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DO DRUG ELUTING DEVICES HAVE A BETTER OUTCOME IN LOWER LIMB ARTERIAL DISEASE?

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Do Drug Eluting Devices Have a Better Outcome in Lower Limb Arterial Disease?

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RESUMO

Introdução: O número de doentes com doença arterial periférica do membro inferior é muito alto, tal como os custos associados em saúde/qualidade de vida/produtividade/económicos. A revascularização endovascular é cada vez mais utilizada e há falta de dados comparativos entre técnicas, especialmente a longo prazo.

Objetivos: A presente revisão da literatura procura analisar/comparar os resultados sobre angioplastia simples, angioplastia com balão com fármacos, *stent* primário e *stent* com fármacos, e consequentemente discutir os mesmos.

Metodologia: A pesquisa foi realizada recorrendo à "PubMed" com os termos MeSH: "Peripheral Arterial Disease", "Angioplasty", "Drug-Eluting Stent", "Stent", "Drug-Eluting Balloon", "Balloon Angioplasty" e "Lower Limb", selecionando artigos de investigação de janeiro 2014 a dezembro 2019. Critérios de inclusão: população-alvo com doença arterial periférica, intervenções aos membros inferiores, intervenção primária e restenose. Critérios de exclusão: artigos não em inglês, título e *abstract* não correspondam ao conteúdo. No total foram incluídos 45 artigos.

Resultados: Apenas 12 artigos apresentaram follow-up superior a 12 meses, tendo a maioria resultados aos dois anos. O balão com fármacos mostrou segurança/eficácia nas lesões femoropoplíteas/infrapoplíteas/de novo/restenóticas (sem *stent*/restenose em *stent* femoropoplítea). O balão com fármacos foi superior à angioplastia simples nas lesões femoropoplíteas, mas no território infrapoplíteo apenas um estudo demonstrou superioridade e outro apresentou uma tendência para maior taxa de amputação major. O *stent* primário mostrou segurança/eficácia ao nível femoropoplíteo. Em lesões femoropoplíteas pequenas o *stent* foi comparável à angioplastia simples, mas superior em lesões longas/restenóticas em *stent*. O *stent* não foi melhor que angioplastia simples nas lesões infrapoplíteas, mostrando-se até inferior na patência/ausência de restenose da lesão alvo. O *stent* com fármacos demonstrou segurança/eficácia em ambos os territórios, embora fatores como lesões longas/restenose em *stent*/diabetes mellitus/calcificação severa e outros possam diminuir a sua eficácia. O *stent* com fármacos foi superior à angioplastia simples em ambos os territórios, mas na restenose em *stent* femoropoplítea apenas foi superior nas lesões oclusivas. O *stent* com fármacos foi superior ao *stent* primário no território femoropoplíteo. O balão com fármacos apresentou uma restenose binária superior ao *stent* com fármacos nas lesões infrapoplíteas.

Conclusão: Apesar das limitações/diferenças dos estudos, os resultados foram consistentes entre eles. São necessários mais estudos, principalmente comparativos entre técnicas/dispositivos, com amostras maiores e períodos de follow-up mais longos.

Bibliografia: Como fontes de referência incluiram-se Guidelines inerentes ao tema (ESC/ESVS/AHA/ACC/SVS), o estudo “Bypass versus angioplasty in severe ischaemia of the leg (BASIL): multicentre, randomized controlled trial” e o livro “Rutherford's Vascular Surgery and Endovascular Therapy”.

Palavras-chave: Doença arterial periférica, membro inferior, angioplastia, balão com fármacos, stent, stent com fármacos.

ABSTRACT

Introduction: The number of patients with lower extremity arterial disease (LEAD) is very high, as are the associated health/quality of life/productivity/economic costs. Endovascular revascularization is increasingly being used and there is lack of comparative data between techniques, especially long-term ones.

Objectives: The present literature review seeks to analyse and compare the results of plain old balloon angioplasty (POBA), drug-eluting balloon (DEB), primary stent, and drug-eluting stent (DES) in LEAD, and consequently discuss results.

Methodology: Research was carried out through "PubMed" with the following MeSH terms: "Peripheral Arterial Disease", "Angioplasty", "Drug-Eluting Stent", "Stent", "Drug-Eluting Balloon", "Balloon Angioplasty", and "Lower Limb", with selection of research articles from january 2014 to december 2019. Inclusion criteria: target population with peripheral arterial disease, lower limb interventions, primary intervention and restenosis. Exclusion criteria: articles not written in English, title and abstract do not match the content. In total, 45 articles were included.

Results: Only 12 articles had follow-up of more than 12 months, and most of these reported results after two years. DEB showed safety/effectiveness in femoropopliteal/infrapopliteal/*de novo*/restenotic (nonstented and femoropopliteal in-stent restenosis (ISR)) lesions. DEB was superior to POBA in femoropopliteal lesions, but in infrapopliteal territory only one study showed superiority and one had a trend towards higher rate of major amputation. Stent demonstrated safety/effectiveness at femoropopliteal level. In small femoropopliteal lesions the stent was comparable to POBA, but was superior in longer lesions/ISR. Stent was not better than POBA in infrapopliteal lesions, even showing inferiority in patency and freedom from target lesion revascularization. DES has demonstrated safety/effectiveness in both arterial territories, although factors such as longer lesions, ISR, diabetes mellitus, severe calcification, and others can decrease its effectiveness. DES was superior to POBA in both territories, but in femoropopliteal ISR DES was superior only in occlusive lesions. DES was superior to stent in femoropopliteal territory. DEB presented a binary restenosis superior to DES in infrapopliteal lesions.

Conclusion: Despite the limitations/differences of the published studies, the results were consistent between them. Further studies are needed, mainly comparative ones between techniques/devices, with larger samples and for longer follow-up periods.

Bibliography: As reference information sources were included Guidelines inherent to the theme (from ESC, ESVS, AHA/ACC and SVS), the study “Bypass versus angioplasty in severe ischaemia of the leg (BASIL): multicentre, randomized controlled trial” and the book “Rutherford's Vascular Surgery and Endovascular Therapy”.

Keywords: Peripheral arterial disease, lower limb, angioplasty, drug-eluting balloon, stent, drug-eluting stent.

LIST OF ABBREVIATIONS

ABI – ankle-brachial índex
BMS – bare-metal stent
BR – binary restenosis
BS – baseline stenosis
BTK – below-the-knee
C – calcification
CD-TLR – clinically-driven TLR
CLI – critical limb ischaemia
CLTI – chronic limb-threatening ischaemia
DEB – drug-eluting balloon
DES – drug-eluting stent
DN – de novo
ESC – European Society of Cardiology
ESVS – European Society for Vascular Surgery
FP – femoropopliteal
GLASS – global anatomic staging system
HR – hazard ratio
IP – infrapopliteal
ISO – in-stent occlusion
ISR – in-stent restenosis
ITT – intention-to-treat
LEAD – lower extremity arterial disease
LL – long lesions
LLL – late lumen loss
m – months
MAE – major adverse events
MALE – major adverse limb event
MeSH – medical subject heading
MITT – modified-intention-to-treat
MLL – mean lesion length
O – occlusion
P – popliteal artery
PAD – peripheral arterial disease
POBA – plain old balloon angioplasty
PP – primary patency
QALY – quality-adjusted life year
RC – Rutherford classification
RE – restenotic
SFA – superficial femoral artery
SL – short lesions
SP – secondary patency
TASC – Trans-Atlantic Inter-Society Consensus
TBI – toe-brachial index
TER – target extremity revascularization
TLL – total lesion length
TLR – target lesion revascularization
TVR – target vessel revascularization
WIfI – wounds, ischaemia, and foot infection
y – years

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INTRODUCTION

Peripheral arterial disease (PAD), peripheral arterial occlusive disease or lower extremity arterial disease (LEAD) can be defined as a chronic atherosclerotic occlusive disease of the lower limb arteries.[1] Nowadays it is a major health issue, affecting about 202 millions of people all across the world, of which almost 40 millions live in Europe. This number is increasing due to the growth/ageing of the population along with incidence of risk factors, such as diabetes, smoking, hypertension and dyslipidemia.[1, 2]

Its etiology lies in atherosclerosis. Atherogenesis displays an evolution which occurs during several years, generally decades, starting with the build-up of low-density lipoprotein (LDL) in intima fostered by hypercholesterolemia, producing a local inflamatory response with leucocyte migration to intima**,** where there are lipids fagocythosis and build-up of fatty streak (this commonly precedes the more advanced build-up of atherosclerotic plaque, but doesn't necessarily progress to a more serious lesion). In advanced injuries plaque disruptions may occur, which allows the clot formation and artery occlusion. As far as plaque progresses there is calcium build-up.[3]

Atherosclerotic lesions commonly occur in areas of artery bifurcation, as they are places prone to hydrodynamic changes, such as greater turbulence, shear stress and tunica intima injury.[3]

Due to the systemic nature of atherosclerosis, patients suffering from PAD have a greater cardiovascular morbimortality. As a matter of fact in 2010, the mortality associated to arterial disease of the lower limbs was of 3.5 per 100000 individuals in Western Europe, the majority related to coronary artery disease and/or stroke.[2] The major amputation (amputation above the ankle) has an yearly incidence of 120-500 per million.[2, 4] In 2010 the estimated years of life lost were 31.7 years per 100000 inhabitants in Western Europe. Due to its implication in terms of health/quality of life/productivity/economic costs, prevention plays an essential role.[1, 2]

PAD shares some risk factors with other pathologies associated to atherosclerosis, such as coronary artery disease and cerebrovascular disease. Risk factors are the following: age (the main risk factor), smoking, diabetes mellitus, hypertension (less considerable than the two previous ones), dyslipidemia, male gender and black race with greater prevalence of more advanced disease, and the presence of atherosclerotic disease in other regions.[1]

Arterial segments are divided in aortoiliac (30% of symptomatic patients), femoropopliteal (80-90% of patients) and infrapopliteal (40-50% of patients). There is a relationship between the disease pattern and the risk factors, namely in case of smokers who have a greater frequence of aortoiliac and femoropopliteal disease, while diabetic patients present more typically a distal involvement, that is, at femoropopliteal and infrapopliteal levels, the latter being usually extensive.[1, 3]

PAD can be classified according to the Fontaine stages or the degrees/categories of Rutherford, presented in Table I. The term minor tissue loss present in Table I represents a nonhealing ulcer/focal gangrene with diffuse pedal ischaemia; the major tissue loss represents an extension above the transmetatarsal level/non-recoverable functional foot.[5]

Table I - Clinical stages of lower extremity artery disease. Source:[2]

Fontaine Classification				**Rutherford Classification**		
Stage	**Symptoms**			**Grade**	**Category**	**Symptoms**
I	Asymptomatic		⟺	**0**	**0**	Asymptomatic
II	**IIa**	Non-disabling intermitente claudication	⟺	**I**	**1**	Mild claudication
				I	**2**	Moderate claudication
	IIb	Disabling intermitente claudication	⟺	**I**	**3**	Severe claudication
III	Ischaemic rest pain		⟺	**II**	**4**	Ischaemic rest pain
IV	Ulceration or gangrene		⟺	**III**	**5**	Minor tissue loss
				III	**6**	Major tissue loss

The majority of the patients are asymptomatic.[1, 2] When symptomatic, patients may show atypical symptoms, which is often observed.[6] Intermittent claudication is characterized by pain/discomfort/numbness/fatigue from vascular origin reproducible in a specific muscle group induced by physical exercise, which relieves with rest (in about 10 minutes).[3, 5, 7] Symptoms location indicates the presence of arterial disease proximal to that level, with calf pain being the most common presentation. The severity of claudication can be evaluated according to the distance in meters that the patient undergoes until the symptoms develop.[1]

Critical limb ischaemia (CLI) or chronic limb-threatening ischaemia (CLTI) represents an advanced stage of the disease, characterized by ischaemic pain at rest (typically a pain that gets worse with decubitus and that improves with hanging of the foot), ulceration or gangrena/necrosis. It includes the stages III and IV from Fontaine and 4-6 from Rutherford.[1, 2, 4]

With regard to diagnosis, the initial evaluation should include anamnesis and objective examination and must be performed along with ankle-brachial index (ABI), the first recommended exam.[5] When ABI values at rest are borderline/normal but there are suggestive symptoms, it is recommended the performance of exercise ABI.[2, 5] Other complementary exams can still be carried out, such as toe-brachial index (TBI), toe systolic pressure, and transcutaneous oxygen pressure or skin perfusion pressure.[2, 5] The latter useful in the evaluation of the severity of ischaemia, when selecting the amputation level and in the assessment of the likelihood of ischaemic ulcers healing.[8]

TBI, transcutaneous oxygen pressure or skin perfusion pressure can be used, in patients with non-healing wounds or gangrene, for CLI diagnosis when ABI is normal/borderline or to evaluate the local perfusion when abnormal ABI or with noncompressible arteries.[5] Image studies are also recommended to evaluate the anatomic location and stenosis severity, such as duplex ultrasound (the first image exam to be carried out), computed tomography angiography, magnetic ressonance angiography, or digital subtraction angiography (gold standard image exam).[2, 3, 5, 7]

All patients need medical treatment for the cardiovascular disease, regardless of the presence/severity of symptoms.[1] This includes risk factors modification: healthy diet, weight loss, regular exercise and smoking cessation; and a pharmacological component with antihypertensive drugs, with angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers the first line procedures, which should be administered in patients with PAD and hypertension, with a decrease in blood pressure values to <140/90 mmHg being recommended, excepting diabetic patients for whom a diastolic pressure of 85 mmHg or less is considered safe[2]; lipid lowering drugs, being recommended the administration of moderate to high intensity statins to all patients with PAD, namely rosuvastatin (20-40mg) and atorvastatin (40-80mg)[2, 4], searching for a decrease in LDL to <70 mg/dL or a decrease of at least 50% if baseline values are 70-135 mg/dL; and antithrombotic drugs, although antiplatelet therapy is not indicated as a routine procedure in patients with isolated and asymptomatic LEAD. There must still be a strict glycaemic control in diabetic patients.[2]

Other therapeutic component is the revascularization that can be done through conventional/open surgery (open endarterectomy, bypass), endovascular intervention or both.[1, 2] Considering the great development of endovascular intervention, this has taken an increasingly greater role.[2] The main endovascular technique is plain old balloon angioplasty (POBA) or percutaneous transluminal angioplasty.[1, 2] Restenosis occurs often in this case, with distally growing rates, due to barotrauma with consequent inflammatory state, hyperplasia of intima, celular proliferation and constrictive vascular remodeling.[9, 10] The risk of restenosis is also higher according to the greater extent of the lesion, calcification density, if runoff is bad, in diabetic patients and in patients with chronic kidney disease.[2] With the aim of mechanically counteract restenosis, stent was introduced[2], which may be associated with fracture and restenosis, the latter being generally harder to treat than restenosis after POBA, which may limit the future therapeutic options.[11, 12] In order to counteract these results drug-eluting balloon/stent appeared, namely with paclitaxel (an anti-proliferative drug).[11, 13] Drug-eluting balloon (DEB) allows the artery to keep its mechanical properties, prevents restenosis produced by barotrauma, increases patency, decreases the need of a stent and the corresponding fractures, and doesn't present any anatomical limitations (unlike the stent).[11, 14] These drug devices when compared with conventional strategies up to 24 months of follow-up present improvements, but in a long-term, in terms of patency and safety, it is not clear

yet.[1, 2] More recently, studies have shown a greater mortality associated to drug-eluting baloon/stent (such as paclitaxel[15]). There are other endovascular techniques such as atherectomy, thromboembolectomy, thrombolysis and devices to overcome chronic total occlusions.[1, 2]

Considering its magnitude, this revealed itself as a relevant area to explore. The European Society for Vascular Surgery (ESVS) identifies gaps in evidence, namely on amputation-free survival, quality of life, wound healing and patency in studies based on POBA, stents, and drug-eluting stent/baloon.

These data motivated the development of the current thesis “Do drug eluting devices have a better outcome in lower limb arterial disease?”, a literature review article with the following objectives: to review and compare the results of plain balloon angioplasty, DEB, primary stent, and drug-eluting stent (DES) in LEAD, and consequently discuss results.

METHODOLOGY

The current work consists of a literature review article. For this review a scientific literature research was conducted through the PubMed database with the following terms from Medical Subject Heading (MeSH) from Index Medicus as keywords: “Peripheral Arterial Disease”, “Angioplasty”, “Drug-Eluting Stent”, “Stent”, “Drug-Eluting Balloon”, “Balloon Angioplasty” and “Lower Limb”. The research was limited to articles published from 1 january 2014 to 27 december 2019. Referenced articles from the research considered as relevant were also included.

As inclusion criteria observational analytical articles and experimental studies (specially randomized clinical trials) were considered, which target population has peripheral arterial disease, lower limbs interventions, primary intervention and restenosis. As exclusion criteria were considered systematic review articles, along with meta-analysis and clinical cases, articles which are not written in English language, articles which title and abstract don’t match the content, and also the ones that don’t address plain balloon angioplasty techniques and/or angioplasty with drug-eluting balloon and/or primary stent and/or drug-eluting stent.

The articles were initially selected based on the title and abstract and, subsequently, a more detailed analysis of these allowed to exclude those that did not meet the established criteria. In total, 45 articles were included (Figure 1).

