (DEB 76%, UCB 40%, p=0.04), and TLR (DEB 12%, UCB 35%, p<0.05). Werk *et al.* (2012) (n=81) also reported significant TLR differences with 8% in the DEB group versus 25% (p=0.02) in the UCB group. The remaining two RCTs by Tepe *et al.* (2008) (n=102) and Scheinert *et al.* (2014) (n=101) reported TLR (DEB 10% and 29%, BMS 48% and 33%, respectively, both n.s.). Scheinert *et al.* 2014 also reported PP (DEB 67%, UCB 55%, n.s.).

Conclusion: DEB (paclitaxel) compared with UCB above and/or below the knee, may reduce restenosis measured by angiographic outcomes and need for revascularisation in a mixed patient population with critical ischemia and intermittent claudication, Low certainty of evidence (GRADE ⊕⊕○○).

Rutherford score (symptom severity) (Appendix 2 and Appendix 4:5)

Drug eluting stent (DES) with paclitaxel vs. bare metal stent (BMS) – Above the knee

DES with paclitaxel vs. BMS (above the knee) was compared in one RCTs (n=479) at 12 months (Dake *et al.*, 2011a), with no significant differences in Rutherford score classification over time between the groups (n.s., ΔRuth data not shown).

Conclusion: It is uncertain whether there is any difference in symptom severity as measured by Rutherford score classification, comparing DES (paclitaxel) with BMS below the knee, in a mixed patient population with critical ischemia and intermittent claudication. Very low certainty of evidence (GRADE ⊕○○○).

Drug eluting stent (DES) with sirolimus vs. bare metal stent (BMS) – Above the knee

Not reported at 12 months.

Drug eluting stent (DES) with sirolimus vs. bare metal stent (BMS) – Below the knee

DES with sirolimus vs. BMS in below the knee lesions regarding restenosis was compared in three RCTs at 6, 12, and 36 months, respectively Falkowski *et al.*, 2009; Rastan *et al.*, 2011; 2012).

Rastan *et al.* (2001) (n=161) reported symptom severity at 12 months, with an improvement in Rutherford score classification (DES -2, BMS -1, p=0.004).

Conclusion: DES (sirolimus) compared with BMS in lesions below the knee, in a mixed patient population with critical ischemia and intermittent claudication, may slightly reduce symptom severity as measured by Rutherford score classification. Low certainty of evidence (GRADE ⊕⊕○○).

Drug eluting balloon (DEB) with paclitaxel vs. uncoated balloon (UCB) – Above and/or below the knee

One RCT (n=101) reported Rutherford score change at 12 months, with ΔRuth 1.6 for DEB and 2.1 for UCB (p not stated) (Scheinert *et al.*, 2014).

Conclusion: It is uncertain whether there is any difference in symptom severity as measured by Rutherford score classification, comparing DEB (paclitaxel) with UCB above and/or below the knee, in a mixed patient population with critical ischemia and intermittent claudication. Very low certainty of evidence (GRADE ⊕○○○).

P 1-3: Complications and adverse events (Appendix 4:6)

Complications and adverse events associated to DES or DEB were reported in 33 studies. 16 were RCTs, 4 were cohort studies and 13 were case-series. There was a vast variation in how major complications/SAEs were defined and reported across the studies. TLR was relatively commonly regarded as a major complication which contributed to very high major complication frequencies (up to 95%). Thus, TLR was common among these patients. Deaths within 12 months occurred between 0-18%, mainly related to the underlying atherosclerosis, and were sometimes reported as an SAE and sometimes a study outcome. Commonly encountered SAEs were amputations, mortality, pseudo aneurysms and thromboses, detailed in Appendix 4:6

Medical societies or health authorities that recommend drug eluting balloons and stents in peripheral arterial disease

In an HTA-report from UK National Institute for Health and Care Excellence (NICE, 2012) it was concluded that low (or very low) quality of evidence suggests that drug eluting stents in the femoropopliteal vascular segments may increase the patency one year after treatment for intermittent claudication. Patient related outcomes (walking distance and quality of life) were not studied, and the technology was not recommended.

Moreover, it was concluded that drug eluting stents in femoropopliteal arteries, reduce the need of reinterventions within two years after invasive treatment (low quality of evidence, based on one study), and that drug eluting stents in infrapopliteal areas increase the ankle brachial index (i.e. ratio of the blood pressure in the lower legs to the systemic blood pressure) two years after treatment of critical lower limb ischemia (high quality of evidence, based on one study).

Ongoing research

A search in the Clinicaltrials.gov database was conducted (2014-05-05), with the search terms (*iliac artery OR iliac arteries OR arteria iliaca OR iliacal arteries OR aortoiliac disease OR lower limb arterial disease OR femoropopliteal OR infrapopliteal OR crural OR "below the knee" OR peripheral arterial disease OR peripheral artery disease OR intermittent claudication OR critical limb ischemia OR critical limb ischaemia OR PAD OR chronic limb ischemia OR chronic limb ischaemia OR femoro-popliteal OR infra-popliteal OR superficial femoral artery OR superficial femoral arteries*) AND (*paclitaxel OR everolimus OR sirolimus OR drug-eluting OR drug-coated OR drug-releasing OR drug-emitting*).

121 studies were identified, of which 78 were considered relevant for the question at issue. Twenty-one of the studies had not started recruitment of participants, 37 were recruiting participants, 16 were completed, and four studies were discontinued. 42 of the studies were industry financed and 36 reported some other source of funding.

After the literature searches and data extraction were completed an additional RCT which was consistent with our PICO was published (IN.PACT SFA trial, n=331, Tepe *et al.*, 2015). The RCT compared DEB (paclitaxel) with UCB above and/or below the knee in a mixed patient population (intermittent claudication or critical ischemia). The primary outcome was primary patency (PP at 12 months), defined as freedom from restenosis. In this RCT there was a higher PP at 12 months in the DEB group (82%) compared with the UCB group (52%, $p<0.001$), with neither device- or procedure related deaths nor major amputations (Tepe *et al.*, 2015).

9. Ethical consequences

Drug eluting balloons and stents is a new technology for treatment of symptomatic PAD in the lower extremities, but the patient benefits and risks have thus far not been thoroughly studied. The marketing activities are industry driven and several devices for PAD in the lower extremities have been introduced on the Scandinavian market. Introduction of new expensive, although promising, technologies into routine care on the basis of uncertain research evidence constitutes an ethical dilemma. The lack of evidence for patient benefits needs to be related to the risk of adverse effects and the cost increase.

10. Organisation

When drug-eluting balloons and stents can be put into practice

Provided financing, the technology could be introduced immediately. Suitable devices are available on the Swedish market.

Use of drug-eluting balloons and stents for peripheral artery disease in other hospitals in Region Västra Götaland of Sweden

The use of drug-eluting balloons and stents for peripheral artery disease has been rather limited at Swedish hospitals. This technology has recently been included in the national quality register of vascular surgery, and a few vascular surgery departments are increasingly using the technology, especially in more challenging cases where failure may substantially increase the risk of amputation.

Consequences of drug-eluting balloons and stents in peripheral artery disease for personnel

Introduction of the technology would not contribute to any substantial changes for the personnel, patient flows, or care related processes.

Consequences for other clinics or supporting functions at the hospital or in the whole Region Västra Götaland of Sweden

Introduction of the technology would not affect other departments or services at the Sahlgrenska University Hospital or in the Region Västra Götaland.

11. Economic aspects

Present costs of treatment of peripheral artery disease

The patient group with PAD is heterogeneous with regard to both health care needs and resources required in conjunction with endovascular interventions. Thus, it is difficult to specify the total cost of a routinely conducted endovascular intervention. Patients with critical ischemia in the extremities tend to have more widespread and extensive vascular disease, which may involve extended interventions, longer hospital stays, and higher material costs than for treatment of intermittent claudication. The need of hospitalisation associated with endovascular surgery has a substantial variation which is related to the severity of the PAD, and on the hospital organization. If some are treated as out-patients, without overnight stay in the hospital, the total cost for endovascular procedures may be decreased.

Estimated costs based on current figures from the Vascular-Thoracic Department at Sahlgrenska University Hospital gives a total cost for routine endovascular intervention (including perioperative inpatient care) of approximately 130,000 SEK (range: 25,000-450,000). The isolated mean cost of the endovascular intervention is 54,000 SEK (range: 7,000-125,000).

Length of hospital stay varies from one to 34 days (mean 6.5 days), and is related to individual needs of pain management, advanced treatment of ulcerations, etc.

Provided that the proportion of endovascularly treated patients remains unchanged (70%), the total annual cost (including procedure related inpatient care) of 400 patients/year in Region Västra Götaland is estimated to $130,000 \times 400 \times 0.7 = 36.4$ MSEK, of which the isolated cost of the endovascular intervention contributes to $54,000 \times 400 \times 0.7 = 15.1$ MSEK per year.

Expected costs of treatment with drug-eluting balloons and stents

Drug-eluting balloons and stents are more expensive than conventional devices. In some cases (e.g. stent placement in femoral artery) also a more extensive antiplatelet treatment is needed, which also contributes to a cost increase. Other procedure related costs will remain virtually unchanged.

In extended lesions several devices are needed, since the longest available balloon is 15 cm long, and the longest stent is 12 cm. The mean lesion length in Swedish studies is 15 cm in critical ischemia, and shorter in intermittent claudication. Thus, in average approximately 1.5-2 balloons/stents would be needed for each patient.

The cost of a drug-eluting balloon is 5-6,000 SEK (price is declining) and a conventional balloon costs about 1,000 SEK. A similar cost ratio exists for stents. Thus, the cost increase per device is approximately 5,000 SEK.

Total change of cost

If all eligible patients (400) should be treated with drug eluting devices, the cost increase in Region Västra Götaland would be three to four MSEK, as compared to conventional devices. The cost increase should be weighed against the effectiveness of the new technology in comparison to existing treatment. If the number of renarrowing, restenosis and reinterventions or conversion to open surgery is reduced by the drug eluting devices the total cost is reduced. With conventional devices the need of reinterventions is relatively high, mostly due to restenosis.

Possibility to adopt and use drug-eluting balloons and stents in peripheral artery disease within the present hospital budget

No.

Available published health economy analyses

The report from NICE did not identify any health economic analyses related to drug-eluting balloons and stents for PAD in the legs (NICE, 2013)

Recently Kearns *et al.*, (2013) analysed the cost effectiveness of eight different adjuvant therapies in the endovascular treatment of infrainguinal PAD (drug-eluting balloons and stents was compared to conventional treatment). Among the eight therapies, drug eluting balloons was considered the most cost-effective treatment, both in critical ischemia and intermittent claudication.

12. Unanswered questions

Important gaps in scientific knowledge

The SBU database on 'knowledge gaps' denotes lack of evidence for an effect of drug-eluting balloons and stents for PAD in the lower extremities (SBU, 2015).

Interest in the own organisation to start studies within the research field at issue

A register-based controlled study on the effect of drug eluting balloons and stents compared with conventional therapy in infrainguinal PAD is ongoing. This national SWEDEPAD-study will analyse treatment effects with both clinical and patient centred outcomes (e.g. quality of life in intermittent claudication, risk of amputation in critical ischemia). The study will be coordinated from Sahlgrenska University Hospital. Principal investigators: Dr Mårten Falkenberg, and Dr Joakim Nordanstig. ClinicalTrials.gov Identifier: NCT02051088; <http://www.clinicaltrials.gov/ct2/show/NCT02051088?term=SWEDEPAD&rank=1>)

Appendix 1, Search strategy, study selection and references

Question at issue:

Do drug eluting balloons and stents improve the effectiveness and reduce the risks compared with uncoated balloons and stents in endovascular treatment of lower limb symptomatic peripheral arterial disease (PAD)?

PICO

P= Patients, I= Intervention, C= Comparison, O=Outcome

P1 = Adults with intermittent claudication due to PAD in lower extremity

P2 = Adults with critical ischemia due to PAD in lower extremity

P3 = Mixed populations of P1 or P2

I= Endovascular treatment with drug (antiproliferative) eluting balloons or stents

C= Endovascular treatment with non-drug eluting balloons and stents

Critical for decision making

O1= Mortality (Mort)

O2= Amputation (Amp)

O3= Restenosis (rest) (measured as: binary patency late lumen loss, primary patency, target lesion, revascularization (see also O6)

Important for decision making

O4 = Health related quality of life (HRQoL)

O5 = Walking distance (Wd), pain free

O6 = Reintervention (in the same vascular segment)

O7 = Rutherford score (Ruth), symptom severity (1-6)

Eligibility criteria

RCT \geq 25 patients in each group

Non-randomized controlled studies \geq 25 patients in each group

Case series >100 patients

Systematic reviews

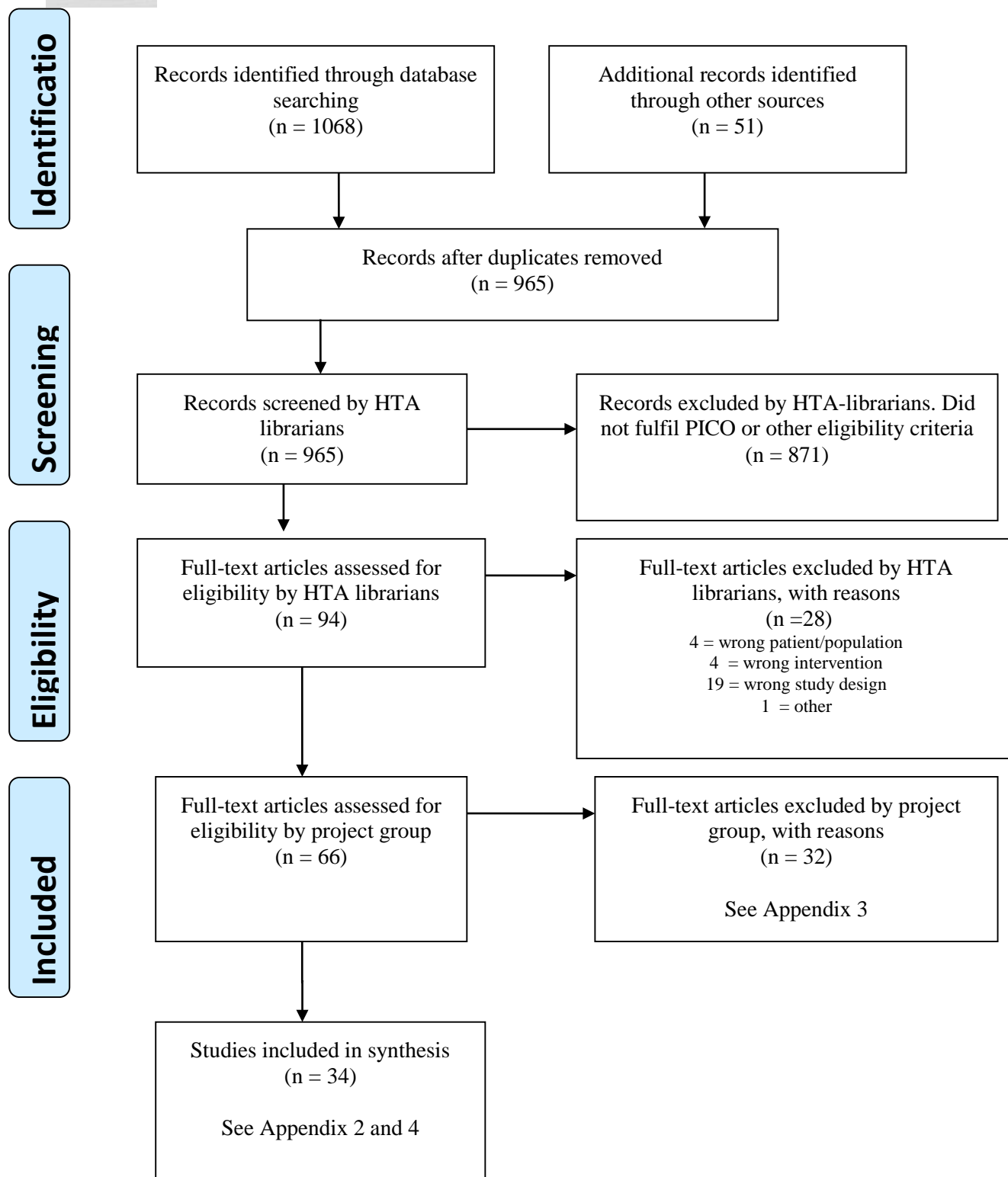
Publication year:

2000-

Language:

Engelska, svenska, norska, danska

Selection process – flow diagram



Search strategies

Database: PubMed

Date: 2013-05-14

No of results: 309

Search updated: 2014-04-08 with 135 items found and 2014-11-19 with 119 items found

Search	Query	Items found
#17	Search #16 NOT #6	309
#16	Search #15 NOT #7	326
#15	Search (#14) AND #2	393
#14	Search (#13) OR #1	51072
#2	Search iliac artery OR iliac arteries OR arteria iliaca OR iliacal arteries OR aortoiliac disease OR lower limb arterial disease OR femoropopliteal OR infrapopliteal OR crural OR "below the knee" OR peripheral arterial disease OR peripheral artery disease OR intermittent claudication OR critical limb ischemia OR critical limb ischaemia OR PAD OR chronic limb ischemia OR chronic limb ischaemia	108564
#1	Search (paclitaxel OR paclitaxel* OR everolimus OR everolimus* OR sirolimus OR sirolimus* OR drug-elut* OR drug-coat* OR drug-releas* OR drug-emitt*)	51072
#13	Search "Drug-Eluting Stents"[Mesh]	4830
#7	Search ((animals[mh]) NOT (animals[mh] AND humans[mh]))	3778933
#6	Search (Editorial[ptyp] OR Letter[ptyp] OR Comment[ptyp])	1236704

Database: Embase

Date: 2013-05-14

No of results: 275

Search updated: 2014-04-08 with 71 items found and 2014-11-19 with 49 items found

#	Searches	Results
1	(paclitaxel or everolimus or sirolimus or rapamycin or drug-elut\$ or drug-coat\$ or drug-releas\$ or drug-emitt\$).ti,ab,tn.	72716
2	exp drug eluting stent/ or exp paclitaxel/ or exp everolimus/ or exp rapamycin/	99968
3	1 or 2	125365
4	exp iliac artery/ or exp Leriche syndrome/ or exp intermittent claudication/ or exp peripheral occlusive artery disease/ or exp leg ischemia/ or exp popliteal artery/ or exp critical limb ischemia/	126626
5	(iliac artery or iliac arteries or arteria iliaca or iliacal arteries or aortoiliac disease or lower limb arterial disease or femoropopliteal or infrapopliteal or crural or "below the knee" or peripheral arterial disease or peripheral artery disease or intermittent claudication or critical limb ischemia or critical limb ischaemia or PAD or chronic limb ischemia or chronic limb ischaemia).ti,ab.	48599
6	4 or 5	156336
7	3 and 6	4430
8	limit 7 to (embase and (danish or english or norwegian or swedish) and yr="2000 -Current" and (article or conference paper or "review"))	2718
9	limit 8 to exclude medline journals	275