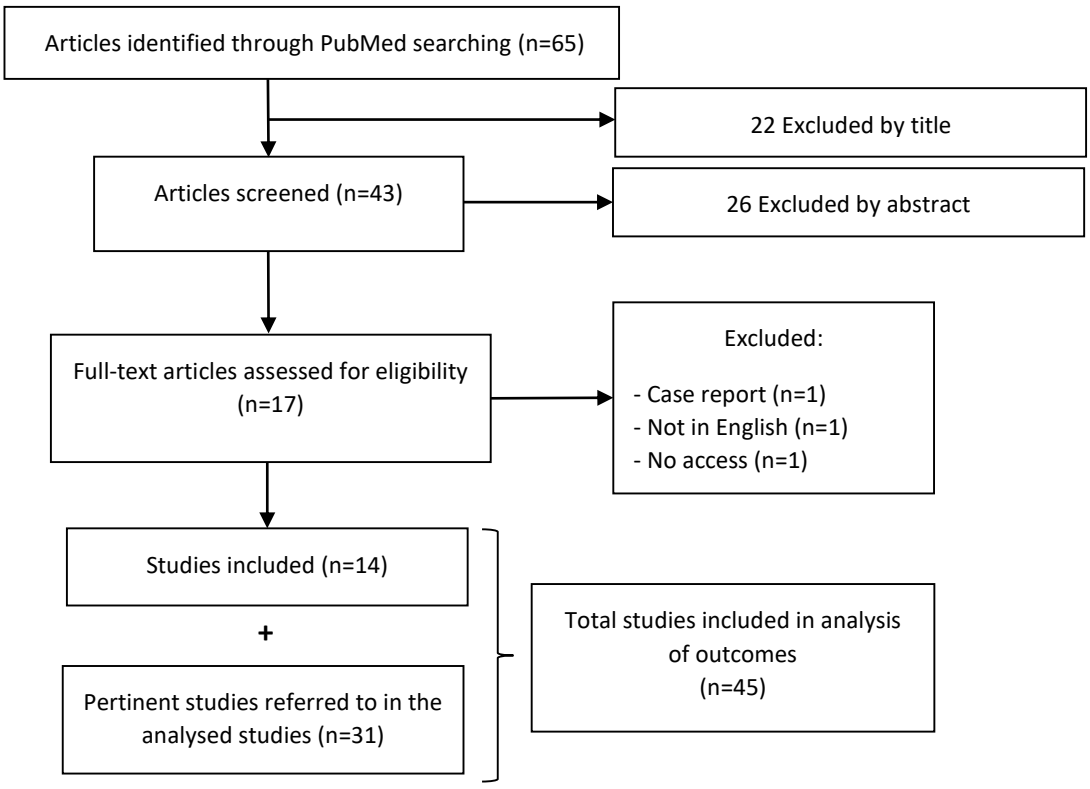

Figure 1 - Research diagram.

As reference information sources were included “Editor’s Choice - 2017 ESC Guidelines on the Diagnosis and Treatment of Peripheral Arterial Diseases, in collaboration with the European Society for Vascular Surgery (ESVS)”, “2016 AHA/ACC Guideline on the Management of Patients With Lower Extremity Peripheral Artery Disease”, “Society for Vascular Surgery practice guidelines for atherosclerotic occlusive disease of the lower extremities: Management of asymptomatic disease and claudication”, “Global Vascular Guidelines on the Management of Chronic Limb-Threatening Ischemia”, “Bypass versus angioplasty in severe ischaemia of the leg (BASIL): multicentre, randomised controlled trial”, and “Rutherford’s Vascular Surgery and Endovascular Therapy”.

Taking into account the possible complications, it’s necessary to define outcomes which allow to evaluate if the treatment was successful and make comparisons between techniques, therefore the following were selected for the present work: primary patency (maintenance of unobstructed vessel) and secondary patency (after reintervention); major adverse events (MAE); major adverse limb event (MALE) (amputation, transtibial or above, or any vascular reintervention (thrombectomy, thrombolysis, plain balloon angioplasty, stenting, or surgery)); restenosis; reocclusion; late lumen loss (LLL); target lesion revascularization (TLR)/freedom from TLR; target extremity revascularization (TER)/freedom from TER; survival (freedom from death); mortality; amputation-free survival (time to major/above the ankle amputation of the index limb); amputation; reintervention; stent fractures/freedom from fractures; thrombosis/freedom from thrombosis; ABI; wound healing; clinical improvement; mean walking distance; quality of life; quality-adjusted life year (QALY).[1, 4, 7, 16]

RESULTS

Plain Old Balloon Angioplasty (POBA)

One of the most relevant performed studies was "Bypass versus angioplasty in severe ischaemia of the leg (BASIL): multicentre, randomised controlled trial", which compares an initial endovascular approach (baloon angioplasty) directly with conventional surgery (bypass) in severe/critical ischaemia of the limb due to infrainguinal disease.[4] In this study 452 patients from 27 hospitals from United Kingdom participated and it took place during 5,5 years (between 1999 and 2004). The follow-up finished when patients reached the endpoint: amputation above the ankle of the affected limb or death. After six months there were no statistically significant differences between both techiques in terms of amputation-free survival or quality of life, but the economic costs were superior with the bypass. In a short-term period the surgery with bypass presented a higher morbidity rate and economical costs, but a lower reintervention rate. In the long-term analysis (two years after the initial intervention) the surgery seemed to be associated to a lower risk of amputation/death.[17]

To confirm these data, the patients were monitored for more 2,5 years, concluding that the patients initiallly undergoing a bypass presented a superior overall survival and a tendency for an amputation-free survival also superior when compared to angioplasty.[18] Consequently, the advantage of opting for bypass as an initial intervention becomes apparent after the first two years after the intervention.[1]

Therefore, it's suggested that patients with a life expectancy of at least two years undergo a bypass as initial intervention, while patients with an inferior life expectancy, and possibly in those without available vein for bypass, undergo a balloon angioplasty first. In patients with short survival it's more likely that they present a greater morbimortality associated to the surgery, with angioplasty being significantly safer than surgery in the short-term.[18]

Drug-Eluting Balloon (DEB)

From the research carried out, six studies address the safety and effectiveness of DEB. From these studies, five refer to femoropopliteal lesions and one refers to both femoropopliteal and infrapopliteal lesions. Of the five articles concerning femoropopliteal lesions, four are single-arm studies, two of them are specific for situations related to in-stent restenosis (ISR). The results of studies are displayed in Table II, and these are more detailed in Table XII from Appendices.

Table II - Drug-eluting balloon studies.

Author (Year), Trial, Study Design	Type	Arterial Territory	Lesions	N. Patients	Outcomes										
					PP	LLL (mm)	TLR	Freedom from TLR	Freedom from TER	Clinical or RC Improvement	ABI change	MAE	Amputation Rate	Survival Rate	Mortality Rate
Schroeder et al. (2015), ILLUMENATE[19] Prospective, single-arm, multicentre study	DEB (StellarexTM DEB, paclitaxel – 2 µg/mm^2)	FP	MLL 7.2 cm. BS 75.1%. C 62.1%. O 12.1%	50	12/24 m: 89.5%/ 80.3%	6 m: 0.54	CD-TLR; 12/24 m: 12%/14.9%.	Freedom from CD-TLR; 12/24 m: 90%/85.8%		Mean walking distance 6/12/24 m: 185±182 m/139±95 m/190±87 m (p≤0.01)	Baseline/6 m: 0.71±0.13/ 0.91±0.16 (p<0.001)	6 m: 4%	0%		
Stabile et al. (2016)[20] Prospective, single-arm, multicenter study	DEB (LEGFLOW®, Cardionaovum DEB, paclitaxel – 3 µg/mm^2)	FP	MLL: DN 95.1 ± 57.0 mm; restenosis 96.1 ± 32.1 mm; ISR 114.3 ± 24.1 mm	123			No TLR was observed in patients with ISR. Lesion length did not affect TLR rates but the presence of diabetes did.	6 m: 88.6% Patients with DN lesions/ restenosis: 88.1%/80.7%							
Bague et al. (2017), PLAISIR trial[21] Prospective, single-arm, multicenter, cohort study	DEB (paclitaxel – 3.5 µg/mm^2)	FP	FP ISR	53	12/18 m: 83.7%/ 78.1%		TLR was required in 5 patients	12/18 m: both 90.2 ± 4.2%	12/18 m: 87.7 ± 4.7%/ 78.6 ± 6.1%	12/18 m: 77%/67% asymptomatic; primary sustained clinical improvement 78.6±5.7%/ 63.2±6.7%; secondary sustained clinical improvement 92.0±3.8%/ 79.2±5.9%	Baseline/12/ 18 m: 0.54 ± 0.37/0.96 ± 0.54/0.92 ± 0.23 (p=0.01)		1 minor and 1 major amputation	12 m: 96 ± 2.7%	18 m: 4%
Virga et al. (2014)[22] Prospective, single-arm study	DEB (IN.PACT balloon, paclitaxel – 3.5 µg/mm^2)	FP	FP ISR. MLL 82.9 ± 78.9 mm	39	24 m: 70.3%			24 m: 78.4%		Baseline/24 m: RC; 2.9±0.7/ 0.6±0.7; p<0.05	Baseline/24 m: 0.77±0.09/ 0.94±0.09; p<0.05				12/24 m: 2.56%/ 5.12%
Herten et al. (2015)[10] Prospective study	Efficacy of paclitaxel DEBs (IN.PACT Admiral and Freeway, paclitaxel – 3 µg/mm^2) in RE (stented and nonstented) vs DN lesions	FP	MLL: RE 99±76 mm; DN 77±68 mm; p=0.05. Total O: RE 25%; DN 27%; p0.935	61 RE vs 39 DN	6/12 m: RE 81%/68%; DN 93%/85%; p=0.093/ p=0.021		6/12 m: RE 19%/32%; DN 7%/15%			Improvement in RC ≥ 1; 12 m: RE 78%; DN 83% (p=0.568)	Baseline/12 m: RE 0.57 ± 0.29/ 0.85 ± 0.20 (p<0.001); DN 0.68 ± 0.25/ 0.90 ± 0.12 (p<0.001)		0%	No difference (p=0.965)	
Brodmann et al. (2017)[11] Prospective, single-arm, observational study	DEB (Passeo-18 Lux, paclitaxel – 3 µg/mm^2)	SFA 56.4%; P 23%; IP 13.2%	MLL 75.1 ± 69.4 mm; O 20%; C 76.3%	203	12 m: 85.4%		6/12 m: CD-TLR; 8%/16%	Freedom from CD-TLR; 12 months: 93.2%		Improvement in RC ≥ 1; 12 months: 82.7%. 75.4% improved on the Pain Scale	ABI at 12 month changed 0.17±0.26 since baseline (p<0.001)	6/12 m: 5.5%/ 10.1%	12 m: 4.2%		12 m: 6.5%

Abbreviations: ABI, ankle-braquial index; BS, baseline stenosis; C calcification; CD-TLR, clinically-driven TLR; DEB, drug-eluting balloon; DN, *de novo*; FP, femoropopliteal; IP, infrapopliteal; ISR, in-stent restenosis; LLL, late lumen loss; m, months; MAE, major adverse events; MLL, mean lesion length; O, occlusion; P, popliteal artery; PP, primary patency; RC, Rutherford classification; RE, restenotic; SFA, superficial femoral artery; TER, target extremity revascularization; TLR, target lesion revascularization.

Through the data presented above, in a general way, primary patency presents high values (68%-93%), with a decrease throughout the follow-up, with the lowest values referring to ISR/restenotic lesions. TLR values are low (7%-32%), but they increase throughout the follow-up, displaying higher values in restenotic lesions. On their turn, the freedom from TLR values are good (78.4%-93.2%), with a reduction taking place throughout the follow-up. In study carried out by Stabile et al. (2016)[20] restenotic lesions display lower values regarding *de novo* lesions (80.7% vs 88.1%).

As far as clinical or RC improvement are concerned, all studies that evaluated these showed an improvement. ABI improved significantly in all studies, however in Herten et al. (2015)[10] study the results are significantly better for DN lesions than for RE lesions, but it must be taken into account that RE group included patients with lower baseline ABI and longer lesions, so they could display a higher risk.

The MAE percentage in the studies was low (4%-10.1%), the same occuring for the amputation rate (maximum of 4.2%) and mortality rate (2.56%-5.12%).

This way, all presented studies, despite having different characteristics, both morphology and lesion characteristics, as far as clinic is concerned showed safety and effectiveness in the use of DEB as a therapeutic option in femoropopliteal and infrapopliteal lesions, both in *de novo* lesions as in restenosis (nonstented and femoropopliteal ISR) for a maximum follow-up period of two years.

Plain Old Balloon Angioplasty (POBA) Versus Drug-Eluting Balloon (DEB)

17 Studies make a comparison between an approach with POBA or with DEB. 13 Only include femopopliteal territory, two of these being specific for ISR situations. One study includes both the femoropopliteal and the infrapopliteal territories, and three studies only include infrapoliteal territory. Data are presented in Table III, with more detailed information in Table XIII from Appendices.

Table III - Plain old balloon angioplasty versus Drug-eluting balloon studies.

Author (Year), Trial, Study Design	Type	Arterial Territory	Lesions	N. Patients	Outcomes										
					PP	LLL (mm)	BR	Freedom from BR	TLR	Freedom from TLR	Clinical or RC Improvement	ABI change	MAE	Amputation Rate	Mortality Rate
Bausback et al. (2017)[23] Prospective, multicenter, randomized, controlled trial	POBA vs DEB (Ranger DEB TransPax, paclitaxel – 2 µg/mm^2)	FP	DN or restenotic lesions. MLL: POBA 60±48 mm; DEB 68±46 mm; p=0.731. Moderate to severe C: >50% lesions. O: 34% in both groups (p>0.999).	34 POBA vs 71 DEB	6 m: POBA 60%; DEB 87%; p=0.014	6 m: POBA 0.76±1.4; DEB −0.16±0.99 (p=0.002).		6 m: POBA 64.0%; DEB 91.7%; p=0.005	6 m: POBA 12%; DEB 5.6%; p=0.475		Significant improvement in RC in both groups	Improved significantly over baseline in both groups (p<0.02). 6 m: POBA 0.82±0.2; DEB 0.95±0.17; p=0.006		0%	No device-related deaths in both groups
Steiner et al. (2018)[24] 12-month results of the previous study	POBA vs DEB (Ranger DEB TransPax, paclitaxel – 2 µg/mm^2)	FP	DN or restenotic lesions. MLL: POBA 60±48 mm; DEB 68±46 mm; p=0.731. >50% lesions had moderate to severe C. O: 34% in both groups (p>0.999).	34 POBA vs 71 DEB	POBA 56.5%; DEB 86.4%; p<0.001. Subgroup without bare metal stent: POBA 52%; DEB 84%; p=0.016				POBA 26.5%; DEB 8.5%; p=0.030. Subgroup analysis without bailout stent: POBA 23%; DEB 8.9%; p=0.131	POBA 69.9%; DEB 91.2%; p=0.010	Significant improvement in RC in both groups, but difference between groups was not statistically significant (p=0.638)	Improved significantly over baseline in both groups. 12 months: POBA 0.93±0.22; DEB 0.96±0.16; p=0.642		0%	No device-related deaths in both groups
Tepe et al. (2015), IN.PACT SFA trial[25] Prospective, multicenter, international, single-blinded, randomized trial	POBA vs DEB (IN.PACT Admiral DEB, paclitaxel – 3.5 µg/mm^2)	FP	DN or nonstented restenotic lesions. MLL: POBA 8.81±5.12 cm; DEB 8.94±4.89 cm; p=0.82. O: POBA 19.5%; DEB 25.8%; p=0.22. Severe C: POBA 6.2%; DEB 8.1%; p=0.66	111 POBA vs 220 DEB	12 m: POBA 52.4%; DEB 82.2%; p<0.001				12 m: CD-TLR; POBA 20.6%; DEB 2.4%; p<0.001		12 m: Sustained clinical improvement; POBA 68.9%; DEB 85.2%; p<0.001	12 m: POBA 0.886±0.169; DEB 0.951±0.221; p=0.002		0% major amputation in both groups	No procedure or device-related deaths in both groups.
Laird et al. (2015) – IN.PACT SFA trial[26] 24-month results of the previous study	POBA vs DEB (IN.PACT Admiral DEB, paclitaxel – 3.5 µg/mm^2)	FP	DN or nonstented restenotic lesions. MLL: POBA 8.81±5.12 cm; DEB 8.94±4.89 cm; p=0.82. O: POBA 19.5%; DEB 25.8%; p=0.22. Severe C: POBA 6.2%; DEB 8.1%; p=0.66	111 POBA vs 220 DEB	POBA 50.1%; DEB 78.9%; p<0.001		POBA 46.9%; DEB 19.8%; p<0.001		CD-TLR; POBA 28.3%; DEB 9.1%; p<0.001		Sustained clinical improvement; POBA 59.2%; DEB 76.9%; p=0.003	POBA 0.938 ± 0.184; DEB 0.924 ± 0.261; p=0.611	POBA 31.1%; DEB 19.2%; p=0.023	0% major amputation in both groups	All-cause mortality: POBA 0.9%; DEB 8.1%; p=0.008. No procedure or device-related deaths in both groups.
Rosenfield et al. (2015)[12] Prospective, randomized controlled trial	POBA vs DEB (Lutonix paclitaxel-coated balloon, paclitaxel – 2 µg/mm^2)	FP	DN or non-stented restenotic lesions. TLL: POBA 63.2±40.4 mm; DEB 62.7 ± 41.4 mm. Total O: POBA 21.9%; DEB 20.6%. Severe C: POBA 8.1%; DEB 10.4%	160 POBA vs 316 DEB	12 m: POBA 52.6%; DEB 65.2%; p=0.02				12 m: POBA 16.8%; DEB 12.3%; p=0.21		12 m: RC change; POBA −1.7±1.1; DEB −1.9±1.1	12 m: ABI change; POBA 0.18±0.25; DEB 0.17±0.22.		12 m: Major amputation; POBA 0%; DEB 0.3%; p=0.37	12 m: POBA 2.8%; DEB 2.4%; p=0.82
Scheinert et al. (2015), BIOLUX P-I trial[27]	POBA vs DEB (Passeo-18	FP	DN or restenotic lesions.	30 POBA vs 30 DEB		6 m: ITT; POBA 1.04±1.00;	6 m: ITT; POBA 34.6%; DEB		6/12 m: ITT; CD-TLR; POBA 4.2%/ 41.7%;		Improvement in RC ≥ 1; 12 m: POBA	At 6 and 12 m: POBA 1.0±0.2; DEB 0.9±0.2	6/12 m: ITT; POBA 7.7%/ 41.2%; DEB	0% major amputation	6/12 m: ITT; POBA 3.7%/ 7.6%; DEB