Database: Cochrane

Date: 2013-05-14

No of results: 53

Cochrane reviews 8

Other reviews 2

Trials 42

Economic evaluations 1

Search updated: 2014-11-19

No of results: 53

Cochrane reviews 6

Other reviews 6

Trials 39

Technology Assessments 1

Economic evaluations 3

ID	Search	Hits
#1	iliac artery or iliac arteries or arteria iliaca or iliacal arteries or aortoiliac disease or lower limb arterial disease or femoropopliteal or infrapopliteal or crural or "below the knee" or peripheral arterial disease or peripheral artery disease or intermittent claudication or critical limb ischemia or critical limb ischaemia or PAD or chronic limb ischemia or chronic limb ischaemia:ti,ab,kw (Word variations have been searched)	4554
#2	paclitaxel* or everolimus* or sirolimus* or (drug next elut*) or (drug next coat*) or (drug next releas*) or (drug next emitt*):ti,ab,kw	4707
#3	#1 and #2 from 2000	53

Database: CRD

Date: 2013-05-14

No of results: 4

Search updated:

#	Searches	Hits
#1	(iliac artery or iliac arteries or arteria iliaca or iliacal arteries or aortoiliac disease or lower limb arterial disease or femoropopliteal or infrapopliteal or crural or "below the knee" or peripheral arterial disease or peripheral artery disease or intermittent claudication or critical limb ischemia or critical limb ischaemia or PAD or chronic limb ischemia or chronic limb ischaemia)	
#2	(paclitaxel* or everolimus* or sirolimus* or (drug ADJ elut*) or (drug ADJ coat*) or (drug ADJ releas*) or (drug ADJ emitt*))	
#3	#1 AND #2	4

A comprehensive review of reference lists brought 51 new records.

Reference lists

Included studies

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Project: Drug-eluting balloons and stents**Appendix 2:** Included controlled studies (alphabetically) with study design and patient characteristics

1(5)

Author, Year, Country	Study design PICO P1-3	Follow-up period (years)	Study Groups; Intervention vs control	Patients (n)	Mean Age (years)	Men/women	Outcome variables
Bosiers, 2012	RCT P2	12 months	I: Drug-eluting stents Everolimus (Xience V) C: Bare metal stents (Multi-Link Vision)	140	75-76 (group means)	89/51	Mortality Amputation Lumen loss Primary patency TLR Rutherford score
Dake, 2011a (Zilver PTX trial)	RCT P3	12 months	I: Drug-eluting stents Paclitaxel (Zilver PTX) C: Bare metal stents (Zilver)	474	67.7-67.9 (group means)	307/167	Mortality Amputation Primary patency TLR Rutherford score Complications (adverse events)
Dake, 2013a (Zilver PTX trial)	RCT P3	24 months	I: Drug-eluting stents Paclitaxel (Zilver PTX) C: Bare metal stents (Zilver)	474	67.7-67.9 (group means)	307/167	Mortality Amputation Primary patency TLR Rutherford score Complications (adverse events)
Duda, 2005 (SIROCCO II trial)	RCT P3	6 months	I: Drug-eluting stents Sirolimus (SMART) C: Bare metal stents (SMART)	57	66.1-67.2 (group means)	40/17	Mortality Lumen loss Primary patency Rutherford score Complications (adverse events)

Project: Drug-eluting balloons and stents**Appendix 2:** Included controlled studies (alphabetically) with study design and patient characteristics

2(5)

Author, Year, Country	Study design PICO P1-3	Follow-up period (years)	Study Groups; Intervention vs control	Patients (n)	Mean Age (years)	Men/women	Outcome variables
Duda, 2006 (SIROCCO I & II trials)	RCT P3	24 months	I: Drug-eluting stents Sirolimus (SMART) C: Bare metal stents (SMART)	93	66.3-65.9 (group means)	67/26	Mortality Amputation Primary patency TLR Rutherford score Complications (adverse events)
Falkowski, 2009	RCT P3	6 months	I: Drug-eluting stents Sirolimus (Cypher) C: Bare metal stents (Sonic)	50	68.3-70.5 (group means)	29/21	Mortality Lumen loss Primary patency TLR Rutherford score Complications (adverse events)
Fanelli, 2012 (DEBELLUM trial)	RCT P3	6 months	I: Drug-eluting balloons Paclitaxel (IN.PACT Admiral or Amphirion) C: Uncoated balloons (Admiral or Amphirion)	50	66	37/13	Mortality Amputation Lumen loss TLR Complications (adverse events)
Fanelli, 2014b (DEBELLUM trial)	RCT P3	12 months	I: Drug-eluting balloons Paclitaxel (IN.PACT Admiral or Amphirion) C: Uncoated balloons (Admiral or Amphirion)	50	67	37/13	Mortality Amputation Lumen loss Primary patency TLR Complications (adverse events)
Karnabatidis, 2011	Cohort P2	36 months	I: Drug-eluting stents Everolimus (Xience V or Promus) C: Bare metal stents	81	71	63/18	Mortality Amputation Lumen loss Primary patency TLR Complications (adverse events)

Project: Drug-eluting balloons and stents**Appendix 2:** Included controlled studies (alphabetically) with study design and patient characteristics

3(5)

Author, Year, Country	Study design PICO P1-3	Follow-up period (years)	Study Groups; Intervention vs control	Patients (n)	Mean Age (years)	Men/women	Outcome variables
Liistro, 2013b (DEBATE-BTK trial)	RCT P2	12 months	I: Drug-eluting balloons Paclitaxel (IN.PACT Amphirion) C: Uncoated balloons (Amphirion)	132	74-75 (group means)	106/26	Mortality Amputation Lumen loss Primary patency TLR Rutherford score Complications (adverse events)
Rastan, 2011	RCT P3	12 months	I: Drug-eluting stents Sirolimus (Yukon) C: Bare metal stents	161	72.9-73.4 (group means)	107/54	Mortality Amputation Primary patency TLR Rutherford score Complications (adverse events)
Rastan, 2012	RCT P3	1.016 days (mean period)	I: Drug-eluting stents Sirolimus (Yukon) C: Bare metal stents	161	72.9-73.4 (group means)	107/54	Mortality Amputation TLR Rutherford score
Scheinert, 2014 (Levant I trial)	RCT P3	24 months	I: Drug-eluting balloons Paclitaxel (Lutonix) C: Uncoated balloons	101	67-70 (group means)	64/37	Mortality Amputation Lumen loss Primary patency TLR Rutherford score Complications (adverse events)
Siablis, 2005	Cohort P2	6 months	I: Drug-eluting stents Sirolimus (Cypher) C: Bare metal stents (Evolution, Spiral Force, Tsunami, Zeus)	58	68.7-68.8 (group means)	42/16	Mortality Amputation Primary patency TLR Complications (adverse events)

Project: Drug-eluting balloons and stents**Appendix 2:** Included controlled studies (alphabetically) with study design and patient characteristics

4(5)

Author, Year, Country	Study design PICO P1-3	Follow-up period (years)	Study Groups; Intervention vs control	Patients (n)	Mean Age (years)	Men/women	Outcome variables
Siablis, 2007	Cohort P2	12 months	I: Drug-eluting stents Sirolimus (Cypher) C: Bare metal stents (Evolution, Spiral Force, Tsunami, Zeus)	58	68.7-68.8 (group means)	42/16	Mortality Amputation Primary patency TLR
Siablis, 2009	Cohort P2	36 months	I: Drug-eluting stents Sirolimus (Cypher) C: Bare metal stents (Evolution, Spiral Force, Tsunami, Zeus)	103	69.0-71.6 (group means)	81/22	Mortality Amputation Primary patency TLR Complications (adverse events)
Tepe, 2008 (THUNDER study)	RCT P3	24 months	I: Drug-eluting balloons Paclitaxel (Lutonix) C: Uncoated balloons	102	68-69 (group means)	65/37	Mortality Amputation Lumen loss Primary patency TLR Complications (adverse events)
Tepe, 2013 (THUNDER study Sub group analysis)	RCT P3	24 months	I: Drug-eluting balloons Paclitaxel (Lutonix) C: Uncoated balloons	86	Not stated	52/34	Lumen loss TLR
Werk, 2008	RCT P3	18 months	I: Drug-eluting balloons Paclitaxel (Indena) C: Uncoated balloons(Indena)	87	67.3-70.2 (group means)	52/35	Mortality Amputation Lumen loss TLR Rutherford score Complications (adverse events)

Project: Drug-eluting balloons and stents**Appendix 2:** Included controlled studies (alphabetically) with study design and patient characteristics

5(5)

Author, Year, Country	Study design PICO P1-3	Follow-up period (years)	Study Groups; Intervention vs control	Patients (n)	Mean Age (years)	Men/women	Outcome variables
Werk, 2012 (PACIFIER trial)	RCT P3	12 months	I: Drug-eluting balloons Paclitaxel (IN.PACT Pacific) C: Uncoated balloons(Pacific Extreme)	85	71	50/35	Mortality Amputation Lumen loss TLR Rutherford score Complications (adverse events)
Zeller, 2014b (IN.PACT DEEP trial)	RCT P2	12 months	I: Drug-eluting balloons Paclitaxel (IN.PACT Amphirion) C: Uncoated balloons	358	71.7-73.3 (group means)	266/92	Mortality Amputation Lumen loss TLR Complications (adverse events)

Appendix 3 Excluded articles

Study (author, publication year)	Reason for exclusion
Antoniou, 2013	Earlier systematic review not used for data extraction
Antoniou, 2014	Non-systematic review (incomplete)
Biondi-Zoccai, 2009	Old material
Biondi-Zoccai, 2013	Earlier systematic review not used for data extraction
Bosiers, 2013b	Wrong interventions (not drug-eluting balloons or stents)
Canaud, 2014	Earlier systematic review not used for data extraction
Cassese, 2012	Earlier systematic review not used for data extraction
Chan, 2011	Non-systematic review
De Cock, 2013	Modelling study, budget impact
Diehm, 2013	Wrong outcome (costs)
Fanelli, 2014a	Non-systematic review
Fusaro, 2013a	Earlier systematic review not used for data extraction
Fusaro, 2013b	Earlier systematic review not used for data extraction
Geraghty, 2013	Wrong intervention
Jens, 2014a	Earlier systematic review not used for data extraction

Appendix 3 Excluded articles

Study (author, publication year)	Reason for exclusion
Jens, 2014b	Earlier systematic review not used for data extraction
Katsanos, 2013a	Non-systematic review, wrong outcome
Katsanos, 2013b	Earlier systematic review not used for data extraction
Katsanos, 2014	Earlier systematic review not used for data extraction
Kearns, 2013	Wrong outcome (cost effectiveness)
Kitrou, 2014	Cohort n<25/group
Lammer, 2013	Wrong intervention
Liistro, 2013a	Wrong comparison (balloon vs. stent)
Liistro, 2014	Wrong population (reinterventions)
Miki, 2014	Cohort n<25/group
Razavi, 2014	Earlier systematic review not used for data extraction
Saxon, 2013	Wrong intervention
Scheinert, 2006	Case-series n<100
Scheinert, 2012	Wrong comparison (stent vs. balloon)
Simpson, 2013	Wrong comparison (adjunct to PCA)

Appendix 3 Excluded articles

Study (author, publication year)	Reason for exclusion
Yang, 2014	Drug eluting stents not separated
Zwischenberger, 2013	Non-systematic review

Author, year	Country	Study design Comparison Level	Number of patients Follow-up time	With drawals - dropouts	Result		Comments	Directness*	Study limitations *	Precision *
					Intervention	Control				

Mortality - Stent vs stent below the knee										
Rastan 2011	Germany	RCT DES vs BMS Sirolimus BK _n	I=40 C=46	Not stated*	Mortality: 5/40 (12.5%) n.s.	Mortality: 3/46 (6.5%)	* Regarding subgroup analysis for patients with intermittent claudication at baseline.	-	?	?
Restenosis (late lumen loss, primary patency, target lesion revascularization) - Stent vs stent below the knee										
Rastan 2011	Germany	RCT DES vs BMS Sirolimus BK _n	I=40 C=46	Not stated*	PP: 85.3% p=0.006 TLR: 5.9% n.s.	PP: 55.0% TLR: 20%	* Regarding subgroup analysis for patients with intermittent claudication at baseline.	-	?	?
Rutherford score (symptom severity) (Ruth) - Stent vs stent below the knee										
Rastan 2011	Germany	RCT DES vs BMS Sirolimus BK _n	I=40 C=46	Not stated*	Median ΔRuth: -1.5 (-3 to -1) p=0.01	Median ΔRuth: -1 (-2 to 0)	* Regarding subgroup analysis for patients with intermittent claudication at baseline.	-	?	?

* + No problem
? Some problems
- Major problems

Author, year	Country	Study design Comparison Level	Number of patients Follow-up time	With drawals - dropouts	Result		Comments	Directness*	Study limitations *	Precision *
					Intervention	Control				

Mortality - Stent vs stent below the knee										
Bosiers, 2012	Belgium	RCT DES vs. BMS Everolimus BK _n	I=140 I=74 C=66 12 months	7	12 months survival: 81.9% n.s.	12 months survival: 84.2%	Xienc _e V (everolimus) Destiny trial Causes of death included: myocardial ischemia or heart failure (n=12), cerebrovascular accident (n=4), multiorgan system failure (n=2), renal insufficiency (n=1), gastrointestinal bleeding (n=1), thoracic trauma (n=1), malignancy (n=1), unrelated bleeding (n=1).	?	-	+
Rastan, 2011	Germany	RCT DES vs. BMS Sirolimus BK _n	I=42 C=33	Not stated *	12 months mortality: 9/42 (21.4%) n.s.	12 months mortality: 8/33 (24.3%)	* Regarding subgroup analysis for patients with intermittent claudication at baseline.	-	?	?
Karnabatidis, 2011	Greece	Cohort DES vs. BMS Everolimus BK _n	I=47 C=34	Not stated	12 months survival*: ≈ 95%	12 months survival*: ≈ 85%	* Estimated from figure.	Na	Na	Na

Project: Drug-eluting vs. conventional endovascular treatment in infrainguinal peripheral arterial disease

Appendix 4.2

Outcome variable: Mortality, amputation, restenosis, and Rutherford score (symptom severity), P2

* + No problem
? Some problems
- Major problems

Author, year	Country	Study design Comparison Level	Number of patients Follow-up time	With drawals - dropouts	Result		Comments	Directness*	Study limitations *	Precision *
					Intervention	Control				
Siablis, 2007	Greece	Cohort DES vs. BMS Sirolimus BK _n	I=29 C=29	I=11 C=9	Mortality 12 months: 4/29 (13.8%) n.s.	Mortality 12 months: 3/29 (10.3%)		Na	Na	Na
Siablis, 2009	Greece	Cohort DES vs. BMS Sirolimus BK _n	I=62 C=41	Not stated at 12 months	Survival at 12 months: ≈92%	Survival at 12 months: ≈88%		Na	Na	Na

* + No problem
? Some problems
- Major problems

Author, year	Country	Study design Comparison Level	Number of patients Follow-up time	With drawals - dropouts	Result		Comments	Directness*	Study limitations *	Precision *
					Intervention	Control				

Mortality - Balloon vs balloon below the knee										
Liistro, 2013b	Italy	RCT DEB vs. PTA Paclitaxel BKn	132 I=65 C=67 12 months	I=5 C=3	12 months mortality: 5/65 (7.7%) n.s.	12 months mortality: 3/67 (4.5%)	IN.PACT Amphiron, Medtronic vs. Amphrion Deep, Medtronic. Diabetics BTK Causes of death included: sudden death (n=3), respiratory failure (n=1), stroke (n=1), heart failure (n=1), sepsis (n=1).	+	+	+
Zeller, 2014b	Multicenter, Europe	RCT DEB vs. PTA Paclitaxel BKn	358 I=239 C=119 12 months	I=86 C=36	12 months mortality: 23/239 (9.6%) p=0.5626 [†] Consort flowchart data, deaths until 12 months *: 44/239 (18.4%) p=0.4631 [†]	12 months mortality: 9/119 (7.6%) Consort flowchart data, deaths until 12 months *: 18/119 (15.1%)	IN.PACT DEEP DEB arm, Amphiron, Medtronic vs Amphrion Deep, Medtronic * Discrepancy in data: more deaths reported in the Consort flowchart than for all-cause mortality at 12 months follow-up [†] Calculated from reported data (Fisher's exact test) including all participants that were randomized.	?	-	+

* + No problem
 ? Some problems
 - Major problems

Author, year	Country	Study design Comparison Level	Number of patients Follow-up time	With drawals - dropouts	Result		Comments	Directness*	Study limitations *	Precision *
					Intervention	Control				

Amputation - Stent vs stent below the knee										
Bosiers 2012	Belgium	RCT DES vs. BMS Everolimus BK _n	140 I=74 C=66 12 months	7	Amputations, 12 months: 1 n.s.	Amputations, 12 months: 2	Xience V (everolimus) Destiny trial	?	-	+
Rastan, 2011	Germany	RCT DES vs. BMS Sirolimus BK _n	I=42 C=33	Not stated *	12 months Minor amputation: 3.4% n.s. Major amputation: 3.4% n.s.	12 months Minor amputation: 4.3% Major amputation: 4.3%	* Regarding subgroup analysis for patients with intermittent claudication at baseline.	-	?	?
Karnabatidis, 2011	Greece	Cohort DES vs. BMS Everolimus BK _n	n=81 I=51 limbs C=36 limbs	Not stated	12 limb salvage*: ≈ 97%	12 limb salvage*: ≈ 92%	* Estimated from figure (on a per limb basis).	Na	Na	Na

Project: Drug-eluting vs. conventional endovascular treatment in infrainguinal peripheral arterial disease

Appendix 4.2

Outcome variable: Mortality, amputation, restenosis, and Rutherford score (symptom severity), P2