Prospective, first-in-human, randomized controlled trial	Lux DEB, paclitaxel – 3 µg/mm^2)		MLL: POBA 68.5±57.0 mm; DEB 51.4±47.2 mm; p=0.307. Total O: 38.2%. Severe C 14.7%			DEB 0.51±0.72; p=0.033	11.5%; p=0.048		DEB 3.8%/ 15.4%; p=0.943/ p=0.064		65.2%; DEB 72.0%; p=0.846		3.8%/ 19.2%; p=0.532/ p=0.139	in both groups. 6/12 m: ITT; minor amputation; POBA 4%/4%; DEB 0%/ 3.8%; p=1.000/ p=0.954	0%/0%; p=1.000/ p=0.492
Schroeder et al. (2017), ILLUMENATE trial[28] Prospective, randomized controlled trial	POBA vs DEB (paclitaxel – 2 µg/mm^2)	FP	DN or restenotic lesions. MLL: POBA 7.1±5.3 cm; DEB 7.2±5.2 cm; p=0.878. Total O: POBA 19.0%; DEB 19.2%; p=0.97. Severe C: POBA 10%; DEB 13%; p=0.78	72 POBA vs 222 DEB	12 m: POBA 60.6%; DEB 83.9%; p<0.001				12 m: CD-TLR; POBA 16.7%; DEB 5.9%; p=0.014	12 m: freedom from CD-TLR; POBA 85.3%; DEB 94.8%; p=0.010	12 m: RC improvement; POBA 86.2%; DEB 89.2%. Walking distance improvement; POBA 72.1%; DEB 77.1%	Baseline/12 m: POBA 0.66 ± 0.27/ 0.90 ± 0.16; DEB 0.71 ± 0.20/0.93 ± 0.14. ABI improvement; POBA 76.8%; DEB 83.9%	12 m: POBA 18.0%; DEB 6.8%; p=0.008	12 m: POBA 0%; DEB 0.5%; p>0.99	
Krishnan et al. (2017)[29] ILLUMENATE Pivotal Study (Prospective, multicentre, single-blind, randomized controlled trial)	POBA vs DEB (Stellarex DEB, paclitaxel 2 µg/mm^2)	FP	DN (POBA 82.0%; DEB 90.5%; p=0.035) or restenotic lesions (POBA 18.0%; DEB 9.5%; p=0.035). MLL: POBA 8.9 cm; DEB 8.0 cm; p=0.105. Total O: POBA 18.0%; DEB 19.0%; p=0.834. Severe C: POBA 43.0%; DEB 43.9%; p=0.877	100 POBA vs 200 DEB	12 m: POBA 57.6%; DEB 76.3%; p=0.003				12 m: CD-TLR; POBA 16.8%; DEB 7.9%; p=0.023	12 m: freedom from CD-TLR; POBA 87.3%; DEB 93.6%; p= 0.025	12 m: RC improvement; POBA 88.3%; DEB 86.9%. RC Baseline/12 months: POBA 2.7 ± 0.6/0.8 ± 1.0 (-1.9 ± 1.1 change); DEB 2.7 ± 0.5/0.9 ± 1.0 (-1.9 ± 1.1 change); p=0.6950	12 m: improvement; POBA 75.8%; DEB 79.0%. Baseline/12 months: POBA 0.76 ± 0.20/ 0.93 ± 0.24 (0.17 ± 0.26 change); DEB 0.73 ± 0.21/ 0.90 ± 0.18 (0.17 ± 0.25 change); p=0.8918	12 m: POBA 17.7%; DEB 9.4%; p=0.043	0%	12 m: all-cause mortality; POBA 2.1%; DEB 2.6%; p>0.999
Scheinert et al. (2016), the German center subanalysis of the LEVANT 2 trial[30] Prospective, randomized controled trial	POBA vs DEB (Lutonix DEB, paclitaxel – 2 µg/mm^2)	FP	MLL: POBA 66.5±45.8 mm; DEB 53.1±37.7 mm; p=0.08. Total O: POBA 27.9%; DEB 20.5%; p=0.35. Severe C: POBA 11.6%; DEB 10.8%; p=0.89	43 POBA vs 83 DEB	12 m: POBA 57.8%; DEB 79.4%; p=0.015				12 m: Lower for DEB group	12 m: POBA 82.0%; DEB 96.1%; p=0.012	12 m: sustained clinical benefit; POBA 58.6%; DEB 85.3%; p<0.001. RC improvement; POBA 78.8%; DEB 91.2%; p=0.081	12 m: change; POBA 0.17±0.32; DEB 0.20±0.25; p=0.689	No difference	0%	12 m: POBA 0%; DEB 1.3%; p=0.364
Scheinert et al. (2014), LEVANT I trial[31] Prospective, randomized trial	POBA vs DEB (Lutonix DEB, paclitaxel – 2 µg/mm^2)	FP	DN or non–in-stent restenotic lesions. MLL: POBA 80.2 ± 37.8 mm; DEB 80.8 ± 37.0 mm; p=0.89. Total O: POBA 42%; DEB 41%; p=0.88	52 POBA vs 49 DEB		6 m: POBA 1.09±1.07; DEB 0.46±1.13; p=0.016			6/12/24 m: POBA 22%/ 33%/ 49%; DEB 13%/ 29%/ 36%		RC improvement; 6/12/24 m: POBA 1.6±1.5/ 2.1±1.3/ 1.8±1.1; DEB 1.7±1.3/ 1.6±1.3/ 2.1±1.1	Improvement; 6/12/24 m: POBA 0.22±0.33/ 0.20±0.46/ 0.18±0.33; DEB 0.20±0.34/ 0.18±0.30/ 0.20±0.34	24 m: POBA 46%; DEB 39%; p=0.45	6/12/24 m: POBA 0%; DEB 2%	6/12/24 m: POBA 6%/ 9%/ 11%; DEB 2%/ 4%/ 9%
Tepe et al. (2015), THUNDER trial[32] Prospective, randomized, multicenter trial	POBA vs DEB (paclitaxel coated balloon - 3 µg/mm^2)	FP	DN or restenotic lesions. MLL 7.4±6.5 cm. Total O 27%. Restenosis 30-42%	54 POBA vs 48 DEB		6/ 12m/ 5y: POBA 1.7 ± 1.8/1.9 ± 1.9/1.5 ± 1.3; DEB 0.4 ± 1.2/	6/ 12m/ 5y: POBA 44%/ 50%/ 54%; DEB 17%/ 24%/ 17%; p=0.01/		6/ 12m/ 5y: POBA 37.0%/ 48.1%/ 56%; DEB 4.2%/ 10.4%/ 21%; p<0.0001/						No difference

						0.7 ± 1.5/ 0.7±1.9; p<0.001/ p=0.01/ p=0.54	p<0.05/ p=0.04		p<0.0001/ p=0.0005						
Kinstner et al. (2016), PACUBA Trial[33] Prospective, randomized trial	POBA vs DEB (FREEWAY balloon, paclitaxel – 3 mg/mm^2)	FP	FP ISR. MLL: POBA 18.4 ± 8.8 cm; DEB 17.3 ± 11.3 cm. O: POBA 28%; DEB 31%	39 POBA vs 35 DEB	12 m: POBA 13.4%; DEB 40.7%; p=0.02					12 m: freedom from CD-TLR; POBA 22.1%; DEB 49.0%; p=0.11	Improvement in RC ≥ 1; 12 m: POBA 54.5%; DEB 68.8%; p=0.87	Baseline/6/ 12 m: POBA 0.65 ± 0.16/ 0.78 ± 0.18/ 0.84 ± 0.30; DEB 0.65 ± 0.16/ 0.79 ± 0.13/ 0.79 ± 0.20; p=0.99/ p=0.96/ p=0.70			
Krankenberg et al. (2015), FAIR trial[34] Prospective, randomized controlled trial	POBA vs DEB (IN.PACT Admiral paclitaxel-eluting balloon, paclitaxel – 3.5 µg/mm^2)	FP	FP ISR. MLL: POBA 81.1 ± 66.2 mm; DEB 82.3 ± 70.9 mm; p=0.991. Total O: POBA 33.3%; DEB 24.2%, p=0.313. Heavy C: POBA 8.8%; DEB 9.7%, p=0.327	57 POBA vs 62 DEB			12 m: POBA 44.7%; DEB 15.4%; p=0.002			12 m: POBA 52.6%; DEB 90.8%; p<0.0001	Improvement in RC ≥ 1; 6/12 m: POBA 57.4%/ 52.3%; DEB 70.6%/ 77.8%; p=0.209/ p=0.015	6/12 m: POBA 0.84 ± 0.33/ 0.90 ± 0.17; DEB 0.90 ± 0.25/ 0.86 ± 0.30; p=0.379/ p=0.502		0% major amputation	All cause death; 6/12 m: POBA 2.1%/ 6.8%; DEB 0%/ 4.3%; p=0.124/ p=0.591
Fanelli et al., DEBELLUM trial[14] Prospective, randomized trial	POBA vs DEB (IN.PACT Admiral paclitaxel-eluting balloon, paclitaxel – 3.5 µg/mm^2)	SFA: POBA 70.8%; DEB 73.7%; p=0.7. P: POBA 3.1%; DEB 3.5%; p=0.89. IP: POBA 26.1%; DEB 22.8%; p=0.67	DN lesions. MLL: POBA 7.8±0.7 cm; DEB 7.6±0.6 cm; p=0.1. O: POBA 21.5%; DEB 21.0%; p=0.94	25 POBA vs 25 DEB	12 m: POBA 39.6%; DEB 76%; p=0.04	Overall LLL; 12 m: POBA 1.81±0.1; DEB 0.64±0.9; p=0.01			Overall TLR; 12 m: POBA 35.3%; DEB 12.2%; p<0.05		Fontaine stage increase (from II b to I); 12 m: POBA 56%; DEB 80%; p<0.05	Improvement; 12 m: POBA 0.68±0.13; DEB 0.81±0.3; p=0.02	12 m: POBA 60%; DEB 24%; p<0.05	12 m: POBA 12%; DEB 4%; p>0.05	0%
Tolva et al. (2016)[35] Cohort, retrospective, non-randomized study	POBA vs DEB (paclitaxel – 2 µg/mm^2)	IP	DN lesions.	68 POBA vs 70 DEB							Improvement in RC; 24 m: POBA 51%; DEB 74%; p=0.024. When matching the improvement in Rutherford Scale, a longer lesion was associated with worst long-term results.	Baseline/24 m: POBA 0.36 ± 0.21/0.52 ± 0.22; DEB 0.35 ± 0.18/0.64 ± 0.35; p=0.231/ 0.039		Superior for DEB group	
Zeller et al. (2014), IN.PACT DEEP trial[36] Prospective, randomized controlled trial	POBA vs DEB (IN.PACT Amphirion DEB, paclitaxel –	IP	Restenotic lesions: POBA 3.7%; DEB 6.7%; p=0.176. MLL: POBA 12.86±9.46 cm; DEB 10.15±9.10 cm; p=0.002. Total O:	119 POBA vs 239 DEB		12 m: POBA 0.62 ± 0.78; DEB 0.61 ± 0.78; p=0.950	12 m: POBA 35.5%; DEB 41.0%; p=0.609		12 m: CD-TLR rate; POBA 13.5%; DEB 11.9%; p=0.682		Wound healing; 12 m: POBA 76.9%; DEB 73.8%; p=0.579.			12 m: major amputation; POBA 3.6%; DEB 8.8%; p=0.08	12 m: all-cause mortality; POBA 8.1%; DEB 10.1%; p=0.551

	3.5 µg/mm^2)		POBA 45.9%; DEB 38.6%; p=0.114. Severe C: POBA 10.5%; DEB 13.7%; p=0.336												
Zeller et al. (2015), BIOLUX P-II trial[37] Prospective, randomized, controlled, first-in-man study	POBA vs DEB (Passeo-18 Lux DEB (paclitaxel – 3 µg/mm^2)	IP	DN or native restenotic lesions. MLL: POBA 115.0 ± 86.9 mm; DEB 113.1 ± 88.1 mm; p=0.960. Lesions without C: POBA 81.6%; DEB 55.9%; p=0.018. Moderate to severe C: POBA 7.9%; DEB 26.5%; p=0.056	36 POBA vs 36 DEB		6 m: POBA 0.54 ± 0.66; DEB 0.56 ± 0.65; p=0.913	6 m: POBA 41.4%; DEB 53.1%; p=0.359		12 m: CD-TLR; POBA 26.9%; DEB 31.3%; p=0.805		Improvement in RC; baseline/6 m: POBA 4.4 ± 1.0/2.7 ± 2.4; DEB 4.5 ± 0.9/2.3 ± 2.3		12 m: POBA 39.1%; DEB 41.1%; p= 0.957	12 m: POBA 25.7%; DEB 23.7%; p=0.988	

Abbreviations: ABI, ankle-braquial index; BR, binary restenosis; C, calcification; CD-TLR, clinically-driven TLR; DEB, drug-eluting balloon; DN, *de novo*; FP, femoropopliteal; IP, infrapopliteal; ISR, in-stent restenosis; ITT, intention-to-treat; LLL, late lumen loss; m, months; MAE, major adverse events; MLL, mean lesion length; O, occlusion; P, popliteal artery; POBA, percutaneous transluminal angioplasty; PP, primary patency; RC, Rutherford classification; SFA, superficial femoral artery; TLL, total lesion length; TLR, target lesion revascularization; y, years.

Through the data presented above, in all studies primary patency presents a statistically significant superiority in DEB group (40.7%-87.0%) compared to POBA group (13.4%-60.6%), being the Kinstner et al. (2016) – PACUBA Trial[33] the only study revealing below-average values. It can be stated that there is a decreasing trend regarding PP values in studies with a longer follow-up.

It should be noted that in Krishnan et al. (2017)[29] – ILLUMENATE Pivotal Study POBA group has a significantly lower number of DN lesions and a significantly higher number of restenotic lesions. The studies related exclusively to infrapoliteal territory do not show results on PP.

With regard to LLL, excepting the studies at the infrapopliteal level that don't present statistically significant differences between groups, the remaining studies reveal a statistically significant lower LLL value in DEB group compared to POBA group, with the exception at 5 years in Tepe et al. (2015) – THUNDER trial[32] which doesn't present statistically significant differences among groups. In all studies from femoropopliteal territory the binary restenosis is significantly superior in POBA group (34.6%-54%) versus DEB group (11.5%-24%), while in the infrapopliteal territory the opposite is true (POBA 35.5%-41.4%; DEB 41.0%-53.1%), despite not being statistically significant.

TLR is higher in POBA group (4.2%-56.0%) when compared to DEB group (2.4%-36.0%), although this difference is not always statistically significant, as for example in the study of the infrapopliteal territory Zeller et al. (2014) – IN.PACT DEEP trial[36]. Besides this, still at the infrapopliteal level, Zeller et al. (2015) – BIOLUX P-II trial[37] reveals an opposite trend with a superior TLR in DEB group, although it is not statistically significant. There is also a growing trend in the TLR percentage throughout the follow-up.

In all studies there is a clinical and ABI improvement in both groups, and when there is a statistically significative difference between these groups, a superiority of DEB group compared to POBA group is observed; in Tolva et al. (2016)[35] study one could state that bigger lesions were associated with worse long-term results.

Regarding MAE, their values are superior in POBA group (7.7%-60.0%) in comparison to DEB group (3.8%-39.0%), although it is not always a statistically significant difference, however in Zeller et al. (2015) – BIOLUX P-II trial[37] (study of the infrapopliteal territory) the opposite is true, with DEB group displaying superior values compared to POBA (DEB 41.1% vs POBA 39.1%; p=0.957).

As far as amputation rate is concerned, this presents low values and there aren't statistically significant differences between the groups, however in five of the studies higher values are aimed for DEB group in comparison with POBA group, comparatively with three studies which show a superior value in POBA group, that difference being superior in the infrapopliteal territory of Zeller et al. (2014) – IN.PACT DEEP trial[36] related to major amputation. Mortality is low, and in four studies it is superior in DEB group compared to POBA group, one of them being the Zeller et al. (2014) –

IN.PACT DEEP trial[36] (infrapopliteal territory), although it is not statistically significant and in one of them, even though statistically significant there were no procedure/device-related deaths.

Summing up, all the presented studies referring only to the femoropopliteal territory (including the specific studies for ISR) and the study that includes both territories display better results in DEB groups compared to POBA groups in terms of effectiveness and patency, even presenting a safety profile equivalent or superior to POBA groups. At a functional level improvements can be identified in both groups, with no differences in terms of quality of life, but DEB group reaches the same level not requiring as many interventions.

In studies only concerning infrapopliteal territory one can state that the results, despite positive, are not replicable among the several studies, as the results are superior for DEB group in Tolva et al. (2016)[35] study, whereas in Zeller et al. (2014) – IN.PACT DEEP trial[36] and in Zeller et al. (2015) – BIOLUX P-II trial[37], besides the existence of a trend towards higher rate of major amputation in the first study, DEB group has an effectiveness comparable to POBA group. It's important to refer that in Zeller et al. (2015) – BIOLUX P-II trial[37] the DEB arm had significantly fewer uncalcified lesions than POBA arm (55.9% versus 81.6%; p=0.018), and more moderate/severe calcified lesions (26.5% versus 7.9%; p=0.056).

Stent

Two single-arm studies report results from treatment of femoropopliteal lesions with stents, and one study compares Supera stent with bare-metal stent (BMS). The results of the studies are presented in Table IV, considering these more detailed in Table XIV from Appendices.

Table IV - Stent studies.

Author (Year), Trial, Study Design	Type	Arterial Territory	Lesions	N. Patients	Outcomes									
					PP	SP	TLR	Freedom from TLR	Clinical or RC Improvement	ABI change	MAE	Amputation Rate	Mortality Rate	Stent Fractures
George et al. (2014), SAKE study[38] Restrospective, single-arm study	BMS	FP	MLL 143±98 mm. O 39%. C 61%. BS 61%	80	12 m: 85.8%	12 m: 100%				Baseline/Last follow-up: 0.60/0.83 (p<0.001)		0%		0
Laird et al. (2014), Complete Self-Expanding (SE) Multicenter trial[39] Prospective, single-arm study	BMS	FP	DN or restenotic lesions. MLL 60.7 mm. Total O 29.9%. Moderate do severe C 91.0%. BS 79.7%	196	12 m: 72.6%	12 m: 78.9%	12 m: CD-TLR; 8.4%	12 m: 90.6%	Improvement in RC ≥ 1; 30 days/12 m: 89.7%/90.9%. Walk without impairment improvement; Baseline/12 months: 39.2%/76%	Baseline/12 m: 0.7±0.2/ 0.9±0.2; p<0.0001	12 m: 11%	12 m: minor amputation; 0.5%		0
Armstrong et al. (2019)[40] Restrospective study	Supera interwoven nitinol stent vs BMS	FP	(Propensity score matched) MLL: Supera 144.5±57.6 mm; BMS 144.6±86.2 mm; p=0.645. Total O: Supera 59.3%; BMS 67.0%; p=0.512. Heavy C: Supera 41.5%; BMS 40.7%; p=0.985	118 Supera interwoven nitinol stent vs 753 BMS			12 m: Supera 8.5%; BMS 16.9%; p=0.04						12 m: Supera 2.5%; BMS 5.1%; p=0.31	

Abbreviations: ABI, ankle-braquial index; BMS, bare-metal sten; BS, baseline stenosis; C, calcification; CD-TLR, clinically-driven TLR; DN, *de novo*; FP, femoropopliteal; m, months; MAE, major adverse events; MLL, mean lesion length; O, occlusion; PP, primary patency; RC, Rutherford classification; SP, secondary patency; TLR, target lesion revascularization.

By analysing the presented data, one can state that primary patency has high values (72.6%-85.8%), which also occurs with secondary patency (78.9%-100%). Regarding TLR, its value is low (8.4%-16.9%), with the highest value appearing in BMS from the study of Armstrong et al. (2019)[40] when comparing with Supera interwoven nitinol stent, verifying that the latter presents a significant superiority at this level, while at the mortality level, despite having a superior value for BMS group, this difference isn't statistically significant. In studies with data about these parameters, it was found that there was a clinical and ABI improvement in all of them. Regarding MAE and amputation rate, the values are low.

With this, the intervention with stent showed safety and effectiveness as far as femoropopliteal lesions are concerned, as well as a lower need for reintervention when comparing new stents, namely Supera, with the standard ones.

Plain Old Balloon Angioplasty (POBA) Versus Stent

Two studies compare between an approach with POBA and another with stent in femoropopliteal territory, one of them being specific for ISR situations, and two studies address only the infrapopliteal territory. Data are presented in Table V, and they are more detailed in Table XV fom Appendices.

Table V - Plain old balloon angioplasty versus Stent studies.

Author (Year), Trial, Study Design	Type	Arterial Territory	Lesions	N. Patients	Outcomes										
					PP	SP	BR	Freedom from TLR	Clinical or RC Improvement	ABI change	Freedom from MAE	Amputation Rate	Survival Rate	Mortality Rate	Stent Fractures
Armstrong et al. (2014)[41] Observational cohort study	POBA vs Stent	FP	DN lesions. SL= lesion length≤ 150 mm; LL= lesion length> 150 mm. SL – MLL: POBA 66±40 mm; Stent 93±41 mm; p<0.001. Total O: POBA 30%; Stent 31%; p=0.8. Moderate-severe C: POBA 19%; Stent 20%. LL – MLL: POBA 247±59 mm; Stent 257±59 mm; p=0.4. Total O: POBA 39%; Stent 63%; p=0.02. Moderate-severe C: POBA 18%; Stent 39%	SL: 75 POBA vs 64 Stent. LL: 31 POBA vs 84 Stent	12 m: SL; POBA 66%; Stent 63%; p=0.7. LL; POBA 34%; Stent 49%; p=0.006	12 m: SL; POBA 76%; Stent 83%; p=0.5. LL; POBA 57%; Stent 78%; p=0.004			Sustained clinical improvement; 12 m: SL; POBA 79%; Stent 61%; p=0.06. LL; POBA 75%; Stent 62%; p=0.3	Baseline/12 m: SL; POBA 0.58±0.17/ 0.82±0.23; Stent 0.66±0.24/ 0.85±0.21; p=0.08/p=0.6. LL; POBA 0.55±0.15/ 0.79±0.27; Stent 0.53±0.16/ 0.79±0.20; p=0.7/p=0.9		Major amputation; 12 m: SL; POBA 7%; Stent 2%; p=0.2. LL; POBA 13%; Stent 7%; p=0.5			
Bosiers et al. (2015)[42] Prospective, randomized controlled trial	POBA vs Stent	FP	FP ISR. MLL: POBA 190.0±72.1 mm; Stent 173.0±77.8 mm; p=0.309. O: POBA 25.0%; Stent 23.1%; p=0.840. BS: POBA 75.0%; Stent 76.9%; p=0.840. C: POBA 25.0%; Stent 33.3%; p=0.447	44 POBA vs 39 Stent	12 m: POBA 28.0%; Stent 74.8%; p<0.001			12 m: POBA 42.2%; Stent 79.9%; p<0.001	Improvement in RC ≥ 1; 1/6/12 m: POBA 97.6%/80.5%/ 87.8%; Stent 100%/97.1%/ 93.6%; only at 6 m the difference was significant (p=0.013)				12 m: POBA 95.3%; Stent 91.9%; p=0.383		0
Brizzi et al. (2018)[43] Prospective, non-randomized study	POBA vs Stent	IP	MLL: POBA 53.1±52.2 mm; Stent 39.4±37.7 mm. Total O: 30.0%. Heavy C: 61.3%.	110 POBA vs 169 Stent	6/12 m: POBA 94.4%/ 87.6%; Stent 91.2%/ 80.6%; p=0.043	6/12 m: POBA 96.9%/ 93.6%; Stent 94.3%/ 89.2%; p=0.071		6/12 m: POBA 94.1%/ 89.9%; Stent 88.4%/ 81.8%; p=0.01	Primary/ secondary sustained clinical improvement: 76.1%/ 82.7%. 12 m: wound healing; 82.7%				6/12 m: POBA 90.1%/ 85.8%; Stent 96.3%/ 91.1%; p=0.32		
Schulte et al. (2015), EXPAND study[44] Prospective, randomized trial	POBA vs Stent	IP	DN lesions. MLL: POBA 39.5±34.9 mm; Stent 34.1±28.3 mm; p=0.49. BS: POBA 75.1±18.2%; Stent 77.5±17.3%; p=0.58.	47 POBA vs 45 Stent	No difference	No difference	12 m: POBA 33.3%; Stent 20.0%	12 m: POBA 77.6%; Stent 76.6%	RC improvement; POBA from 4.2±1.0 to 2.1±2.1; Stent from 4.3±1.0 to 1.5±1.9		12 m: POBA 60.9%; Stent 65.6%	12 m: POBA 13.2% (major: 8.7%); Stent 8.9% (major: 6.7%)		12 m: POBA 2.1%; Stent 7.4%	

Abbreviations: ABI, ankle-braquial index; BR, binary restenosis; BS, baseline stenosis; C, calcification; DN, *de novo*; FP, femoropopliteal; IP, infrapopliteal; ISR, in-stent restenosis; LL, long lesions; m, months; MAE, major adverse events; MLL, mean lesion length; O, occlusion; POBA, percutaneous transluminal angioplasty; PP, primary patency; RC, Rutherford classification; SL, short lesions; SP, secondary patency; TLR, target lesion revascularization.

Considering data analysis, it is noted that at the level of primary patency there are different results, that is, in Schulte et al. (2015) – EXPAND study[44] there is no statistically significant difference between groups, the same occurring in Armstrong et al. (2014)[41] study for short lesions. It should be noted that in this study, with regard to short lesions, MLL is significantly superior in Stent group, and in regard to long lesions the percentage of total occlusions is significantly superior in Stent group. In Bosiers et al. (2015)[42] study, devoted to ISR lesions, there is also a statistically significant superiority for Stent group, whereas in Brizzi et al. (2018)[43] study, devoted to infrapopliteal territory, the opposite is true.

As far as secondary patency is concerned this is superior in Stent group at the femoropopliteal level, being statiscally significant in long lesions, however at the infrapopliteal level it's inferior in Stent group, even without a statistical significance in the study by Brizzi et al. (2018)[43].

This trend is also noticeable in freedom from TLR, with a significantly higher value in Stent group at femoropopliteal level in ISR lesions, and the opposite at the infrapopliteal level in Brizzi et al. (2018)[43] study.

There was a clinical improvement in all studies. The amputation rate is superior for POBA group, although not statistically significant in Armstrong et al. (2014)[41] study. At the femoropopliteal level, in ISR lesions, the survival rate is superior in POBA group and the opposite is true at the infrapopliteal level, even though it is not statistically significant in both cases. In Schulte et al. (2015) – EXPAND study[44] at the infrapopliteal level, mortality is superior in Stent group.

Thus, in femoropopliteal territory it is stated that when dealing with minor lesions the results are similar between POBA and stent, however in long lesions or ISR lesions the results are superior for stent, despite the restenosis and reintervention rates remain high. In case of infrapopliteal lesions stent doesn't reveal superior to POBA with bailout stenting, and may even have inferior results.

Drug-Eluting Stent (DES)

Six studies address the safety and effectiveness of DES. From these studies, four are single-arm studies concerning femoropopliteal lesions and two are single-arm studies concerning infrapopliteal lesions. The studies outcomes are presented in Table VI, and these are more detailed in Table XVI from Appendices.

Table VI - Drug-eluting stent studies.

Author (Year), Trial, Study Design	Type	Arterial Territory	Lesions	N. Patients	Outcomes									
					PP	SP	Freedom from TLR	Clinical or RC Improvement	ABI change	MAE	Amputation Rate	Survival Rate	Mortality Rate	Stent Fractures
Kang et al. (2016)[45] Restrospective, single-arm study	DES (Zilver PTX stent, paclitaxel – 3 µg/mm^2)	FP	Including ISR lesions. MLL 218.9±128.3 mm. Total O 69.8%. Moderate to Severe C 27.0%. BS 95.4±8.5%. ISR lesions 36.5%	63	12 m: 66.7%. Was better in TASC II A and B lesions, native vessel disease, treatment with complete coverage of lesions, or relatively short lesions.						3.2%		3.2%	
Muller-Hulsbeck et al. (2016), MAJESTIC Trial[13] Prospective, single-arm study	DES (Eluvia stent, paclitaxel – 0.167 µg/mm^2)	FP	Stenotic, restenotic or occlusive lesions. MLL 70.8±28.1 mm. BS 86.3%±16.2%. O 46%. Severe C 65%	57	9/12 m: 94% (51/54) /96% (49/51)			Improvement in RC sustained at 12 months	Improvement; Baseline/12 m: 0.73±0.22/ 1.02±0.20	12 m: 4%	0% major amputation		No device or procedure related death	0
Muller-Hulsbeck et al. (2017), MAJESTIC trial[46] Three-year results of the previous study	DES (Eluvia stent, paclitaxel – 0.167 µg/mm^2)	FP	Stenotic, restenotic or occlusive lesions. MLL 70.8±28.1 mm. BS 86.3%±16.2%. O 46%. Severe C 65%	57	24 m: 83.5%		36 m: 85.3%	Improvement in RC ≥ 1; 24 m: without TLR 90.6%; with TLR 96.2%	Improvement; Baseline/12/24 m: 0.73 ± 0.22/ 1.02 ± 0.20/ 0.93 ± 0.26		0%			24 m: 0
Yokoi et al. (2016)[47] Prospective, single-arm study	DES (Zilver PTX stent, paclitaxel – 3 µg/mm^2)	FP	Including ISR lesions. MLL 14.7 cm. Total O 41.6%. BS 91.9 ± 10.7%. ISR lesions 18.6%	907	12 m: 86.4%		12 m: 91.0%	Improvement in RC ≥ 1; 12 m: 84.3%	Improvement; Baseline/12 m: 0.63/0.86		12 m: 0.8%		All-cause mortality; 12 m: 5.1%. 0 device- or procedure-related deaths.	12 m: 1.5%
Bosiers et al. (2017)[48] Prospective, single-arm study	DES (paclitaxel – 3 µg/mm^2)	IP	DN or restenotic lesions. MLL 17.2 mm. O 14.3%. BS 85.7%. C 61.4%.	70	6/12 m: 87.6%/ 72.6%		12 m: 79.1%	Improvement in RC ≥ 1; 12 m: 79.6%	improved 0.33 from baseline			12 m: 89.4%.		0
Bosiers et al. (2017)[49] Prospective, single-arm study	DES (Xience Prime stent, a 1 µg/mm^2 everolimus-coated stent)	IP	DN or restenotic lesions. MLL 47.40±25.06 mm. O 53.3%. BS 45.0%. C 45.0%.	60	12 m: 75.4 %	12 m: 98.1%	12 m: 84.9%	Improvement in RC ≥ 1; 12 m: 85.7%			Rare	Survival rate was 89.3%.		0

Abbreviations: ABI, ankle-braquial index; BS, baseline stenosis; C, calcification; DES, drug-eluting stent; DN, *de novo*; FP, femoropopliteal; IP, infrapopliteal; m, months; MAE, major adverse events; MLL, mean lesion length; O, occlusion; PP, primary patency; RC, Rutherford classification; SP, secondary patency; TLR, target lesion revascularization.

Through the presented data, in a general way, primary patency displays high values in both territories (66.7%-96% in FP lesions and 72.6%-87.6% in IP lesions). The same occurs for freedom from TLR (85.3%-91.0% in FP lesions and 79.1%-84.9% in IP lesions).

A clinical improvement was observed in the Rutherford category and in ABI in the various studies which showcase these results. The amputation values are low (0-3.2%). The studies concerning the infrapopliteal territory revealed good survival rates (~89%). The mortality rate is low (maximum of 5.1%). Only one study, the Yokoi et al. (2016)[47] study, presented stent fractures (1.5%).

Thus, the analysed studies showed safety and effectiveness in the use of DES in the femoropopliteal territory, with high patency rate, low MAE and mortality rate. However, evidence arises proving that there are factors which can negatively interfere with the results, such as longer lesions, ISR lesions, incomplete coverage, higher TASC II classification of lesions, diabetes mellitus, severe calcification, and occlusion.[45] In studies concerning infrapopliteal territory, DES reveals effectiveness and safety.

Analysing the paclitaxel dose in the various DES there seems to be no evidence that higher doses have superior results. However, these parameters weren't assessed and compared in the various studies.

Plain Old Balloon Angioplasty (POBA) Versus Drug-Eluting Stent (DES)

Five studies make a comparison between a POBA approach and a DES approach, two of them regard femoropopliteal territory (one of the studies is specific for ISR situations) and three refer to infrapopliteal territory. Their data can be observed in Table VII and Table VIII, and in further detail in Table XVII from Appendices.

Table VII - Plain old balloon angioplasty versus Drug-eluting stent studies.

Author (Year), Trial, Study Design	Type	Arterial Territory	Lesions	N. Patients	Outcomes										
					PP	Recurrent Restenosis	TLR	Freedom from TLR	Clinical or RC Improvement	ABI change	MALE	Amputation Rate	Survival Rate	Mortality Rate	Stent Fractures
Dake et al. (2016)[50] Prospective, randomized controlled trial	POBA vs DES (Zilver PTX stent, paclitaxel – 3 µg/mm^2)	FP	DN or restenotic lesions. MLL: POBA 63.2±40.5 mm; primary DES 66.4±38.9 mm. BS: POBA 78.4±17.1%; primary DES 79.8±17.0%; p=0.38. O: POBA 27.4%; primary DES 32.8%; p=0.20. Severe C: POBA 34.9%; primary DES 37.3%; p<0.01	238 POBA vs 236 DES 120 of POBA: 61 provisional DES vs 59 provisional BMS*	5 y: POBA 19.0%; primary DES 64.9%; p<0.01. Standard care 43.4%; overall DES 66.4%; p<0.01. Provisional BMS 53.0%; provisional DES 72.4%; p=0.03		5 y: POBA 28.0%; primary DES 16.1%; p<0.01	5 y: freedom from CD-TLR; standard care 67.6%; overall DES 83.1%; p<0.01. Freedom from TLR; provisional BMS 71.6%; provisional DES 84.9%; p=0.06	RC significantly improved (p<0.05) till 5 y in standard care and overall DES group	ABI significantly improved (p<0.05) till 5 y in standard care and overall DES group				5 y: all-cause mortality rate was 13.6% (POBA 10.2%; primary DES 16.9%; p=0.03. 0 procedure or device related deaths	5 y: 1.9%
Murata et al. (2016)[51] Retrospective study	POBA vs DES (Zilver PTX stent, paclitaxel – 3 µg/mm^2)	FP	FP ISR. (after extracting a matched population) No in-stent occlusion group; MLL 11±7 cm in both arms (p=0.965). In-stent occlusion group; MLL 21±7 cm in both arms (p=0.907). Total O 40%	116 POBA vs 112 DES Patients were stratified for analysis by lesions with and without in-stent occlusion		12 m: no in-stent occlusion group; POBA 39; DES 39; p=0.996. In-stent occlusion; POBA 86; DES 51; p=0.014					12 m: no in-stent occlusion group; POBA 24; DES 33; p=0.405. In-stent occlusion; POBA 62; DES 29; p=0.024				
Spreen et al. (2016), PADI trial[52] Randomized controlled trial	POBA vs DES (TAXUS Liberté paclitaxel coated balloon, paclitaxel - 1 µg/mm^2)	IP	MLL: POBA±BMS 23.1±21.8 mm; DES 21.1±19.3 mm. BS: POBA±BMS 83.1±16.7%; DES 83.2±15.3%	64 POBA± BMS; 73 DES	6 m: MITT; POBA±BMS 35.1%; DES 48.0%; p=0.096. Per-protocol analysis; POBA±BMS 35.1%; DES 51.9%; p=0.037				Mean RC improved significantly till 12 m (p≤0.005). Mean RC; 6/12 m: POBA±BMS 2.81/1.81; DES 3.11/1.87; p=0.49/p=0.90	Mean ABI improved significantly till 12 m (p≤0.005). Mean ABI; 6/12 m: POBA±BMS 0.83/0.91; DES 0.85/0.94; p=0.74/ p=0.74		12 m: Major amputation; POBA±BMS 20.5%; DES 11.4%; p=0.066	12 m: POBA± BMS 74.9%; DES 76.7%	12 m: POBA±BMS 25.1%; DES 23.3%; p=0.52	
Spreen et al. (2017), PADI trial[53] 5-year results of the previous study	POBA vs DES (TAXUS Liberté paclitaxel coated balloon, paclitaxel - 1 µg/mm^2)	IP	MLL: POBA±BMS 23.1±21.8 mm; DES 21.1±19.3 mm. BS: POBA±BMS 83.1±16.7%; DES 83.2±15.3%	64 POBA± BMS; 73 DES	Higher after DES than after POBA±BMS at 1, 3, and 4 years of follow-up							POBA±BMS 7.8%; DES 2.7%	POBA± BMS 37.0%; DES 37.7%; p=0.45	POBA±BMS 48.4%; DES 43.8%	

Abbreviations: ABI, ankle-braquial index; BS, baseline stenosis; C, calcification; DN, *de novo*; FP, femoropopliteal; IP, infrapopliteal; ISR, in-stent restenosis; MALE, major adverse limb events; MITT, modified-intention-to-treat; MLL, median lesion length; O, occlusion; POBA, percutaneous transluminal angioplasty; PP, primary patency; RC, Rutherford classification; TLR, target lesion revascularization; y, years.

* Outcomes compare primary DES vs POBA, overall DES (primary and provisional) vs standard care (POBA and BMS), and provisional DES vs provisional BMS.

Table VIII - Plain old balloon angioplasty versus Drug-eluting stent studies, report wound healing outcomes, health-related quality of life changes and QALYs gain.