* + No problem
? Some problems
- Major problems

Author, year	Country	Study design Comparison Level	Number of patients Follow-up time	With drawals - dropouts	Result		Comments	Directness*	Study limitations *	Precision *
					Intervention	Control				
Siablis, 2007	Greece	Cohort DES vs. BMS Sirolimus BK _n	I=29 C=29	I=11 C=9	12 months Limb salvage: 24/25 (96.0%) n.s. Major amputation 1/29 (3.4%) Minor amputation: 3/29 (10.3%) n.s.	12 months Limb salvage: 26/26 (100.0%) Major amputation* 0/29 (0.0%) Minor amputation: 5/29 (17.2%)	* Calculated from reported data (Fisher's test)	Na	Na	Na
Siablis, 2009	Greece	Cohort DES vs. BMS Sirolimus BK _n	I=62 C=41	Not stated at 12 months	Limb salvage at 12 months: ≈92%	Limb salvage at 12 months: ≈90%		Na	Na	Na

* + No problem
? Some problems
- Major problems

Author, year	Country	Study design Comparison Level	Number of patients Follow-up time	With drawals - dropouts	Result		Comments	Directness*	Study limitations *	Precision *
					Intervention	Control				

Amputation - Balloon vs balloon below the knee										
Liistro, 2013b	Italy	RCT DEB vs. PTA Paclitaxel BK _n	132 I=65 C=67 12 months	I=5 C=3	Amputations, 12 months: 0 (0%) n.s.	Amputations, 12 months: 1 (1.5%)	IN.PACT Amphiron, Medtronic vs. Amphrion Deep, Medtronic. Diabetics BTK	+	+	+
Zeller, 2014b	Multicenter, Europe	RCT DEB vs. PTA Paclitaxel BK _n	358 I=239 C=119 12 months	I=86 C=36	Amputations, 12 months: 20/227 (8.8%) p=0.080 Consort flowchart data, major amputations until 12 months *: 37/239 (15.4%) p=0.0181 [†]	Amputations, 12 months: 4/111 (3.6%) Consort flowchart data, major amputations until 12 months *: 8/119 (6.7%)	IN.PACT DEEP DEB arm, Amphiron, Medtronic vs Amphrion Deep, Medtronic * Discrepancy in data: more major amputations reported in the Consort flowchart than for major amputations at 12 months follow-up [†] Calculated from reported data (Fisher's test)	?	-	+

Project: Drug-eluting vs. conventional endovascular treatment in infrainguinal peripheral arterial disease

Appendix 4.2

Outcome variable: Mortality, amputation, restenosis, and Rutherford score (symptom severity), P2

* + No problem
? Some problems
- Major problems

Author, year	Country	Study design Comparison Level	Number of patients Follow-up time	With drawals - dropouts	Result		Comments	Directness*	Study limitations *	Precision *
					Intervention	Control				

Restenosis (late lumen loss, primary patency, target lesion revascularization) - Stent vs stent below the knee										
Bosiers, 2012	Belgium	RCT DES vs. BMS Everolimus BK _n	I=140 I=74 C=66 12 months	7	At 12 months: LLL: 21%, p<0.0001 PP: 85.2%, p=0.001 TLR: 8.7%, p=0.001	At 12 months: LLL: 47% PP: 54.4% TLR: 33.6%	Xience V (everolimus) Destiny trial * Ruth improvement of one or more classes at 12 months	?	-	+
Karnabatidis, 2011	Greece	Cohort DES vs. BMS Everolimus BK _n	I=47 C=34	Not stated	At 12 months: PP: ≈ 87%*	At 12 months: PP: ≈ 59%*	* Estimated from figure on lesion basis.	Na	Na	Na
Rastan, 2011	Germany	RCT DES vs. BMS Sirolimus BK _n	I=42 C=33	Not stated*	At 12 months: PP: 75.0% n.s. TLR: 13.8% n.s.	At 12 months: PP: 56.5% TLR: 13.0%	* Regarding subgroup analysis for patients with intermittent claudication at baseline.	-	?	?

* + No problem
? Some problems
- Major problems

Author, year	Country	Study design Comparison Level	Number of patients Follow-up time	With drawals - dropouts	Result		Comments	Directness*	Study limitations*	Precision*
					Intervention	Control				

Siablis, 2007	Greece	Cohort	I=29	I=11	12 months	12 months	* Estimated from figure	Na	Na	Na
		DES vs. BMS Sirolimus	C=29	C=9	PP: 86.4% p<0.001	PP: 40.5%				
		BKn			TLR: 9.1% p=0.02	TLR: 26.2%				

Restenosis (late lumen loss, primary patency, target lesion revascularization) - **Balloon vs balloon below the knee**

Liistro 2013b	Italy	RCT DEB vs. PTA Paclitaxel BKn	132 I=65 C=67 12 months	I=5 C=3	At 12 months: BR: 27.0%, p<0.001 TLR*: 10%, p=0.02	At 12 months: BR: 74.3% TLR: 20%	IN.PACT Amphiron, Medtronic vs. Amphrion Deep, Medtronic. Diabetics BTK *TLR estimated from figure.	+	+	+
Zeller, 2014b	Multicenter, Europe	RCT DEB vs. PTA Paclitaxel BKn	358 I=239 C=119 12 months	I=86 C=36	At 12 months: BR: 41.0% n.s. LLL: 0.605 (SD 0.775) n.s. TLR: 11.9% n.s.	At 12 months: BR: 35.5% LLL: 0.616 (SD 0.781) TLR: 13.5%	IN.PACT DEEP DEB arm, Amphiron, Medtronic vs. Amphrion Deep, Medtronic	?	-	+

* + No problem
? Some problems
- Major problems

Author, year	Country	Study design Comparison Level	Number of patients Follow-up time	With drawals - dropouts	Result		Comments	Directness*	Study limitations *	Precision *
					Intervention	Control				

Rutherford score (symptom severity) - Stent vs stent below the knee										
Bosiers, 2012	Belgium	RCT DES vs. BMS Everolimus BK _n	140 I=74 C=66 12 months	7	ΔRuth*: 60%, p=0.68	ΔRuth*: 56%	Xience V (everolimus) Destiny trial * Ruth improvement of one or more classes at 12 months	?	-	+
Rastan, 2011	Germany	RCT DES vs. BMS Sirolimus BK _n	I=42 C=33	Not stated*	ΔRuth: -3 (-2 to -4) n.s.	ΔRuth: -2 (0 to -3)	* Regarding subgroup analysis for patients with intermittent claudication at baseline.	-	?	?

Rutherford score (symptom severity) - Balloon vs balloon below the knee										
Liistro 2013b	Italy	RCT DEB vs. PTA Paclitaxel BK _n	132 I=65 C=67 12 months	I=5 C=3	Ruth at baseline: 5.2 (SD 0.4) Ruth at 12 months: 0.9 (SD 1.8) ΔRuth: 4.3 p=0.004	Ruth at baseline: 5.1 (SD 0.4) Ruth at 12 months: 2.0 (SD 2.3) ΔRuth: 3.1	IN.PACT Amphiron, Medtronic vs. Amphrion Deep, Medtronic. Diabetics BTK *TLR estimated from figure.	+	+	+

Author, year	Country	Study design	Number of patients n=	With drawals - dropouts	Result		Comments	Directness*	Study limitations *	Precision *
		Comparison			Intervention	Control				
Level										

Mortality - Stent vs stent above the knee										
Dake, 2011a	Multicenter, Multinational	RCT	I=241	I=6*	12 months: 9 (3.7%) deaths n.s.	12 months: 4 (1.7%) deaths	Zilver PTX trial	?	?	?
		DES vs BMS Paclitaxel	C=238	C=2*	Event-free survival 12 months: 90.4 % p=0.004	Event-free survival 12 months: 82.6 %	Causes of death included e.g.: malignancy, pulmonary disease, congestive heart failure			
		AKn					* Calculated from data at randomization and at zero months post procedure			
Mortality - Stent vs stent below the knee										
Rastan, 2011	Germany	RCT	I=82	I=20	12 months: 14 (17.1%) deaths n.s.	12 months: 11 (13.9%) deaths	Causes of death: major cardiac event (n=8), gastrointestinal and pulmonary infection (n=5), lung- cancer (n=1), uncertain cause of death (n=11).	-	?	?
		DES vs BMS Sirolimus	C=79	C=16						
		BKn								

Author, year	Country	Study design Comparison Level	Number of patients n=	With drawals - dropouts	Result		Comments	Directness*	Study limitations*	Precision*
					Intervention	Control				

Mortality - Balloon vs balloon above and below the knee										
Fanelli, 2014b	Italy	RCT DEB vs UCB Paclitaxel AKn & BKn	I=25 C=25	I=0 C=0	12 months: 0 deaths	12 months: 0 deaths	DEBELLUM trial	+	?	?
Scheinert, 2014	Belgium, Germany, USA	RCT DEB vs UCB Paclitaxel AKn & BKn	I=49 C=52	I=4 C=11	12 months: 2 (4.1%) deaths n.s.*	12 months: 4 (7.7%) deaths	Levant I trial Causes of death (reported at 24 months) included: amputation (with subsequent death), cancer, sepsis, cardiac causes. * Calculated from reported data (Fisher's test).	-	?	+
Werk, 2012	Germany	RCT DEB vs UCB Paclitaxel AKn & BKn	I=41 C=44	I=2 C=4	12 months: 0 (0.0%) deaths n.s.*	12 months: 3 (7.5%) deaths	PACIFIER trial Causes of death: cardiovascular failure (n=2), pneumonia and septic chock (n=1),	-	?	+