Author (Year), Trial, Study Design	Type	Arterial Territory	Lesions	N. Patients	Outcomes		
					Wound Healing	Quality of Life	QALYs gain
Katsanos et al. (2016), ACHILLES Trial[54] Prospective, randomized controlled trial	POBA vs DES (Cypher Select Sirolimus-Eluting Stent, sirolumus – 1.4 µg/mm^2)	IP	DN or restenotic lesions. MLL: POBA 26.8 ± 21.3 mm; DES 26.9 ± 20.9 mm; p=0.913. Total O: POBA 71.4%; DES 81.3%; p=0.334. BS: POBA 74.0 ± 19.0%; DES 68.8 ± 19.3%; p=0.039	101 POBA vs 99 DES	6/12 m: POBA 60%/55.6%; DES 95%/72.9%; p=0.048/p=0.088	12 m: EQ-5D score (to assess health-related quality of life) improved significantly up to 12 m in DES group (p<0.0001), but not in POBA group	Statistically significant at 6 weeks, 6/12 m in DES group, in POBA group the significance was only until 6 m. 12 m: POBA 0.03; DES 0.13

Abbreviations: BS, baseline stenosis; DES, drug-eluting stent; DN, *de novo*; IP, infrapopliteal; m, months; MLL, mean lesion length; O, occlusion; POBA, percutaneous transluminal angioplasty; QALY, quality-adjusted life year.

Through the analysis of displayed data, as far as primary patency is concerned DES is significantly superior both at the femoropopliteal level as well as more distally. In Dake et al. (2016)[50] study, TLR was significantly superior in POBA group versus primary DES, whereas freedom from TLR was superior in overall DES (versus POBA and BMS, $p<0.01$) and provisional DES (versus provisional BMS, $p=0.06$) groups.

In Murata et al. (2016)[51] study, a study of the femoropopliteal territory regarding ISR lesions, POBA group features a recurrent restenosis and MALE significantly higher than DES group in occlusive lesions, the same is not true for non-occlusive lesions.

In studies with data related to clinical improvement, all presented a significant improvement. In studies concerning infrapopliteal territory, the amputation rate was superior in POBA group. Given the mortality, values are slightly superior for POBA group in infrapopliteal territory studies, being that in Dake et al. (2016)[50] study (a femoropopliteal territory study) the all-cause mortality is significantly superior in DES group versus POBA (16.9% vs 10.2%, respectively), although none of the deaths are related to the procedure/device.

This way, it is observed that in light of femoropopliteal lesions DES shows superiority in comparison to POBA, namely in terms of patency and freedom from TLR, the same happening in Dake et al. (2016)[50] study where provisional DES also shows superior results than provisional BMS. As for ISR, DES reveals to be superior to POBA in occlusive lesions, but equally effective to POBA in non-occlusive lesions. As far as infrapopliteal territory studies are concerned, both studies show better results in DES group, namely a greater patency and a lower number of amputations.

Katsanos et al. (2016) – ACHILLES Trial[54] presents an improvement in terms of wound healing and quality of life in DES group compared to POBA group, it's important to refer that POBA group presented a significantly superior percentage of stenosis than DES group at baseline.

Likewise, the paclitaxel dose doesn't seem to affect the outcomes. However, these parameters were also not assessed and compared in the studies.

Stent Versus Drug-Eluting Stent (DES)

Two studies compare between stent or DES use in femoropopliteal territory, one of them refers specifically to situations of in-stent occlusion (ISO). Their data can be observed in Table IX and in further detail in Table XVIII from Appendices.

Table IX - Stent versus Drug-eluting stent studies.

Author (Year), Trial, Study Design	Type	Arterial Territory	Lesions	N. Patients	Outcomes						
					TVR	TLR	Freedom from TLR	Freedom from ISR	ABI change	Freedom from MALE	Mortality Rate
Jeon-Slaughter et al. (2018)[55] Retrospective study	Stent vs DES (Zilver PTX stent, paclitaxel – 3 µg/mm^2)	FP	Including ISR lesions. Unmatched data/Propensity-score matched data; MLL: Stent 156.5±93.7 mm/ 164.8±97.97 mm; DES 162.5±118.7 mm, p=0.93/p=0.50. Total O: Stent 63.65%/63.79%; DES 63.79%; p=0.97/p>0.99. Heavy C: Stent 53.57%/32.76%; DES 32.18%; p<0.001/p=0.91. ISR lesions: Stent 10.97%/27.59%; DES 26.44%; p<0.001/p=0.81.	784 Stent (the propensity-score matched data consisted of 174 patients) vs 174 DES	12 m: unmatched data; Stent 13.8%; DES 9.8%; p=0.16. Propensity-score matched data; Stent 18.4%; DES 9.8%; p=0.02	12 m: unmatched data; Stent 13.8%; DES 9.2%; p=0.10. Propensity-score matched data; Stent 18.4%; DES 9.2%; p=0.01					12 m: unmatched data; Stent 1.8%; DES 5.3%; p=0.03. Propensity-score matched data; Stent 1.3%; DES 5.3%; p=0.04
Tomoi et al. (2016)[56] Retrospective, nonrandomized, observational study	Stent vs DES (paclitaxel – 3 µg/mm^2)	FP	FP ISO. MLL: Stent 221.5±83.9 mm; DES 254.8±61.2 mm; p=0.09.	79 Stent vs 21 DES			24 m: Stent 27.1%; DES 85.7%; p<0.001	24 m: Stent 20.2%; DES 79.3%; p<0.001	Mean ABI; Baseline/Postprocedure: Stent 0.41±0.22/ 0.76±0.16; DES 0.45±0.29/0.90±0.17; p=0.45/p<0.001	24 m: Stent 25.3%; DES 85.7%; p<0.001	

Abbreviations: ABI, ankle-braquial index; C, calcification; DES, drug-eluting stent; FP, femoropopliteal; ISO, in-stent occlusion; ISR, in-stent restenosis; m, months; MALE, major adverse limb events; MLL, mean lesion length; O, occlusion; TLR, target lesion revascularization; TVR, target vessel revascularization.

The presented data reveal that in Jeon-Slaughter et al. (2018)[55] study, based on propensity-score matched data, TVR and TLR are significantly superior in Stent group when compared with DES group, the opposite occuring in terms of mortality, the latter being significantly superior in DES group (5.3% vs 1.3%). It's important to refer that in this study of Jeon-Slaughter et al. (2018)[55], regarding unmatched data, a significantly superior percentage of heavy calcification could be observed in Stent group when compared to DES group at baseline, whereas the percentage of ISR lesions was significantly lower in Stent group compared to DES. In Tomoi et al. (2016)[56] study, which reports to ISO lesions, DES group shows a significant superiority with regard to freedom from TLR, freedom from ISR and freedom from MALE at 24 months.

Thus, in case of femoropopliteal lesions, DES seems to have better results in terms of patency and adverse events when compared to stent. Results that favor the use of DES were also shown in ISO situations.

Drug-Eluting Balloon (DEB) Versus Drug-Eluting Stent (DES)

One study compares DEB with DES in infrapopliteal territory. Its data can be observed in Table X and in further detail in Table XIX from Appendices.

Table X - Drug-eluting balloon versus Drug-eluting stent studies.

Author (Year), Trial, Study Design	Type	Arterial Territory	Lesions	N. Patients	Outcomes							
					LLL (mm)	BR	Total Vessel Reocclusion	TLR	Clinical or RC Improvement	Amputation Rate	Mortality Rate	Stent Fractures
Siablis et al. (2014), IDEAS trial[57] Prospective randomized controlled trial	DEB (IN.PACT Amphirion DEB, paclitaxel – 3.5 µg/mm^2) vs DES (Resolute stent – 1.6 µg/mm^2 zotarolimus-eluting stent; Cypher stent – 1.4 µg/mm^2 sirolimus-eluting stent; Promus stent – 1 µg/mm^2 everolimus-eluting stent)	IP	MLL: DEB 148 ± 56.7 mm; DES 127 ± 46.5 mm; p=0.14. Total O: DEB 12%; DES 23%; p=0.31. BS: DEB 85.3 ± 8.9%; DES 86.8 ± 10.1%. Severe C: DEB 44%; DES 50%; p=0.64.	25 DEB vs 25 DES	6 m: DEB 1.15 ± 0.3; DES 1.35 ± 0.2; p=0.62	6 m: DEB 57.9%; DES 28%; p=0.0457	6 m: DEB 15.8%; DES 20.0%; p=0.72	6 m: DEB 13.6%; DES 7.7%; p=0.65	Median RC; Baseline/6 m: DEB 4.5/1.0; DES 4.5/1.0; p=0.69/p=0.87	6 m: major amputation; DEB 1 of 25; DES 2 of 27; p=1.00	6 m: DEB 2 deaths of 25; DES 3 deaths of 25; p=1.00	0

Abbreviations: BS, baseline stenosis; BR, binary restenosis; C, calcification; DEB, drug-eluting balloon; DES, drug-eluting stent; IP, infrapopliteal; LLL, late lumen loss; m, months; MLL, mean lesion length; O, occlusion; RC, Rutherford classification; TLR, target lesion revascularization.

Considering the displayed data one can state that there are no statistically significant differences in all parameters, excepting binary restenosis which showed to be superior in DEB group comparatively to DES group. Therefore, both groups presented favorable results.

Drug-Coated Devices Versus Non-Drug-Coated Devices

One study compares between drug-coated devices and non-drug coated devices in femoropopliteal territory. Its data can be observed in Table XI and in further detail in Table XX from Appendices.

Table XI - Drug-coated devices versus non-drug coated devices studies.

Author (Year), Trial, Study Design	Type	Arterial Territory	N. Patients	Outcomes
				Mortality Rate
Secemsky et al. (2019)[58] Retrospective, cohort study	Drug-coated devices (DES/DEB) vs non-drug coated devices (POBA/Stent)	FP	5989 drug-coated devices vs 10571 non-drug-coated devices	600 days: all-cause mortality; drug-coated devices 32.5%; non-drug-coated devices 34.3%; p=0.007. Subanalysis; similar trends in DEB vs POBA (p=0.06) and DES vs BMS (p=0.56). Patients with CLI; drug-coated devices 38.1%; non-drug-coated devices 40.1%; p=0.04. Without CLI; drug-coated devices 26.5%; non-drug-coated devices 29.0%; p=0.07. No association was established between drug-coated devices and all-cause mortality with a multivariable adjustment (adjusted HR, 0.97; p=0.43).

Abbreviations: CLI, critical limb ischaemia; DEB, drug-eluting balloon; DES, drug-eluting stent; FP, femoropoplitel; HR, hazard ratio; POBA, percutaneous transluminal angioplasty.

Considering the analysis of presented data, there is a statistically significant difference in terms of all-cause mortality with lower values in drug-coated devices group, also being noticeable a statistically significant difference in the subanalysis of patients suffering from CLI, with inferior mortality in the drug-coated devices group. However, there was no association between all-cause mortality and the use of drug-coated devices with a multivariable adjustment.

DISCUSSION

Nowadays the endovascular approach stands out in LEAD treatment. This evolution is reflected in the results of the conducted research, as there is currently a greater number of publications that compare POBA versus DEB (17 studies), followed by studies with DEB and DES (six studies each), what shows an attempt to improve techniques/devices and the results.

These considerations are particularly important at the femoropopliteal territory. Achieving long-term results, such as patency/stents durability, represents an ongoing challenge due to mobility/dynamics of this territory and to the mechanical wear which lead to both stent fracture and an increased risk of ISR.[2, 28, 40, 59] In the search carried out more POBA versus DEB studies performed at a femoropopliteal level and studies with DES are identified, where devices with new features are tested.

With the obtained data it's possible to understand which intervening factors can be considered and improved with regard to drug-eluting devices. The restenosis stage with proliferation of smooth muscle cells and formation of extracellular matrix, inhibited by paclitaxel, only occurs several weeks/months after the procedure, so the paclitaxel effect can be more effective if it remains for a longer period of time in the arterial wall[13]. In restenosis the innermost vascular layer consists mostly of acellular material, making it difficult for the cytotoxic effect of paclitaxel, so that atherectomy could be an option to remove this layer promoting paclitaxel action.[10]

Another factor to consider is the role of calcium which acts like a barrier to the absorption of paclitaxel and that the fact of the compressive force exerted by calcified plaque against the stents avoid a complete expansion of these, resulting in a higher LLL and lower primary patency rates[29, 38], with a worse result in the presence of calcium in 360°.[60] Besides this, different outcomes will arise according to the excipients, paclitaxel dose, coating type, and balloon design which interfere in the pharmacokinetics. The presence of diabetes mellitus, greater lesions, ISR lesions, higher TASC II classification of lesions, and occlusion are factors that can diminish the effectiveness of drug-eluting devices.[21, 28, 29]

From the 45 analysed articles in the present work, only 12 present results after 12 months of intervention (the majority with follow-up at 24 months).

Despite the diminute number of studies with long-term results, there is a follow-up loss, which shows the difficulty of carrying out long-term studies, as it's necessary to consider that patients with LEAD usually have other associated comorbidities that may contribute to their mortality, neither LEAD nor the procedure itself being the cause of death.[52] Therefore, more studies must be carried out to understand the medium-long term evolution of treated patients.

The results obtained by the studies can be hardly generalized to the remaining population due to the existing differences in samples, in the study design and in the different used devices, which hardens the comparison between studies.[23, 24] However, despite the several differences, the results shown are consistent across the studies.

The included studies in the current work cover a population with symptomatic PAD, more specifically intermittent claudication and CLTI, in infrainguinal arterial territory, so that the analysed interventions are related to these conditions.

In view of the analysis of the included studies, regarding studies about DEB, the results showed safety and effectiveness in femoropopliteal and infrapopliteal lesions, as well as in *de novo* lesions or restenosis (nonstented and femoropopliteal ISR), so that it can be an option of treatment in intermittent claudication/CLTI. When comparing the use of DEB with POBA in the femoropopliteal level, studies reveal a superior patency and effectiveness of DEB, with a safety profile at least equivalent to POBA (even in ISR situations). This also applies to a longer follow-up period, as shown in Tepe et al. (2015) – THUNDER trial[32] LLL and TLR were inferior with DEB.

In infrapopliteal territory the effectiveness of DEB is superior only in one study (Tolva et al. (2016)[35]) and similar in the remaining two, with one of them, the Zeller et al. (2014) – IN.PACT DEEP trial[36], showing a trend towards higher rate of major amputation.

The use of stent showed safety and effectiveness at femoropopliteal level. By comparing the stent with POBA in the femoropopliteal territory, when it's about smaller lesions results are similar between the techniques, but in longer lesions (> 150mm) or ISR the results are superior for stent, despite the fact that the restenosis/reintervention rates remain high.

In studies related to infrapopliteal lesions, stent doesn't show superiority over POBA with bailout stenting, and may even have inferior results regarding patency and freedom from TLR.

As far as studies about DES are concerned, these demonstrate safety and effectiveness in both arterial territories (femoropopliteal and infrapopliteal), and some factors that can decrease its effectiveness at a femoropopliteal level have been identified, such as longer lesions, ISR lesions, incomplete coverage, higher TASC II classification of lesions, diabetes mellitus, severe calcification, and occlusion. When comparing DES with POBA, at femoropopliteal and infrapopliteal level, the former reveals superiority (namely with regard to patency and freedom from TLR), considering that in case of femoropopliteal ISR it is superior just for occlusive lesions. DES also shows superiority when compared to stent in femoropopliteal territory. By comparing DEB with DES in infrapopliteal territory, DEB presented a binary restenosis superior to DES. When drug-coated devices (DES/DEB) are compared to non-drug coated devices (BMS/POBA) there is a statistically significant lower all-cause mortality in drug-coated devices group, however after a multivariable adjustment there is no association between all-cause mortality and the use of drug-coated devices.

Regarding wound healing, one of the parameters identified as a gap in the investigation, only one comparative study, the Katsanos et al. (2016) – ACHILLES Trial[54] (infrapopliteal territory), presented this parameter and the quality of life as central topics of the trial. This study seeks to report the results of health-related quality of life, QALYs gain and wound healing in POBA and DES groups, with an improvement being found in terms of wound healing and quality of life in DES group compared to POBA group. Zeller et al. (2014) – IN.PACT DEEP trial[36] mentioned wound healing as a result, but without statistically significant differences between DEB and POBA groups at the infrapopliteal level, the same happening with Siablis et al. (2014) – IDEAS trial[57], in which results were similar between DEB and DES groups at the infrapopliteal level. In general, there are no differences between techniques, excepting the first mentioned, in which DES is superior to POBA.

The impact on the quality of life is a gap identified in different studies. The Bausback et al. (2017)[23] study compares POBA versus DEB in femoropopliteal territory, with no statistically significant differences being found between groups at six months. The Krishnan et al. (2017)[29] study also compares POBA versus DEB in the femoropopliteal territory, and quality of life was comparable, but the double of revascularizations was necesary in POBA group. The same occured in the Laird et al. (2015)[26] study, which also compares POBA versus DEB in the femoropopliteal territory, where patients in the DEB group reached comparable levels of quality of life but with 58% less reinterventions. In this case, all data concern POBA versus DEB studies in the femoropopliteal territory and show that both groups present similar results but with less reinterventions in DEB group.