Project: Drug-eluting vs. conventional endovascular treatment in infrainguinal peripheral arterial disease
Appendix 4-4
Outcome variable: 12 months, amputation, P3

* + No problem
? Some problems
- Major problems

Author, year	Country	Study design Comparison Level	Number of patients n=	With drawals - dropouts	Result		Comments	Directness*	Study limitations *	Precision *
					Intervention	Control				

Amputation - Stent vs stent above the knee										
Dake, 2011a	Multicenter, Multinational	RCT DES vs BMS Paclitaxel AKn	I=241 C=238	I=6* C=2*	Amputation 12 months: 1 (0.5%) n.s.	Amputation 12 months: 0 (0.0%)	Zilver PTX trial Amputation reported as an adverse event. * Numbers calculated from data at randomization and at zero months post procedure	?	?	?
Amputation - Stent vs stent below the knee										
Rastan, 2011	Germany	RCT DES vs BMS Sirolimus BKn	I=82 C=79	I=20 C=16	Amputation 12 months: 2 (3.2%) Minor amputation (n=1), Major amputation (n=1) n.s.*	Amputation 12 months: 4 (6.4%) Minor amputation (n=2), Major amputation (n=2)	Amputation reported as an adverse event. *p=0.6798 (Fisher's test) calculated from reported data.	-	?	?

Project: Drug-eluting vs. conventional endovascular treatment in infrainguinal peripheral arterial disease
Appendix 4-4
Outcome variable: 12 months, amputation, P3

* + No problem
? Some problems
- Major problems

Author, year	Country	Study design Comparison Level	Number of patients n=	With drawals - dropouts	Result		Comments	Directness*	Study limitations *	Precision *
					Intervention	Control				

Amputation - Balloon vs balloon above and below the knee										
Fanelli, 2014b	Italy	RCT DEB vs UCB Paclitaxel AKn & BKn	I=25 C=25	I=0 C=0	Amputation 12 months: 1 (4.0%) n.s.	Amputation 12 months: 3 (12.0%)	DEBELLUM trial	+	?	?
Scheinert, 2014	Belgium, Germany, USA	RCT DEB vs UCB Paclitaxel AKn & BKn	I=49 C=52	I=4 C=11	Amputation 12 months: 1 (2.0%) n.s.*	Amputation 12 months: 0 (0.0%)	Levant I trial *p=0.4851 (Fisher's test) calculated from reported data. .	-	?	+
Werk, 2012	Germany	RCT DEB vs UCB Paclitaxel AKn & BKn	I=41 C=44	I=2 C=4	Amputation 12 months: 0 (0.0%) n.s.	Amputation 12 months: 0 (0.0%)	PACIFIER trial Amputation reported as an adverse event.	-	?	+

Project: Drug-eluting vs. conventional endovascular treatment in infrainguinal peripheral arterial disease

Appendix 4-5

Outcome variable: 12 months, Restenosis and Rutherford score (symptom severity), P3

* + No problem
? Some problems
- Major problems

Author, year	Country	Study design Comparison Level	Number of patients n=	With drawals - dropouts	Result		Comments	Directness*	Study limitations *	Precision *
					Intervention	Control				

Restenosis - Stent vs stent above the knee										
Dake, 2011a	Multicenter, Multinational	RCT DES vs BMS Paclitaxel AKn	I=241 C=238	I=6* C=2*	12 months: PP:83.1% p<0.001 TLR: 9.5% p=0.01	12 months: PP:32.8% TLR: 17.5%	Zilver PTX trial * Numbers calculated from data at randomization and at zero months post procedure	?	?	?
Restenosis - Stent vs stent below the knee										
Rastan, 2011	Germany	RCT DES vs BMS Sirolimus BKn	I=82 C=79	I=20 C=16	12 months: PP: 80.6%, p=0.004 TLR: 9.7% n.s.	12 months: PP: 55.6% TLR: 17.5.	.	-	?	?

Project: Drug-eluting vs. conventional endovascular treatment in infrainguinal peripheral arterial disease
Appendix 4-5
Outcome variable: 12 months, Restenosis and Rutherford score (symptom severity), P3

* + No problem
? Some problems
- Major problems

Author, year	Country	Study design Comparison Level	Number of patients n=	With drawals - dropouts	Result		Comments	Directness*	Study limitations*	Precision*
					Intervention	Control				

Restenosis - Balloon vs balloon above and below the knee										
Fanelli, 2014b	Italy	RCT DEB vs UCB Paclitaxel AKn & BKn	I=25 C=25	I=0 C=0	12 months: LLL: 0.64 (SD 0.9) mm p=0.01 PP:76.0%, p=0.04 TLR: 12.2%, p<0.05	12 months: LLL: 1.81 (SD 0.1) mm PP:39.6% TLR: 35.3%	DEBELLUM trial	+	?	?
Scheinert, 2014	Belgium, Germany, USA	RCT DEB vs UCB Paclitaxel AKn & BKn	I=49 C=52	I=4 C=11	12 months: PP: 67%, n.s.* TLR: 29%, n.s.*	12 months: PP: 55% TLR: 33%	Levant I trial * Calculated from reported data (Fisher's test).	-	?	+
Tepe, 2008	Germany	RCT DEB vs UCB Paclitaxel AKn & BKn	I=48* C= 54*	I=2* C=1*	12 months: TLR: 10% n.s.	12 months: TLR: 48%	THUNDER study * Withdrawals and dropouts at 6 months (not stated at 12 months)	-	-	?
Werk, 2012	Germany	RCT DEB vs UCB Paclitaxel AKn & BKn	I=41 C=44	I=2 C=4	12 months: TLR: 7.7% p=0.02	12 months: TLR: 25%	PACIFIER trial	-	?	+

Project: Drug-eluting vs. conventional endovascular treatment in infrainguinal peripheral arterial disease
Appendix 4-5
Outcome variable: 12 months, Restenosis and Rutherford score (symptom severity), P3

* + No problem
? Some problems
- Major problems

Author, year	Country	Study design Comparison Level	Number of patients n=	With drawals - dropouts	Result		Comments	Directness*	Study limitations *	Precision *
					Intervention	Control				

Rutherford score (symptom severity) - Stent vs stent above the knee										
Dake, 2011a	Multicenter, Multinational	RCT DES vs BMS Paclitaxel AKn	I=241 C=238	I=6* C=2*	ΔRuth improvement from baseline p<0.001, within group	ΔRuth improvement from baseline p<0.001, within group	Zilver PTX trial * Numbers calculated from data at randomization and at zero months post procedure	?	?	?
Rutherford score (symptom severity) - Stent vs stent below the knee										
Rastan, 2011	Germany	RCT DES vs BMS Sirolimus BK _n	I=82 C=79	I=20 C=16	ΔRuth from baseline: -2 (-3 to -1) p=0.004	ΔRuth from baseline: -1 (-2 to 0)	.	-	?	?
Rutherford score (symptom severity)- Balloon vs balloon above and below the knee										
Scheinert, 2014	Belgium, Germany, USA	RCT DEB vs UCB Paclitaxel AK _n & BK _n	I=49 C=52	I=4 C=11	ΔRuth from baseline: 1.6 (SD 1.3) p not stated	ΔRuth from baseline: 2.1 (SD 1.3)	Levant I trial	-	?	+

Author, year	Country	Study design PICO 1-3 Level Drug coating	Number of patients n= Follow-up n=	With drawals - dropouts	Result		Comments
					Intervention	Control	

Balzer, 2010	Germany	Case series, prospective P2 DES Bkn Sirolimus	114	Not stated	Minor complications in 8.8% of the patients* No major complications	NA	DES infrapop critical ischemia Cypher stents (Sirolimus) *dissection (n=3), embolization (n=4), hematoma (n=3)
Bosiers, 2012	Belgium	RCT P2 DES/BM Bkn Everolimus	140 12 months	7	No technical complications or early failures	No technical complications or early failures	
Bosiers, 2013a	Multicentre International	Case-series P3 DES Akn Paclitaxel	787 12 months		Major adverse events 12 months: 21 (2 deaths*, 19 TLRs) Other adverse events: 7 cardiac 2 pulmonary 2 renal 3 wound infections 1 amputation 18 other vascular Stent fracture rate 12 months: 2.1%	NA	* Procedure related deaths

Project: Drug-eluting vs. conventional endovascular treatment in infrainguinal peripheral arterial disease

Appendix 4-6

Outcome variable: Complications

Author, year	Country	Study design PICO 1-3 Level Drug coating	Number of patients n= Follow-up n=	With drawals - dropouts	Result		Comments
					Intervention	Control	

Dake, 2011a (Zilver PTX trial)	Multicentre International	RCT P3 DES/BM Akn Paclitaxel	479 12 months	I=6* C=2*	Major adverse events at 12 months Clinically driven TLRs: 21 (9.5%) p=0.01 Worsening of Δ Ruth* 0 (0.0%) Stent fracture rate 12 months: 0.9%	Major adverse events at 12 months clinically driven TLRs: 39 (17.5%) Worsening of Δ Ruth* 2 (0.9%) Stent fracture rate 12 months: 0.9%	No procedure or device related deaths * Numbers calculated from data at randomization and at zero months post procedure * Worsening of Ruth by two classes to 5 or 6.
Dake, 2011b	USA	Single arm, prospective multicentre P3 DES/BM Akn Paclitaxel	787	9	Major adverse events at 12 months: 4 procedure related deaths 9.5% clinically driven TLR 5 Ruth worsening to class 5 Other adverse events: 3 hematoma 25 cardiac ischemia 3 myocardial infarction* 3 stroke 4 reaction to contrast 2 renal failure [†] 2 pulmonary edema 2 pulmonary embolism Stent fractures at 12 months: 1,5 %	NA	 * Non-Q-wave infarction [†] Requiring dialysis

Project: Drug-eluting vs. conventional endovascular treatment in infrainguinal peripheral arterial disease

Appendix 4-6

Outcome variable: Complications

Author, year	Country	Study design PICO 1-3 Level Drug coating	Number of patients n= Follow-up n=	With drawals - dropouts	Result		Comments
					Intervention	Control	

Dake, 2013a (Zilver PTX trial)	Multicentre International	RCT P3 DES/BM Akn Paclitaxel	24 months		No device related deaths	No device related deaths	Other adverse events reported as all-cause death or TLR, or not detailed per study group. See Dake 2011a and 2011b.
Duda, 2005 (SIROCCO II trial)	Multicentre International	RCT P3 DES/BM Akn Sirolimus	57 6 months	2	Serious adverse events at 6 months: 33 (44.8%) 1 stent thrombosis* 1 Pseudoaneurysm* 2 Revascularization† 2 Death 1 TVR 1 Atypical chest pain 1 Spinal cord stenosis 1 Severe internal bleeding 3 Revascularization‡	Serious adverse events at 6 months: 13(46.4%) 1 stent thrombosis* 1 bleeding* 2 Revascularization† 1 Death 3 TVR 1 Hematoma at puncture site* 1 Hospitalization for CABG 1 Suspected coronary disease 2 Revascularization‡	* Probably procedure related † Contralateral leg before discharge TVR=Target vessel revascularization CABG=Coronary artery bypass grafting ‡ Contralateral leg after discharge

Project: Drug-eluting vs. conventional endovascular treatment in infrainguinal peripheral arterial disease

Appendix 4-6

Outcome variable: Complications

Author, year	Country	Study design PICO 1-3 Level Drug coating	Number of patients n= Follow-up n=	With drawals - dropouts	Result		Comments
					Intervention	Control	

Duda, 2006 (SIROCCO I & II trials)	Multicentre International	RCT P3 DES/BM Akn Sirolimus	93 24 months	21*	Adverse event rates at 24 months: Death 7 (15%) TLR 3 (6%) Total occlusion 0 (0%) No amputations as complication Stent fractures at 24 months 10/25 (40%) n.s.	Adverse event rates at 24 months: Death 2 (4%) TLR 6 (13%) Total occlusion 3 (6%) No amputations as complication Stent fractures at 24 months 8/40 (20%)	* Calculated from 'n' in Table 2.
Falkowski, 2009	Poland	RCT P3 DES/BM Bkn Sirolimus	50 6 months	0	Serious complications: 1 large hematoma of the common femoral artery Minor complications: 2 insignificant hematomas	Serious complications: 1 large hematoma of the common femoral artery Minor complications: 1 insignificant hematoma	
Fanelli, 2012 (DEBELLUM trial)	Italy	RCT P3 DEB/UCB Akn/Bkn Paclitaxel	54* 6 months	4*	Adverse events at 6 months: No deaths 1 major amputation 1 thrombosis at 48 h post procedure	Adverse events at 6 months: No deaths 1 major amputation 2 minor amputations 2 thrombosis at 48 h post procedure	* Discrepancy between report (n=50) and flow chart (n=54).

Project: Drug-eluting vs. conventional endovascular treatment in infrainguinal peripheral arterial disease

Appendix 4-6

Outcome variable: Complications

Author, year	Country	Study design PICO 1-3 Level Drug coating	Number of patients n= Follow-up n=	With drawals - dropouts	Result		Comments
					Intervention	Control	

Fanelli, 2013	Italy	Case-Series P3 DES Akn Paclitaxel	787 12 months	120*	Diabetic: Major adverse events: 29/285 89.7% clinically driven TLR 3 died within 30 days (1 cardiac ischemia 1 MI, 1 renal fail) Non-diabetic: Major adverse events 60/502 95.0% clinically driven TLR 1 died within 30 days (pulmonary embolism)	NA	* Calculated from patients remaining at risk data in Figure 2. DES (ZilverPTX); a comparison between diabetic and non diabetic patients
Fanelli, 2014b (DEBELLUM trial)	Italy	RCT P3 DEB/UCB Akn/Bkn Paclitaxel	50 12 months	0	Major adverse events: 6/25 (24%)	Major adverse events: 15/25 (60%)	
Feiring, 2010 (PaRADISE trial)	USA	Case series, prospective P2 DES Bkn Sirolimus or Paclitaxel	106 3 years	0	Major adverse events: 1 procedure related amputation 6 Major adverse events during the first year, none thereafter 4 contrast nephropathies (0 dialysis)	NA	DES infrapopliteal to prevent amputation

Project: Drug-eluting vs. conventional endovascular treatment in infrainguinal peripheral arterial disease

Appendix 4-6

Outcome variable: Complications

Author, year	Country	Study design PICO 1-3 Level Drug coating	Number of patients n= Follow-up n=	With drawals - dropouts	Result		Comments
					Intervention	Control	

Karnabatidis, 2011	Greece	Cohort (historical controls) P2 DES/BM Bkn Everolimus	87 36 months	Not stated	Major adverse events: 0 within 30 days	Major adverse events: 0 within 30 days	
Lammer, 2011 (STRIDES trial)	MulticenterEurope	Case series, prospective P3 DES Akn/Bkn Everolimus	104 12 months	1*	Major adverse events: 2 major amputations 1 access site hematoma 2 access site pseudoaneurysm 3 non access site bleeding 14 cardiac 11 pulmonary 1 stroke 6 carcinoma 3 gastrointestinal 4 infectious 4 miscellaneous No stent fractures at 12 months	NA	* 99% follow-up at 12 months.

Project: Drug-eluting vs. conventional endovascular treatment in infrainguinal peripheral arterial disease

Appendix 4-6

Outcome variable: Complications

Author, year	Country	Study design PICO 1-3 Level Drug coating	Number of patients n= Follow-up n=	With drawals - dropouts	Result		Comments
					Intervention	Control	

Liistro, 2013b	Italy	RCT P2 DEB/UCB Bkn Paclitaxel	132 12 months	8	Major adverse events at 12 months*: 20 (31%) p=0.02	Major adverse events at 12 months*: 34 (51%)	* Included deaths, major amputation, TLR, or Rutherford class 4 or greater). IN.PACT Amphiron, Medtronic vs Amphrion Deep, Medtronic 1 year follow-up Diabetics BTK
Micari, 2012	Italy Multicenter	Case series Registry P3 DEB Akn/Bkn Paclitaxel	105 12 months	13	Adverse events were not reported explicitly: 2 deaths 'unrelated to procedure or device' TLR at 12 months: 7.6% Device success: 100%	NA	IN.PACT Admiral (paclitaxel)
Micari, 2013	Italy Multicenter	Case series Registry P3 DEB Akn/Bkn Paclitaxel	105 27 months	7	Major adverse events at 27 months: 17 (17.5%) with 2 (2.2%) deaths 1 (1.0%) amputation 14 (14.3%) TLR	NA	IN.PACT Admiral (paclitaxel)

Author, year	Country	Study design PICO 1-3 Level Drug coating	Number of patients n= Follow-up n=	With drawals - dropouts	Result		Comments
					Intervention	Control	

Rastan, 2010	Germany	Case series, prospective P1, P2, P3 DES Bkn Sirolimus	146 12 months	42*	No major complications at 12 months 10 (7%) minor complications at 12 months: 6 (4%) groin hematomas 4 (3%) pseudoaneurysms	NA	Sirolimus eluting stents * 27 died and 15 lost to follow-up
Rastan, 2011	Germany	RCT P1, P2, P3 DES/BM Bkn Sirolimus	161 12 months	36	22 (27.1%) adverse events at 12 months: 14 (17.1%) deaths n.s. 2 (3.3%) amputations* (one major, one minor) n.s.	29 (36.7%) adverse events at 12 months: 11 (13.9%) deaths 3 (6.4%) amputations* (two major, one minor) 3 myocardial infarctions	* Due to insufficiently controlled wound infection.
Rastan, 2012	Germany	RCT P3 DES/BM Bkn Sirolimus	161 1,016 days (mean period)	45	Adverse events In comparison to DES, BMS placement associated with HR: 1.8 (CI95%: 1.1 to 2.9) p=0.02 Adjusted HR*: 1.7 (CI95%: 1.1 to 2.8) p=0.03	See intervention	* Adjusted for renal insufficiency, critical limb ischemia, and body mass index

Project: Drug-eluting vs. conventional endovascular treatment in infrainguinal peripheral arterial disease

Appendix 4-6

Outcome variable: Complications

Author, year	Country	Study design PICO 1-3 Level Drug coating	Number of patients n= Follow-up n=	With drawals - dropouts	Result		Comments
					Intervention	Control	

Scheinert 2014	International Multicenter	RCT P3 DEB/UCB Akn/Bkn Paclitaxel	101 24 months	15	Composite major adverse event rate: 14/49 (39%) n.s. TLR: 15/42 (36%) n.s. Amputation: 1*/42 (2%) n.s. Death: 4/42 (9%) n.s. Thrombosis: 0/42 (0%) n.s.	Composite major adverse event rate: 24/52 (46%) TLR=n=20/41 (49%) Amputation: 0/41 (0%) Death: 5/41 (11) n.s. Thrombosis: 1/42 (2%)	DEB vs. PTA; Rutherford 2-5, femoropopliteal lesions * Died subsequently
Schmidt, 2011	Australia	Case series, prospective P3 DEB Bkn Paclitaxel	104 12 months	18	Periprocedural complications: 1 death (as result of major amputation) 3 femoral pseudoaneurysms 16 additional deaths at 12 months*	NA	 * Causes of death: 7 cardiac disease, 1 cancer (diagnosed before intervention), 8 unrelated.