The European Society of Cardiology (ESC) guidelines in collaboration with ESVS refer that in case of intermittent claudication, revascularization could be considered when there is compromise of daily life activities. Thus, revascularization of femoropopliteal disease in intermittent claudication and in severe chronic limb ischaemia must be performed by an endovascular approach as first line in lesions smaller than 25cm. In bigger lesions, the endovascular approach continues to be possible, but a surgical approach with bypass presents a superior long-term patency and should be the first line approach in these cases, whenever patients don't present a high surgical risk, when there is an available autologous vein and when life expectancy is superior to two years. Primary stent, DEB and DES placement can be considered in lesions smaller than 25cm; DEB can be considered for ISR treatment.[2]

Also according to ESC/ESVS guidelines, whenever possible, revascularization is indicated for limb salvage in CLTI.[2] More specifically, in case of average risk patients with infrainguinal CLTI, the decision on the procedure choice is based on the severity of the threat it may represent to the limb (Wounds, Ischaemia, and foot Infection (WIfI Stage)), or the anatomic pattern of disease/anatomic

complexity (Global Anatomic Staging System (GLASS Stage)), and the availability of an autologous vein.[4]

If a vein is available, patients with WIfI stage ≥2 and GLASS stage I, or patients with WIfI stage 2 and GLASS stage I or II must undergo an endovascular procedure, and patients with WIfI stage ≥3 and GLASS stage 3 must undergo bypass, the remaining stages (WIfI stage 2 with GLASS stage III, and WIfI stage 3 and 4 with GLASS stage II) are undetermined in relation of what procedure select.[4]

There are few comparative studies with quality that allow to conclude which is the best option in the context of CLTI. POBA can be inferior than DEB and stent for treatment of intermediate-length superficial femoral artery disease in patients with intermittent claudication and possibly pain at rest, however there are insufficient data to identify which is the preferred endovascular approach for femoropopliteal disease. In endovascular treatment of femoropopliteal disease, consider the use of adjuncts to POBA (such as stents or drug-eluting devices) when there is a non desirable result like residual stenosis, or when there is an advanced complexity of lesion (for example, GLASS femoropopliteal grade 2-4).[4]

In case of infrapopliteal arterial disease in the context of CLTI, revascularization is indicated for limb salvage, bypass with great saphenous vein is indicated for revascularization of infrapopliteal arteries, and the endovascular approach can be considered.[2] For anatomically adequate infrapopliteal disease POBA remains a suitable primary endovascular intervention, as DEB didn't prove to be superior to POBA in this one.[2, 4] DES can be an option after technical complications (such as dissection) or POBA failure for small and proximal infrapoliteal lesions. Thus, according to the 2019 Global Vascular Guidelines on the Management of Chronic Limb-Threatening Ischemia, given the lack of current evidence to support other techniques, POBA remains the standard option.[4] If an endovascular procedure is initially performed, the regions which can serve as anchorage for a potential bypass must be preserved.[2] No revascularization procedures should be carried out in patients with LEAD just to prevent the progression to CLTI.[5]

Although more studies are needed to prove the effectiveness of the different options for endovascular intervention and to enable a comparison between the various data obtained, allowing to define with certainty which is the most appropriate approach for each situation, considering the results of the existing analysed studies, a proposal is made about the kind of approach to have initially (even if sometimes it doesn't match with what is currently described in literature). Nevertheless, the indications for conventional surgery mentioned above must be respected whenever the clinical condition allows it.

Therefore, one could think of an initial endovascular approach with DEB or DES in femoropopliteal lesions, given their superiority over POBA. Since some factors that may decrease DES effectiveness at the femoropopliteal level have been identified, namely long lesions or ISR

situations, DEB should be considered in these situations. Besides this, if one considers a perspective in which there is no placement of foreign material to the organism, DEB would be the first approach to consider. As far as femoropopliteal ISR is concerned DEB reveals itself superior to POBA, so it could be the initial approach in this condition; DES only reveals superiority regarding POBA in occlusive lesions, and can be considered as an option when they are present. In case of infrapopliteal lesions, DEB and stent didn't show superiority over POBA, however, DES showed to be superior to DEB and POBA, so DES could be the initial approach in infrapopliteal lesions.

What happens is that drug-coated devices have acquired importance in the LEAD treatment.[58] Given the improvements observed in terms of long-term patency obtained by DEB in comparison with POBA, DEB has already been recommended as an initial strategy for femoropopliteal revascularization.[61] Brizzi et al. (2018)[43], in his study, concludes that a first endovascular approach in the infrapopliteal territory based on POBA with bailout stenting remains an effective strategy and should be the first line until DES role is well defined, highlighting the importance that DES may come to acquire at this level. In Spreen et al. (2016) – PADI trial[52] and Spreen et al. (2017) – PADI trial[53] it's concluded that the therapeutic strategy with DES should be considered in the infrapopliteal territory, as it is associated to a better patency and a lower number of amputations when compared with POBA±BMS.

One kind of device that could be a viable option to stent, with the purpose of not leave foreign material, is a version of the Absorb Everolimus-Eluting Bioresorbable Vascular Scaffold device which is a bioresorbable device.[62]

With regard to complications related to the procedure, no statistically significant differences were identified between the groups, with the exception of the Zeller et al. (2014) – IN.PACT DEEP trial[36] in which the overall complication rate was superior in DEB group compared to POBA group (9.7% versus 3.4%; p=0.035); despite this, complications have been successfully treated, not interfering with the requiring for provisional stenting. In general, some of the identified complications were: peripheral embolization, thrombosis, dissection, bleeding, groin hematoma, perforation, pseudoaneurysm, vasospasm, wound infection, and stent fracture. In Scheinert et al. (2014) – LEVANT I trial[31] eight malfunctions resulting in failed deployments were identified which caused a device success lower in the DEB group, although procedure success was achieved with adjunctive measures. None of the deaths that occurred was directly associated to the procedure/device. The identification of complications and statistically significant differences at this level is importante, as this can interfere with the expected results and lead to bias in the conclusions.

Recently, in a systematic review and meta-analysis investigating paclitaxel-coated devices in femoropopliteal arteries, long-term all-cause mortality at two and at five years follow-up was

significantly higher in paclitaxel-coated devices versus non-drug-coated devices group, and a meta-regression showed an association between paclitaxel exposure and absolute risk of death ($p<0.001$). It's necessary to take into account that the majority of the included studies didn't identify the causes of death, not allowing to objectify a causal link to the use of paclitaxel, and data about patient withdrawal and loss to follow-up were not considered.[15, 58] Besides this, these results were not found in other studies, at least of which we are aware. Nevertheless, these results led to the suspension of some under development studies, and promoted the realization of new ones, namely that of Schneider et al. (2019)[63] which goal was to determine the existence of a correlation between paclitaxel exposure and mortality through a meta-analysis with data up to five years of follow-up. The resuts revealed that there were no statistically significant differences as far as all-cause mortality is concerned between the groups, both in comparison with all patients (unadjusted $p=0.092$) and in comparison between patients displaying similar characteristics (adjusted $p=0.188$), despite having as limitations the heterogeneity of populations, the small number of patients in POBA group, which may not be representative, and the low number of events associated to mortality that limit the study capacity to compare DEB versus POBA.[63]

CONCLUSION

Lower limb peripheral arterial disease, as a chronic occlusive atherosclerotic pathology of the lower limb arteries, is a major health issue, with a high prevalence and tending to increase.[1, 2] Considering the systemic characteristic of atherosclerosis, these patients present an increased cardiovascular morbimortality.[2] Therefore, the economic costs/quality of life are considerable, so that a timely and effective intervention is essential.[1, 2]

As endovascular revascularization is an increasingly important therapeutic option, the current work aimed to review the techniques of plain balloon angioplasty, angioplasty with drug-eluting balloon, primary stent and drug-eluting stent, compare and discuss results.

Seeking to answer the question "Do drug eluting devices have a better outcome in lower limb arterial disease?", one can state that DEB was superior to POBA at the femoropopliteal level (even in ISR situations), the same not happening at infrapopliteal level; DES was also superior to POBA in both territories, but in case of femoropliteal ISR it is only superior in occlusive lesions and when compared to bare stent in femoropopliteal territory.

Despite the Katsanos et al. (2018)[15] study shows a higher mortality associated to paclitaxel use, in results displayed by Schneider et al. (2019)[63] this doesn't occur, being a question under study at the moment.

The current review allowed to meet the defined objectives.

The limitations of this review have to do with the fact that the included studies display samples and interventions with characteristics which do not allow generalizations and make it hard to carry out comparisons, the existence of scarce studies with comparisons between the various tehniques (specially studies about DEB vs DES at a femoropliteal and infrapopliteal level, POBA vs DEB at an infrapopliteal level, POBA vs DES in both territories, and ISR situations), and a reduced number of studies with results after 12 months of intervention, what makes long-term conclusions impossible.

There are currently some studies underway, namely "Bypass versus angioplasty in severe ischaemia of the leg - 2 (BASIL-2) trial" and "Balloon versus Stenting in severe Ischaemia of the Leg-3 (BASIL-3)" stand out, which may help to find the answer.

At last, the following suggestions are made: the conduct of comparative studies between techniques with greater samples and between devices with different technologies, namely with paclitaxel, carrying out longer follow-up periods, and the performance of meta-analysis that can integrate the results of the several studies.

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APPENDICES

Appendix 1

Table XII - Drug-eluting balloon studies, long version.

Femoropopliteal territory:

Study	Patients	Intervention	Outcomes
Schroeder et al. (2015) – ILLUMENATE study[19] Prospective, single-arm, multicenter, first-in-human study	50 patients with symptomatic PAD (Rutherford Clinical Classification 2, 3, or 4) with *de novo* or restenotic lesions located in the superficial femoral artery (SFA) and/or popliteal artery.	StellarexTM drug-eluting balloon (paclitaxel-coated balloon – 2 µg/mm^2).	Mean lesion length was 7.2 cm, baseline stenosis was 75.1%, there were 62.1% calcified lesions and 12.1% occluded lesions. Primary endpoint – mean late lumen loss (LLL) at 6 months postprocedure was 0.54 mm. Major secondary endpoint – rate of major adverse events (MAE) at 6 months postprocedure was 4%. <u>Two-year results:</u> Clinically-driven target lesion revascularization (CD-TLR) rate at 12 and 24 months was 12 and 14.9%, respectively. Freedom from CD-TLR rate at 12 and 24 months was 90.0 and 85.8%, respectively. Primary patency rate at 12 and 24 months was 89.5 and 80.3%, respectively. There were no amputations and cardiovascular deaths. Mean walking distance increased significantly (p≤0.01) with distances of 185±182 m at 6, 139±95 m at 12 and 190±87 m at 24 months. Mean baseline ABI was 0.71±0.13, and it increased significantly at 6 months to 0.91±0.16 and so it remained.
Stabile et al. (2016)[20] Prospective, single-arm, multicenter study	123 patients with intermittent claudication and CLI with *de novo*, restenotic or in-stent restenotic lesions located in the SFA and/or popliteal artery.	LEGFLOW DEB (a 3 µg/mm^2 paclitaxel-coated balloon).	In 61.8% patients POBA was performed for *de novo* lesions (MLL 95.1 ± 57.0 mm), in 21.1% patients for restenosis (MLL 96.1 ± 32.1 mm) and in 17.1% patients for in-stent restenosis (MLL 114.3 ± 24.1 mm). <u>Six-month results:</u> Freedom from TLR was 88.6%. Freedom from TLR in patients with claudication was 93.6% and in patients with CLI was 79.5%. Freedom from TLR in patients with *de novo* lesions was 88.1% and in patients with restenosis was 80.7%. There was no TLR in patients with ISR. TLR rates were not affected by lesion length, but they were affected by the presence of diabetes.
Femoropopliteal territory, In-Stent Restenosis lesions:			
Bague et al. (2017) – PLAISIR trial[21] Prospective, single-arm,	53 Adults/55 limbs with symptomatic PAD (Rutherford Class 1-5), clinical degradation by at	Paclitaxel eluting balloon (coated with a paclitaxel dose density	<u>18-Month results:</u> Total mortality rate: 4%. 5 patients required TLR. At 12 and 18 months freedom from TLR rates were 90.2 ± 4.2%. Survival rate at 1 year was 96 ± 2.7%.

multicenter, cohort study	least 1 Rutherford stage or absence of healing of all skin lesions, symptoms related to SFA ISR defined by PSVR>2.4 within 3-24 months after SFA stenting of *de novo* atherosclerotic lesions.	of 3.5 μg/mm^2).	Freedom from TER rates at 12 and 18 months were 87.7 ± 4.7% and 78.6 ± 6.1%, respectively. Primary patency rate was 83.7% at 12 months and 78.1% at 18 months. At 12 and 18 months, 77% and 67% of the patients were asymptomatic, respectively. The primary sustained clinical improvement was 78.6±5.7% at 12 months and 63.2±6.7% at 18 months. The secondary sustained clinical improvement was 92.0±3.8% at 12 months and 79.2±5.9% at 18 months. Mean ABI: there was an increased from 0.54 ± 0.37 at baseline level to 0.96 ± 0.54 at 12 months (p<0.001) and remained elevated at 18 months (0.92 ± 0.23) (p=0.01). One minor amputation and one major amputation were made. Quality of life: there was a tendency to an improvement, but it wasn't significant.
Virga et al. (2014)[22] Prospective, single-arm study	39 Patients with SFA in-stent restenosis.	IN.PACT balloon (coated with a paclitaxel dose density of 3.5 μg/mm^2)	At baseline, MLL was 82.9 ± 78.9 mm. <u>Two-year results:</u> Rates of all-cause and cardiovascular mortality were 2.56% at one year and 5.12% at two years. Primary patency was 70.3%. Freedom from TLR rate was 78.4%. Secondary patency rate was a 87%. Rutherford class: 0.6±0.7 (at baseline it was 2.9±0.7; p < 0.05). ABI: 0.94 ± 0.09 (at baseline it was 0.77 ± 0.09; p<0.05). Treatment of classes II and III ISR lesions with DEB had a higher rate of recurrent restenosis versus class I lesions (33.3% and 36.3% versus 12.5%; p=0.05).
Femoropopliteal territory, Restenotic vs *De Novo* Lesions:			
Herten et al. (2015)[10] Prospective study Assessed the efficacy of DEB in restenotic (stented and nonstented) versus *de novo* (DN) stenotic femoropoplite al arteries.	100 Patients/105 limbs/111 lesions with intermittent claudication or CLI were categorized in restenosis group (RE) (included stented and nonstented restenotic arteries; 61 patients/65 lesions), or in DN group (only native stenotic vessels; 39 patients/46 lesions)	Paclitaxel-DEB (IN.PACT Admiral or Freeway, both with a paclitaxel concentration of 3 μg/mm^2)	There was no significant difference in between groups, excepting the longer lesion length that was higher in RE group (99±76 versus 77±68mm in DN group, p=0.05). Total occlusion was identified in 25% of lesions in RE group vs 27% of lesions in DN group, p=0.935. <u>12-Month results:</u> Primary patency (PP) was 86% at 6 months and 74% at 12 months. PP was superior in DN group vs RE group at 6 months (93% versus 81%, p=0.093) and was significantly higher at 12 months (85% versus 68%; p=0.021). PP without provisional stenting subanalysis: DN group presented higher values at 6 months (97% versus 80%; p=0.028) and at 12 months (89% versus 67%; p=0.007). ABI significantly increased from 0.61 at baseline to 0.87 at 12 months (p=0.037) (the RE group showed an significantly increased from 0.57

			± 0.29 to 0.85 ± 0.20 (p<0.001) and the DN group showed an significantly increased from 0.68 ± 0.25 to 0.90 ± 0.12 (p<0.001)). Secondary sustained clinical improvement: there was a rise of at least one Rutherford category at 12 months (p<0.001) without difference between the groups (RE 78%; DN 83%; p=0.568). TLR was inferior in DN group vs RE group at 6 and 12 months (DN: 7% and 15%, respectively, vs 19% and 32% for RE group). TLR without provisional stenting subanalysis: DN group had higher values at 6 (3% versus 20%, p=0.028) and 12 months (10% versus 32%; p=0.007). Cumulative survival rates did not differ significantly in both groups (p=0.965). There was no amputation. The results are significantly better for DN lesions than for RE lesions, but it must be taken into account that RE group included patients with lower baseline ABI and longer lesions, so they could display a higher risk
Infrapopliteal territory:			
Brodmann et al. (2017)[11] Prospective, single-arm, observational study	203 patients/257 lesions with *de novo* or restenotic lesions (Rutherford category 1-6) in the infrainguinal arteries (SFA (56.4%), popliteal artery (23%) and infrapopliteal territory (13.2%)) were enrolled.	Passeo-18 Lux drug-coated balloon (coated with 3 µg/mm^2 of paclitaxel using butyryl-tri-n-hexyl citrate as an inert excipiente)	At baseline, MLL was 75.1 ± 69.4 mm, there were 20% occlusions and 76.3% lesions were calcified. <u>12-Month results:</u> Primary patency: 85.4%. CD-TLR at 6 and 12 months was 8% and 16%, respectivelly. Freedom from clinically-driven TLR: 93.2%. ABI changed 0.17±0.26 since baseline (p<0.001); there was a significant improvement of at least one Rutherford category in 82.7% of patients; there was a significant improvement in 75.4% according to the Pain Scale. At 6 months, MAE rate was 5.5%, and 10.1% at 12 months. 12 Months all causes mortality: 6.5%. 12 Months overall amputation rate: 4.2%.

Table XIII - Plain old balloon angioplasty versus Drug-eluting balloon studies, long version.

Femoropopliteal territory:

Study	Patients	Intervention	Outcomes
Bausback et al. (2017)[23] Prospective, multicenter, randomized, controlled trial	105 Patients with symptoms of lower limb ischaemia (Rutherford category 2-4), and a hemodynamically significant *de*	<u>DEB arm:</u> 71 patients treated with the Ranger DEB TransPax (coated with paclitaxel at a dose density of 2 µg/mm^2	At baseline, MLL was 68±46mm in DEB group versus 60±48 mm in POBA group, p=0.731. > 50% of lesions had moderate to severe calcification. Both groups had the same proportion of occlusions (34%, p>0.999). <u>Six-month results:</u> Control group had a late lumen loss of 0.76±1.4 mm and DEB group had a LLL of

	novo or restenotic lesion located in the native nonstented SFA or proximal popliteal segment were randomized to treatment with the Ranger DEB or an uncoated balloon.	and acetyl tri-n-butyl citrate excipiente). <u>Control arm:</u> 34 patients were with uncoated balloon angioplasty.	−0.16±0.99 mm (p=0.002). When an analysis without provisional stents was made lumen loss remained significantly inferior for DEB group (–0.18±1.1 mm) vs control group (0.63±1.5 mm; p=0.014). In DEB group lumen loss didn't significantly differ (p=0.839) between patients with and without bailout stent. Freedom from binary restenosis (≥50% diameter stenosis) was 91.7% for DEB group versus 64.0% (p=0.005). Primary patency was 87% for DEB group versus 60% (p=0.014). TLR rate was 5.6% in DEB group versus 12% in control group (p=0.475). Both groups had a significant improvement in Rutherford categories. 76.0% Patients in control group achieved clinical success and 82.3% patients in DEB group achieved clinical success (p=0.713). Both groups had a significant improvement in ABI since baseline (p<0.02) (mean ABI at six months was 0.95±0.17 in DEB group versus 0.82±0.2 in control group; p=0.006). There were no amputations or device-related deaths. There were no significant differences between groups at baseline and at 6 months for walking function and for health-related quality of life scores.
Steiner et al. (2018)[24]			<u>12-month results of the previous study:</u> The Kaplan-Meier estimate of primary patency rate was 86.4% for the DEB group and 56.5% for the control group (p<0.001). Freedom from TLR was significantly superior in DEB group (91.2%) versus control group (69.9%); p=0.010. TLR was 8.5% in DEB group versus 26.5% in control group (p=0.030). In a subgroup analysis without bailout stents the differences between groups were alike to the overall sample for primary patency rate (84% versus 52%, p=0.016) and for TLR rate (8.9% versus 23%, p=0.131). Both groups showed a significant improvement in Rutherford categories (there was no statistically significant difference between groups; p=0.638). ABI significantly improved from baseline to 12 months in both groups; there was no statistically significant difference between groups (0.96±0.16 in DEB group versus 0.93±0.22 in POBA group; p=0.642). 92.6% Patients in DEB group achieved clinical success and 81.5% patients in control group achieved clinical success (p=0.261). There were no amputations or device-related deaths.