Project: Drug-eluting vs. conventional endovascular treatment in infrainguinal peripheral arterial disease

Appendix 4-6

Outcome variable: Complications

Author, year	Country	Study design PICO 1-3 Level Drug coating	Number of patients n= Follow-up n=	With drawals - dropouts	Result		Comments
					Intervention	Control	

Siablis, 2005	Greece	Cohort P2 DES/BM Bkn Sirolimus	58 6 months	5	Major adverse events at 6 months: 1 periprocedural myocardial infarction* Minor complications: at 6 months: 5 hematomas n.s. 1 pseudoaneurysm n.s.	Major adverse events at 6 months: None Minor complications: at 6 months: 4 hematomas 1 pseudoaneurysm	Sirolimus DES vs. BMS * Died during 6-month follow-up
Siablis, 2007	Greece	Cohort P2 DES/BM Bkn Sirolimus	58 12 months	7	Not explicitly reported One major amputation due to occlusion of two stented lesions	Not explicitly reported	
Siablis, 2009	Greece	Cohort P2 DES/BM Bkn Sirolimus	103 1 to 36 months	Not stated	Major complications: 1 retroperitoneal hemorrhage 1 periprocedural myocardial infarction*	Major complications: 1 retroperitoneal hemorrhage	* Died during the first 6-months

Outcome variable: Complications

[illegible]

Tepe, 2008 (THUNDER study)	Germany Multicenter	RCT P3 DEB/UCB Akn/Bkn Paclitaxel	102 24 months	3	Serious adverse events during intervention 3/48 (6%): 1 toe amputation 1 abrupt total occlusion 1 cerebellar infarction n.s. Serious adverse events 2 weeks to 6 months after intervention: 22/48 (46%) n.s.	Serious adverse events during intervention 2/54 (4%): 1 left ventricular failure 1 peripheral-artery occlusion Serious adverse events 2 weeks to 6 months after intervention: 28/54 (52%)	
Werk, 2008	Germany	RCT P3 DEB/UCB Akn/Bkn Paclitaxel	87 18 months	60*	Adverse events (during and shortly after the intervention): 1 peripheral embolism 1 skin rash Serious adverse events: 22 (48.9%)† 1 unrelated death (multiple organ failure)	Adverse events (during and shortly after the intervention): 1 allegoid reaction 1 temp. s-creatinine increase Serious adverse events: 22 (52.4%)† 1 bilateral below-knee amputation	* According to flow diagram † Most due to vascular disorders including TLR.
Werk, 2012 (PACIFIER trial)	Germany	RCT P3 DEB/UCB Akn/Bkn Paclitaxel	85 12 months	5	Major adverse events* at 12 months: 3/42 (7.1%) p=0.003	Major adverse events* at 12 months: 15/43 (34.9%)	* Death, amputation, TLR

Project: Drug-eluting vs. conventional endovascular treatment in infrainguinal peripheral arterial disease

Appendix 4-6

Outcome variable: Complications

Author, year	Country	Study design PICO 1-3 Level Drug coating	Number of patients n= Follow-up n=	With drawals - dropouts	Result		Comments
					Intervention	Control	
Werner, 2012	Germany	Case-series, Retrospective P2 DES Bkn Sirolimus	158 31 months	14	Major complications: 2 (1%) transfusion demanding bleeding Minor complications 11 (7%): 5 non-transfusion demanding bleeding 3 pseudoaneurysms 3 contrast-nephropathy 27 (18.8%) deaths 4 (2.8%) amputations	NA	Infrapopliteal sirolimus stenting Cypher select
Zeller 2013	Germany	Case-series, Retrospective P3 DEB Akn Paclitaxel	108 2 years	Subgroup analysis	Major adverse events: 40 TLR No deaths No amputations	NA	Case-series including the patients with in-stent restenosis in the Zilver-PTX study

Project: Drug-eluting vs. conventional endovascular treatment in infrainguinal peripheral arterial disease

Appendix 4-6

Outcome variable: Complications

Author, year	Country	Study design PICO 1-3 Level Drug coating	Number of patients n= Follow-up n=	With drawals - dropouts	Result		Comments
					Intervention	Control	

Zeller, 2014b (IN.PACT DEEP trial)	Germany	RCT P2 DEB/UCB Bkn Paclitaxel	358 12 months	122	<p>Adverse events:</p> <p>12 months mortality: 23/239 (9.6%) n.s.</p> <p>Consort flowchart data, deaths until 12 months *: 44/239 (18.4%) n.s.[†]</p> <p>Amputations, 12 months: 20/227 (8.8%) p=0.080</p> <p>Consort flowchart data, major amputations until 12 months *: 37/239 (15.4%) p=0.0181[†]</p>	<p>Adverse events:</p> <p>12 months mortality: 9/119 (7.6%)</p> <p>Consort flowchart data, deaths until 12 months *: 18/119 (15.1%)</p> <p>Amputations, 12 months: 4/111 (3.6%)</p> <p>Consort flowchart data, major amputations until 12 months *: 8/119 (6.7%)</p>	<p>IN.PACT DEEP DEB arm, Amphiron, Medtronic vs Amphrion Deep, Medtronic</p> <p>* Discrepancy in data: more deaths reported in the Consort flowchart than for all-cause mortality at 12 months follow-up</p> <p>[†] Calculated from reported data (Fisher's test)</p>
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Project: Drug-eluting vs. conventional endovascular treatment in infrainguinal peripheral arterial disease

Appendix 4-6

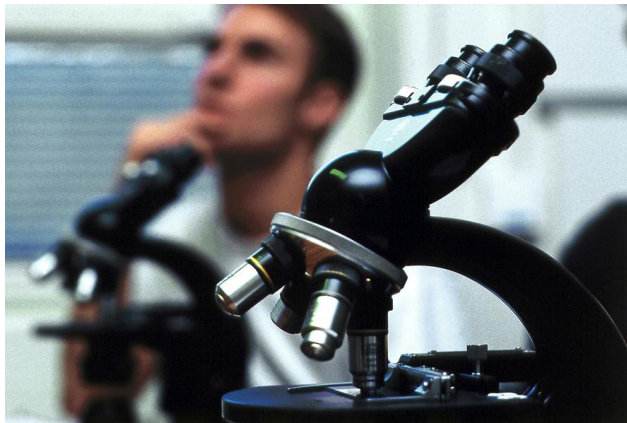
Outcome variable: Complications

Author, year	Country	Study design PICO 1-3 Level Drug coating	Number of patients n= Follow-up n=	With drawals - dropouts	Result		Comments
					Intervention	Control	

Zeller 2014a	Germany	Case-series P2 DES DEB BK _n Paclitaxel	228 12 months	40	Major adverse events at 12 months: Deaths DEB 4/109 (3.7%) Deaths DES 2/79 (2.5%) TLR DEB 21 (19.3%) TLR DES 17 (21.5%) No procedure related deaths in either cohort	NA	Two cohorts DCB and DEB
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Region Västra Götaland, HTA-centrum

Health Technology Assessment
Regional activity-based HTA



HTA

Health technology assessment (HTA) is the systematic evaluation of properties, effects, and/or impacts of health care technologies, i.e. interventions that may be used to promote health, to prevent, diagnose or treat disease or for rehabilitation or long-term care. It may address the direct, intended consequences of technologies as well as their indirect, unintended consequences. Its main purpose is to inform technology-related policymaking in health care.

To evaluate the quality of evidence the Centre of Health Technology Assessment in Region Västra Götaland is currently using the GRADE system, which has been developed by a widely representative group of international guideline developers. According to GRADE the level of evidence is graded in four categories:

High quality of evidence	= (GRADE ⊕⊕⊕⊕)
Moderate quality of evidence	= (GRADE ⊕⊕⊕⊖)
Low quality of evidence	= (GRADE ⊕⊕⊖⊖)
Very low quality of evidence	= (GRADE ⊕⊖⊖⊖)

In GRADE there is also a system to rate the strength of recommendation of a technology as either “strong” or “weak”. This is presently not used by the Centre of Health Technology Assessment in Region Västra Götaland. However, the assessments still offer some guidance to decision makers in the health care system. If the level of evidence of a positive effect of a technology is of high or moderate quality it most probably qualifies to be used in routine medical care. If the level of evidence is of low quality the use of the technology may be motivated provided there is an acceptable balance between benefits and risks, cost-effectiveness and ethical considerations. Promising technologies, but a very low quality of evidence, motivate further research but should not be used in everyday routine clinical work.

Christina Bergh, Professor, MD.
Head of HTA-centrum