			There was an increased from 38 ± 22 at baseline to 66 ± 26 at 6 months with a sustained value of 64 ± 28 at 12 months in DEB group in mean total Walking Impairment Questionnaire scores, control group had a similar increase.
Tepe et al. (2015) – IN.PACT SFA trial[25] Prospective, multicenter, international, single-blinded, randomized trial	331 Patients with symptomatic femoropopliteal *de novo* or non-stented restenotic lesions (Rutherford 2-4) were randomly assigned.	<u>DEB arm:</u> 220 patients treated with IN.PACT Admiral DEB (coated with paclitaxel 3.5 µg/mm^2 with urea as the excipiente). <u>POBA arm:</u> 111 Patients treated with standard POBA.	At baseline, MLL was 8.94±4.89 cm for DEB group versus 8.81±5.12 cm for POBA group (p=0.82). There were 25.8% total occlusions for DEB group and 19.5% for POBA group (p=0.22). 8.1% of lesions from DEB group and 6.2% of lesions from POBA group had severe calcification (p=0.66), respectively. <u>12-month results:</u> DEB group had a primary patency rate of 82.2% vs 52.4% in POBA group (p<0.001). CD-TLR was lower in DEB group (2.4% vs 20.6%; p<0.001). There was a significantly superior primary sustained clinical improvement in DEB group (85.2%) versus POBA group (68.9%; p<0.001). ABI was significantly higher in the DEB group (0.951±0.221 in DEB group vs 0.886±0.169 in POBA group; p=0.002). Vessel thrombosis rate was low in both groups (1.4% in DEB group vs 3.7% in POBA group; p=0.10). There were no amputations and procedure/device-related deaths. Comparable functional outcomes were achieved by both arms, but POBA arm required 8.6 times more CD-TLR to reach the same levels.
Laird et al. (2015) – IN.PACT SFA trial[26]			<u>24-month results of the previous study:</u> Primary patency rate was significantly higher in DEB group versus POBA group (78.9% versus 50.1%; p<0.001). CD-TLR rate was 9.1% in DEB group and 28.3% in POBA group (p<0.001). DEB group had a cumulative binary restenosis rate of 19.8% when compared to 46.9% in POBA group (p<0.001). ABI was 0.924±0.261 in DEB group vs 0.938±0.184 in POBA group; p=0.611. There was a significantly superior primary sustained clinical improvement in DEB group versus POBA group (76.9% versus 59.2%; p=0.003). Freedom from 30-day device/procedure-related death and target limb major amputation and clinically driven target vessel revascularization (CD-TVR): 87.4% in DEB group compared to 69.8% in POBA group (p<0.001). MAE was 19.2% in DEB group vs 31.1% in POBA group; p=0.023. All-cause mortality rate was superior in DEB group versus POBA group (8.1% versus 0.9%;

			p=0.008). There were no major amputations and procedure/device-related deaths. Vessel thrombosis rate was low: 1.5% in DEB group versus 3.8% in POBA group (p=0.243). There was an improvement in all functional outcomes in both groups; patients the DEB group reached comparable levels of quality of life but with 58% less reinterventions.
Rosenfield et al. (2015)[12] Prospective, randomized controlled trial	Patients with symptomatic femoropopliteal *de novo* or non-stented restenotic lesions (Rutherford 2-4) and an angiographically significant atherosclerotic lesion were randomly assigned.	<u>DEB arm:</u> 316 patients treated with Lutonix paclitaxel-coated balloon (2 μg/mm^2 of paclitaxel and the excipients polysorbate and sorbitol). <u>POBA arm:</u> 160 patients treated with standard POBA.	At baseline, total lesion length was 62.7±41.4 mm in DEB group vs 63.2±40.4 mm in POBA group. Total occlusions were identified in 20.6% in DEB group vs 21.9% in POBA group. Severe calcification was identified in 10.4% in DEB group vs 8.1% in POBA group. <u>12-month results:</u> Primary patency was significantly higher in the DEB group (65.2% vs. 52.6%; p=0.02). Total TLR was 12.3% in DEB group vs 16.8% in POBA group, p=0.21. There was a significant improvement (p<0.001) in ABI, Rutherford stage and Walking Impairment Questionnaire scores from baseline in both groups. ABI change was 0.17±0.22 for DEB vs 0.18±0.25 for POBA. Rutherford stage change −1.9±1.1 for DEB vs −1.7±1.1 for POBA. There were no statistically significant differences for death (2.4% in DEB vs 2.8% in POBA group (p=0.82)), major amputation (0.3% vs 0.0%, respectively (p=0.37)) and thrombosis requiring reintervention (0.4% vs 0.7%, respectively (p=0.62)).
Scheinert et al. (2015) – BIOLUX P-I trial[27] Prospective, first-in-human, randomized controlled trial	60 Patients/68 lesions with symptomatic *de novo* or restenotic lesions of SFA and popliteal arteries (Rutherford category 2-5) were randomized.	<u>DEB arm:</u> 30 patients/33 lesions treated with Passeo-18 Lux DEB (coated with 3 μg/mm^2 of paclitaxel using butyryl-tri-n-hexyl citrate as an inert excipiente). <u>Control arm:</u> 30 patients/35 lesions treated with Passeo-18 uncoated balloon.	At baseline, MLL was 61.2±53.1 mm (51.4±47.2 mm in DEB group vs 68.5±57.0 mm in POBA group, p=0.307). There were 14.7% severe calcified lesions; and 38.2% total occlusions. Groups presented no difference in lesion characteristics. <u>Six-month results:</u> (intention-to-treat (ITT) population) DEB group had a significantly lower LLL versus control group (0.51±0.72 versus 1.04±1.00 mm; p=0.033), and binary restenosis (11.5% in DEB group versus 34.6% in POBA group; p=0.048). CD-TLR rates were 3.8% in DEB group versus 4.2% in POBA group (p=0.943). MAE rates were 3.8% in DEB group versus 7.7% in POBA group (p=0.532). Death rate was 0% in DEB group vs 3.7% in POBA group, p=1.000. 0% major amputation in both groups. Minor amputation was 0% in DEB group vs 4% in POBA group, p=1.000. <u>12-month results:</u> (intention-to-treat (ITT) population)

			CD-TLR was inferior in DEB group (15.4% versus 41.7% in POBA group; p=0.064). MAE rates were 19.2% in DEB group compared to 41.2% in POBA group (p=0.139). Death rate was 0% in DEB group versus 7.6% in POBA group; p=0.492. 0% major amputation in both groups. Minor amputation was 3.8% in DEB group vs 4% in POBA group; p=0.954. 72.0% patients of DEB group showed an improvement of at least one Rutherford category compared to 65.2% patients of POBA group (p=0.846). At follow-up ABI was in normal and at the 6 and 12 months was 0.9±0.2 for DEB group and 1.0±0.2 for POBA group.
Schroeder et al. (2017) – ILLUMENATE trial[28] Prospective, randomized controlled trial	294 Patients with *de novo* or restenotic femoropopliteal lesions (Rutherford class 2–4) were randomized.	<u>DEB arm:</u> 222 patients/254 lesions treated with DEB (coated with 2 µg/mm^2 of paclitaxel with a polyethylene glycol excipiente). <u>POBA arm:</u> 72 patients/79 lesions treated with standard POBA.	At baseline, MLL was 7.2±5.2 cm in DEB group vs 7.1±5.3 cm in POBA group, p=0.878. There were 19.2% total occlusions in DEB group and 19.0% in POBA group (p=0.97). Severe calcification was identified in 13% in DEB group vs 10% in POBA group, p=0.78. <u>12-month results:</u> Freedom from CD-TLR: 94.8% in DEB group vs 85.3% in POBA group (p=0.010). CD-TLR was 5.9% in DEB group compared to 16.7% in POBA group (p=0.014). 14 Patients in DEB group (6.8%) suffered 20 MAEs and 11 patients in POBA group suffered 12 MAEs (18.0%); p=0.008. Primary patency was 83.9% in DEB group and 60.6% in POBA group (p<0.001). This parameter was not statistically different in patients treated with and without bailout stent in DEB group; p=0.09. Target limb amputation was 0.5% in DEB group versus 0% in POBA group (p > 0.99), and this was a minor amputation. There were no major amputations in both groups. There was a comparable improvement in the percentage of patients in both groups in terms of ABI (83.9% in DEB group vs 76.8% in POBA group), Rutherford classification (89.2% in DEB group vs 86.2% in POBA group) and walking distance (77.1% in DEB group vs 72.1% in POBA group). There was a comparable ABI improvement in DEB group (0.71 ± 0.20 to 0.93 ± 0.14) and in POBA group (0.66 ± 0.27 to 0.90 ± 0.16).
Krishnan et al. (2017)[29] This article encompasses results of 2 studies: ILLUMENATE Pivotal Study	Patients with symptomatic leg ischaemia (Rutherford class 2–4), angiographic evidence of *de novo* or restenotic lesion or chronic	<u>ILLUMENATE Pivotal Study</u> <u>DEB arm:</u> 200 patients treated with Stellarex DEB (with a 2 µg/mm^2 paclitaxel	<u>ILLUMENATE Pivotal Study</u> POBA group had a mean reference vessel diameter significantly superior when compared to DEB group (5.2 mm versus 4.9 mm, respectively; p=0.017), and more restenotic lesions (9.5% in DEB group and 18.0% in POBA group; p=0.035); there were 82.0% DN lesions in POBA group vs 90.5% in DEB group (p=0.035); there were no more statistically significant differences between

(Prospective, multicentre, single-blind, randomized controlled trial), and ILLUMENATE PK study (prospective, single-arm study)	total occlusions within the SFA and/or popliteal artery. ILLUMENATE Pivotal Study: 300 patients were randomized.	dose and polyethylene glycol as excipiente). <u>POBA arm:</u> 100 patients treated with standard POBA.	groups. MLL was 8.0 cm in DEB group vs 8.9 cm in POBA group (p=0.105). Total occlusion was identified in 19.0% in DEB group vs 18.0% in POBA group (p=0.834). Severe calcification was identified in 43.9% of lesions in DEB group vs 43.0% in POBA group (p=0.877). <u>12-month results:</u> DEB group showed superiority over POBA group in freedom from device/procedure-related death through 30 days, freedom from target limb major amputation and CD-TLR (92.1% vs 83.2%, respectively; p=0.025). Primary patency rate was significantly higher in DEB than in POBA group (76.3% versus 57.6%, p=0.003). CD-TLR rate was significantly inferior in DEB group compared to POBA group (7.9% versus 16.8%; p=0.023). DEB group presented a significantly superior freedom from CD-TLR compared to POBA group (93.6% versus 87.3%, respectively; log-rank p-value=0.025). MAE was 9.4% for DEB group vs 17.7% for POBA group, p=0.043. 0% amputation rate. All-cause mortality was 2.6% in DEB group vs 2.1% in POBA group; p>0.999. Rutherford category for DEB group was 2.7 ± 0.5 at baseline and 0.9 ± 1.0 at 12 months, with a change of -1.9 ± 1.1, 86.9% patients improved. Rutherford category for POBA group was 2.7 ± 0.6 at baseline and 0.8 ± 1.0 at 12 months, with a change of -1.9 ± 1.1, 88.3% patients improved (p=0.6950). ABI for DEB group was 0.73 ± 0.21 at baseline and 0.90 ± 0.18 at 12 months, with a change of 0.17 ± 0.25, 79.0% patients improved. ABI for POBA group was 0.76 ± 0.20 at baseline and 0.93 ± 0.24 at 12 months, with a change of 0.17 ± 0.26, 75.8% patients improved (p=0.8918). Quality of life was similar, but the double of revascularizations was necesary in POBA group. <u>ILLUMENATE PK study:</u> Mean lesion length: 5.5 cm. 14.7% Lesions were intervened with two DEB. Levels of paclitaxel were detectable in all cases after the last DEB and they decreased rapidly in the first hour (54.4±116.9 ng/mL to 1.4±1.0 ng/mL); then a gradual decline was identified to 0.3±0.1 ng/mL over 24 hours. After 24 hours, concentrations of paclitaxel were inferior to lower limit of detection (<0.100 ng/mL) in 96% patients.

Scheinert et al. (2016) - the German center subanalysis of the LEVANT 2 trial[30] Prospective, randomized controled trial	This subanalysis shows the results from 126 patients with symptomatic SFA and/or popliteal lesions (Rutherford categories 2–4) and angiographically significant atherosclerotic lesions enrolled at eight participating German sites.	<u>DEB arm:</u> 83 patients treated with the Lutonix DEB (coated with 2 µg/mm^2 of paclitaxel formulated with polysorbate and sorbitol). <u>POBA arm:</u> 43 patients treated with standard POBA.	At baseline, MLL was 53.1±37.7 mm in DEB group vs 66.5±45.8 mm in POBA grup, p=0.08. There were 20.5% total occlusions in DEB group vs 27.9% in POBA group, p=0.35. Severe calcification was presente in 10.8% of lesions in DEB group vs 11.6% in POBA group, p=0.89. <u>12-month results:</u> Primary patency was 79.4% in DEB group versus 57.8% in POBA group (p=0.015). DEB group had an inferior TLR rate. Freedom from TLR was 96.1% in DEB group versus 82.0% in POBA group (p=0.012). Target vessel revascularization (TVR) rate: 6.8% in DEB group versus 28.2% in POBA group (p=0.002). There was a sustained clinical benefit in 85.3% of DEB group versus 58.6% for POBA group (p<0.001). Improved Rutherford category was 91.2% in DEB group vs 78.8% in POBA group, p=0.081. Improvement in ABI from baseline was 0.20±0.25 in DEB group vs 0.17±0.32 in POBA group, p=0.689. Death was 1.3% for DEB group vs 0.0% for POBA group, p=0.364. Amputation rate of 0%. There were no differences in major adverse events for both groups.
Scheinert et al. (2014) – LEVANT I trial[31] Prospective, randomized trial	101 Patients with symptomatic single *de novo* or non–in-stent restenotic lesions (Rutherford categories 2-5) were enrolled.	<u>DEB arm:</u> 49 patients treated with the Lutonix DEB (a low-dose DEB coated with 2 µg/mm^2 paclitaxel with a polysorbate/sorbitol carrier). <u>POBA arm:</u> 52 patients treated with standard POBA.	At baseline, MLL was 80.8 ± 37.0 mm in DEB group vs 80.2 ± 37.8 mm in POBA group, p=0.89. There were 41% total occlusions in DEB group vs 42% in POBA group, p=0.88. At six months primary LLL was significantly inferior in DEB group versus POBA group (0.46±1.13mm versus 1.09±1.07mm; p=0.016). <u>24-month results:</u> DEB group had a composite major adverse event rate of death/thrombosis/amputation/reintervention of 39% versus 46% in POBA group (p=0.45). Patients with successful DEB deployment had a LLL of 0.39 ± 1.11 mm and patients with failed deployment had a LLL of 0.71 ± 1.27 mm. In successful deployment primary patency was 66% compared tos 0% in failed deployment (p=0.002). TLR rate at 6/12/24 months was 13%/29%/36% in DEB group vs 22%/33%/49% in POBA group. TLR was 24% in patients with successful DEB deployment and 63% in patients with failed deployments (p=0.031). Improvement in ABI from baseline to 6/12/24 months was 0.20±0.34/ 0.18±0.30/

			0.20±0.34 in DEB group vs 0.22±0.33/ 0.20±0.46/ 0.18±0.33 in POBA group. Rutherford class improvement from baseline to 6/12/24 months was 1.7±1.3/ 1.6±1.3/ 2.1±1.1 in DEb group vs 1.6±1.5/ 2.1±1.3/ 1.8±1.1 in POBA group. Amputation rate at 6/12/24 months was 2%/2%/2% in DEB group vs 0%/0%/0% in POBA group. Death rate at 6/12/24 months was 2%/4%/9% in DEB group vs 6%/9%/11% in POBA group.
Tepe et al. (2015) – THUNDER trial[32] Prospective, randomized, multicenter trial	154 Patients with symptomatic PAD (Rutherford stages 1-5), with *de novo* or restenotic lesions were randomized.	Control arm: 54 patients treated with standard POBA and nonionic contrast medium. DEB arm: 48 patients treated with a 3 µg/mm^2 paclitaxel coated balloons and nonionic contrast medium. Contrast medium (CM) arm: 52 patients treated with POBA with paclitaxel added to the contrast medium (100 ml of contrast medium was added to 17.1 mg of paclitaxel in 1 ml of absolute ethanol).	At baseline, MLL was 7.4 ± 6.5 cm. 27% of lesions were total occlusions. 30 to 42% of lesions were restenoses. Five-year results: Cumulative number of patients with TLR at 6/12 months was 4.2%/10.4% in DEB group vs 37.0%/48.1% in POBA group (p<0.0001/ p<0.0001), and remained significantly lower in the DEB group (21%) than in the control group (56%) (p=0.0005) at 5 years. Time between the intervention and TLR was 607 days in DEB group compared to 206 days in control group (p=0.04). At six months, LLL in DEB group was significantly lower versus control group (0.4 ± 1.2 mm versus 1.7 ± 1.8 mm; p<0.001); at 12-month there was a significant difference, with DEB group presenting lower values (LLL: 0.7 ± 1.5 mm in DEB group versus 1.9 ± 1.9 mm in control group; p=0.01); at 5-year LLL was 0.7±1.9 in DEB group vs 1.5±1.3 in POBA group; p=0.54. At six months and 12 months, binary restenosis rate was significantly better for DEB group (6 months: 17% in DEB group versus 44% (p=0.01); 12 months: 24% in DEB group versus 50% (p<0.05)). At 5-year, the rate of binary restenosis was lower in DEB group (17% versus 54%; p=0.04). Independent of lesion length there was an advantage of DEB in terms of LLL and TLR. There were no statistically significant differences between groups in terms of major amputation rate/death at the 5-year follow-up.
Femoropopliteal Territory, In-Stent Restenosis Lesions:			
Kinstner et al. (2016) – PACUBA Trial[33]	74 Patients (> 50 years), with symptomatic PAD (Rutherford categories 2-3), with ISR in the SFA and popliteal	DEB arm: 35 patients treated with FREEWAY balloon (a paclitaxel eluting	At baseline, DEB group had a MLL of 17.3 ± 11.3 cm vs POBA group that had a MLL of 18.4 ± 8.8 cm. There were 31% occlusions in DEB group vs 28% in POBA group. 12-Month results:

Prospective, randomized trial	artery were randomly assigned.	balloon with a concentration of 3 mg/mm^2). POBA arm: 39 patients treated with standard POBA.	Primary patency rate was higher for DEB group than for POBA group (40.7% vs 13.4%, respectively; log-rank p=0.02). Freedom from CD-TLR was 49.0% in the DEB group vs 22.1% in the POBA group (log-rank p=0.11). 68.8% of DEB group had a clinical improvement of at least one Rutherford-Becker category compared to 54.5% of POBA group (p=0.87). ABI at baseline/6/12 months was 0.65 ± 0.16/ 0.79 ± 0.13/ 0.79 ± 0.20 in DEB group and 0.65 ± 0.16/ 0.78 ± 0.18/ 0.84 ± 0.30 in POBA group (p=0.99/ p=0.96/p=0.70).
Krankenberg et al. (2015) – FAIR trial[34] Prospective, randomized controlled trial	119 Patients with Rutherford categories 2-4 and SFA ISR were randomly assigned.	DEB arm: 62 patients treated with a drug-coated balloon (IN.PACT Admiral paclitaxel-eluting balloon, with a paclitaxel dose of 3.5 µg/mm^2 and urea). POBA arm: 57 patients treated with a over-the-wire POBA balloon.	At baseline, MLL was 82.3 ± 70.9 mm in DEB group vs 81.1 ± 66.2 mm in POBA group, p=0.991. There were 24.2% total occlusions in DEB group vs 33.3% in POBA group, p=0.313. Heavy calcification was identified in 9.7% of lesions in DEB group vs 8.8% in POBA group, p=0.327. 12-Month results: Recurrent restenosis was 29.5% in DEB group vs 62.5% in POBA group (p=0.004). Binary recurrent restenosis was 15.4% in DEB group vs 44.7% in POBA group (p=0.002). Freedom from TLR was 90.8% in DEB group vs 52.6% in POBA group (p<0.0001). Clinical improvement of ≥1 Rutherford category at 6/12 months was 70.6%/ 77.8% in DEB group vs 57.4%/52.3% in POBA group (p=0.209/p=0.015). ABI at 6/12 months was 0.90 ± 0.25/ 0.86 ± 0.30 in DEB group vs 0.84 ± 0.33/ 0.90 ± 0.17 in POBA group (p=0.379/p=0.502). There was no major amputation in both groups. All cause death at 6/12 months was 0%/4.3% in DEB group vs 2.1%/6.8% in POBA group (p=0.124/p=0.591).
Femoropopliteal and Infrapopliteal Territory:			
Fanelli et al. – DEBELLUM trial[14] Prospective, randomized trial	50 patients with symptomatic PAD (Fontaine stage IIb to IV), with *de novo* SFA, popliteal and below-the-knee (BTK) lesions were enrolled.	DEB arm: 25 patients/33 limbs/57 lesions treated with IN.PACT drug eluting balloons (paclitaxel DEB), IN.PACT Admiral (paclitaxel-eluting balloon, with a paclitaxel dose of 3.5	70.8% of lesions in POBA group were in SFA vs 73.7% in DEB group, p=0.7. 3.1% of lesions in POBA group were in popliteal artery vs 3.5% in DEB group, p=0.89. 26.1% of lesions in POBA group were in bellow the knee territory vs 22.8% in DEB group, p=0.67. MLL was 7.6±0.6 cm in DEB group vs 7.8±0.7 cm in POBA group, p=0.1. There were 21% occlusions in DEB group vs 21.5% in POBA group, p=0.94. 12-month results: Primary patency rate was 76% in DEB group compared to 39.6% in POBA group (p=0.04). DEB group had an overall LLL of 0.64±0.9 mm compared to POBA group that had an overall LLL

		µg/mm^2) were used for femoropoplite al lesions and IN.PACT Amphirion (with a paclitaxel dose of 3.5 µg/mm2) for BTK lesions) <u>POBA arm:</u> 25 patients/38 limbs/65 lesions treated with Admiral and Amphirion uncoated balloons).	of 1.81±0.1 mm (p=0.01); a non-stented segment subanalysis showed a LLL of 0.63±0.9 mm in DEB group compared to 1.70±0.6 mm in POBA group (p<0.01); DEB group had an overall LLL of 0.61±0.8 mm compared to 1.84±0.3 mm in POBA group (p=0.02) in the femoropopliteal region and 0.66±0.9 mm in DEB group compared to 1.69±0.5 mm in POBA group (p=0.03) in the BTK region. DEB group had an overall TLR of 12.2% versus 35.3% in POBA group (p<0.05); TLR was 13.5% in DEB group compared to 38.6% in POBA group (p<0.05) in patients treated only with angioplasty. 80% of DEB group had an increase in Fontaine stage (from II b to I) compared to 56% of POBA group (p<0.05). DEB group had a greater ABI improvement (0.81±0.3 versus 0.68±0.13; p=0.02). MAE rate was significantly lower in DEB group (24% versus 60% in POBA group; p<0.05). DEB group had an amputation rate of 4% compared to 12% in POBA group (p>0.05). 0 deaths occured in both groups.
Infrapopliteal Territory:			
Tolva et al. (2016)[35] Cohort, retrospective, non-randomized study	138 Patients with chronic limb ischaemia (Rutherford class >4) with tibial artery *de novo* lesions were enrolled.	<u>DEB arm:</u> 70 patients treated with a 2 µg/mm^2 paclitaxel DEB. <u>POBA arm:</u> 68 patients.	<u>24-month results:</u> DEB group had a greater improvement in the Rutherford Scale in cumulative and single TASC lesions classification (74% compared to 51% in POBA group; p=0.024); with the matching of the improvement in Rutherford Scale, longer lesions were related to worst long-term outcomes. ABI at baseline/24 months was 0.35 ± 0.18/0.64 ± 0.35 in DEB group vs 0.36 ± 0.21/0.52 ± 0.22 in POBA group (p=0.231/0.039). DEB was more favorable for TASC B lesions, with a significant ABI increase and a lower rate of restenosis (from 0.35 ± 018 to 0.71 ± 0.23 (DEB) vs from 0.36 ± 0.21 to 0.48 ± 0.12 (POBA); p=0.025). DEB group had significantly better results in terms of cumulative survival rate and amputation rate.
Zeller et al. (2014) – IN.PACT DEEP trial[36] Prospective, randomized controlled trial	358 Patients with symptomatic Rutherford class 4-6 CLI were randomized.	<u>DEB arm:</u> 239 patients treated with IN.PACT Amphirion DEB (coated with 3.5 µg/mm^2 of paclitaxel). <u>POBA arm:</u> 119 patients. Patients were subdivided into Angio	At baseline, significant differences between groups were identified, these included MLL (10.15±9.10 cm in DEB group versus 12.86±9.46 cm in POBA group; p=0.002), impaired inflow (40.7% in DEB group versus 28.8% in POBA group; p=0.035) and previous TLR (32.2% in DEB group versus 21.8% in POBA group; p=0.047). There were 38.6% total occlusions in DEB group vs 45.9% in POBA group, p=0.114. There were 6.7% restenotic lesions in DEB group vs 3.7% in POBA group, p=0.176. Severe calcification was identified in 13.7% of lesions in DEB group vs 10.5% in POBA group, p=0.336. <u>12-month results:</u>

		Cohort (patients with angiographic inclusion criteria) (167 patients): DEB arm with 113 patients and POBA arm with 54 patients; and into Clinical Cohort (191 patients): DEB arm with 126 patients and POBA arm with 65 patients.	DEB group had a CD-TLR rate (assessed in the protocol-specified amputation-free surviving population) of 9.2% versus 13.1% in POBA group (p=0.291). When assessed in the entire 358-patient population DEB group had a CD-TLR of 11.9% versus 13.5% in POBA group (p=0.682) with respective cumulative TLR rates of 15.5% in DEB group versus 20.2% in POBA group (p=0.2665). LLL was 0.61 ± 0.78 mm in DEB group compared to 0.62 ± 0.78 mm in POBA group (p=0.950). Binary restenosis rate was 41.0% in DEB group vs 35.5% in POBA group; p=0.609. There were no differences between groups in LLL (p=0.950), in binary restenosis rate (p=0.609) and reocclusion rate (p=0.531) in the 167-patient angiography cohort. Through 6 months the composite of all cause death, major amputation and CD-TLR rates were 17.7% in DEB group versus 15.8% in POBA group. All-cause mortality was 10.1% in DEB group versus 8.1% in POBA group, p=0.551. DEB group had an all-cause death/major or minor amputation rate of 35.2% versus 25.2% in POBA group (p=0.064). Major amputation was 8.8% in DEB group vs 3.6% in POBA group, p=0.08. Major amputation-free survival was 81.1% in DEB group versus 89.2% in POBA group (p=0.057). Wound healing was 73.8% in DEB group compared to 76.9% in POBA group (p=0.579).
Zeller et al. (2015) – BIOLUX P-II trial[37] Prospective, randomized, controlled, first-in-man trial	72 Patients with claudication and CLI, with *de novo* or native restenotic lesions of the infrapopliteal arteries were randomized.	<u>DEB arm:</u> 36 patients/50 lesions treated with Passeo-18 Lux DEB (coated with 3 µg/mm^2 of paclitaxel). <u>POBA arm:</u> 36 patients/55 lesions.	At baseline, MLL was 113.1 ± 88.1 mm in DEB group vs 115.0 ± 86.9 mm in POBA group, p=0.960. There were significantly fewer uncalcified lesions in DEB group compared to POBA group (55.9% versus 81.6%; p=0.018), and more moderate/severe calcified lesions (26.5% versus 7.9%; p=0.056). At six months DEB lesions had a LLL of 0.56 ± 0.65 mm compared to 0.54 ± 0.66 mm in POBA lesions (p=0.913). At six months binary restenosis was 53.1% in DEB group versus 41.4% in POBA group, p=0.359. <u>12-month results:</u> CD-TLR was 31.3% in DEB group vs 26.9% in POBA group, p=0.805. MAE occurred in 41.1% of DEB patients and in 39.1% of POBA patients (p= 0.957). Amputation target extremity was 23.7% in DEB group vs 25.7% in POBA group, p=0.988. 50.8% Lesions in DEB group suffered patency loss versus 45.6% lesions in POBA group (p=0.908). Excluding major amputation, DEB group improved in mean Rutherford class from 4.5 ± 0.9 at baseline to 2.3 ± 2.3 at 6 months versus 4.4 ± 1.0 to 2.7 ± 2.4 in POBA group.

Table XIV - Stent studies, long version.

Femoropopliteal Territory:

Study	Patients	Intervention	Outcomes
George et al. (2014) – SAKE study[38] Restrospective, single-arm study	80 Patients/98 limbs/98 segments with femoropopliteal PAD.	SUPERA stent (a interwoven-wire self-expanding nitinol stent).	At baseline, MLL was 143±98 mm. There were 39% total occlusions. There were 61% calcified lesions. Baseline stenosis was 61%. <u>12-month results:</u> Primary patency rate was 85.8%. Assisted patency rate was 96.8%. Secondary patency was 100%. Reintervention was required in 15 limbs. There was an increase in ABI from 0.60 at baseline to 0.83 at last follow-up (p<0.001). There were no stent fractures in any of the limbs subject to reintervention. No major complications (like amputation) were identified.
Laird et al. (2014) – Complete Self-Expanding (SE) Multicenter trial[39] Prospective, single-arm study	196 Patients/214 *de novo* or restenotic lesions with femoropopliteal PAD (Rutherford categories 2–4).	The Complete SE stent (a lasercut, self-expanding nitinol stent).	At baseline, there were 29.9% chronic total occlusions. MLL was 60.7 mm. 91.0% of lesions had moderate to severe calcification. Baseline stenosis was 79.7±16.1%. <u>12-month results:</u> CD-TLR was 8.4%. Freedom from TLR: 90.6%. Primary patency was 72.6%. Assisted primary patency rate was 78.3%. Secondary patency rate was 78.9%. There was a 89.7% improvement in Rutherford class ≥ 1 category at 30 days and a 90.9% improvement at 12 months. Mean ABI increased from 0.7±0.2 at baseline to 0.9±0.2 (p<0.0001). There was an improvement in the ability to walk without impairment from 39.2% at baseline to 76%. Cumulative MAE rate: 11%. Minor amputation rate: 0.5%. There were no stent fractures.
Femoropopliteal territory, Supera interwoven nitinol stent vs BMS:			
Armstrong et al. (2019)[40] Restrospective study	871 patients with femoropopliteal lesions were enrolled	<u>Supera arm:</u> 118 patients were treated with Supera interwoven nitinol stent. <u>BMS arm:</u> 753 patients treated with BMS. To compare with the Supera group a propensity-score matched	Propensity score matched: MLL was 144.6±86.2 mm in BMS group vs 144.5±57.6 mm in Supera group, p=0.645; there were 67.0% chronic total occlusions in BMS group vs 59.3% in Supera group, p=0.512; there were 40.7% heavily calcified lesions in BMS group vs 41.5% in Supera group, p=0.895. There was an accelerated TLR rate at six months in BMS group, whereas there were constant TLR rates in Supera group over 12 months. Propensity score-matched data: there was a nonsignificant difference (p=0.08) in 1-year TVR (8.5% in Supera group compared to 16.1% in BMS group).

		data group was created with 118 patients treated with BMS.	At one year, TLR was significantly inferior in Supera group versus BMS group (8.5% vs 16.9%; p=0.04). In the matched groups: mortality at one year was 2.5% in Supera group versus 5.1% in BMS group (p=0.31).

Table XV - Plain old balloon angioplasty versus Stent studies, long version.

Femoropopliteal Territory:

Study	Patients	Intervention	Outcomes
Armstrong et al. (2014)[41] Observational cohort study	254 patients with intermitent claudication and CLI and *de novo* femoropopliteal lesions were enrolled.	139 patients had lesion length≤150 mm/short lesion: POBA arm - 75 patients were treated with POBA; Stent arm – 64 patients were treated with stent. 115 patients had lesion length>150 mm/long lesion: POBA arm - 31 patients were treated with POBA; Stent arm - 84 patients were treated with stent.	Short Lesions – MLL was 66±40 mm in POBA group vs 93±41 mm in Stent group (p<0.001). Total occlusions were identified in 30% os lesions in POBA 30 group vs 31% in Stent group; p=0.8. Moderate/severe calcification was identified in 19% of lesions in POBA group vs 20% in Stent group. Long Lesions – MLL was 247±59 mm in POBA group vs 257±59 mm in Stent group; p=0.4. Total occlusions were identified in 39% of lesions in POBA group vs 63% in Stent group; p=0.02. Moderate/severe calcification was identified in 18% of lesions in POBA group vs 39% in Stent group. 12-month results: Primary patency rates of short lesions were 66% in POBA group compared to 63% in Stent group (p=0.7), and for long lesions were 34% in POBA group compared to 49% in Stent group (p=0.006). Assisted primary patency for short lesions was 75% in POBA group compared to 77% in Stent group (p=0.8), and for long lesions was lower (45% in POBA group compared to 65% in Stent group; p=0.001). Secondary patency for short lesions was 76% in POBA group compared to 83% in Stent group (p=0.5), and for long lesions was 57% in POBA group compared to 78% in Stent group (p=0.004). ABI for short lesions at baseline was 0.58±0.17 in POBA group vs 0.66±0.24 in stent group (p=0.08); for long lesions at baseline was 0.55±0.15 in POBA group vs 0.53±0.16 in stent group (p=0.7); ABI for short lesions at 12 months was 0.82±0.23 in POBA group vs 0.85±0.21 in stent group (p=0.6); for long lesions at 12 months was 0.79±0.27 in POBA group vs 0.79±0.20 in stent group (p=0.9). Sustained clinical improvement at 12 months for short lesions was 79% in POBA group vs 61% in

			stent group (p=0.06); for long lesions was 75% in POBA group vs 62% in stent group (p=0.3). Major amputation at 12 months for short lesions was 7% in POBA group vs 2% in stent group (p=0.2); for long lesions was 13% in POBA group vs 7% in stent group (p=0.5).
Femoropopliteal territory, In-Stent Restenosis Lesions:			
Bosiers et al. (2015)[42] Prospective, randomized controlled trial	83 patients with with superficial femoral artery in-stent and Rutherford category 2 to 5 ischaemia were enrolled.	POBA arm: 44 patients. Stent arm: 39 patients were treated with the Viabahn endoprosthesis with PROPATEN Bioactive Surface – a helical wirewound nitinol stent lined with an ultra-thin expanded polytetrafluoroethylene tube and a heparin-bonded surfasse.	At baseline, MLL was 190.0±72.1 mm in POBA group vs 173.0±77.8 mm in Stent group (p=0.309). Occlusion was identified in 25.0% of lesions in POBA group vs 23.1% in Stent group (p=0.840). Baseline stenosis was 75.0% in POBA group vs 76.9% in Stent group (p=0.840). There were 25.0% calcified lesions in POBA group vs 33.3% in Stent group (p=0.447). <u>12-month results:</u> Primary patency rate: 74.8% in Stent arm versus 28.0% in POBA arm (p<0.001); excluding nine cases of POBA with bailout stenting, primary patency was 37.0% in POBA arm (p<0.001). Freedom from TLR: 79.9% in Stent arm versus 42.2% in POBA arm (p<0.001). There was a 100% improvement of the Rutherford classification by at least one category at 1 month, 97.1% at 6 months and 93.6% at 12 months in Stent arm versus 97.6%, 80.5%, and 87.8% in POBA arm, respectively. A significant difference between groups was only identified at six months (p=0.013). Survival rates were 91.9% in Stent arm versus 95.3% in POBA arm (p=0.383). There were no stent fractures.
Infrapopliteal territory:			
Brizzi et al. (2018)[43] Prospective, non-randomized study	282 patients/550 lesions with critical limb ischaemia	<u>BMS arm:</u> 169 patients/228 lesions were treated with stent (nitinol stent was used in 79 patients and balloon-expandable stent was used in 76 patients). <u>POBA arm:</u> 110 patients/309.	At baseline, MLL was 53.1±52.2 mm in POBA group compared to 39.4±37.7 mm in BMS group. There were 30.0% chronic total occlusions and 61.3% heavily calcified lesions. Primary patency rates were 91.2% at six months and 80.6% at 12 months in BMS group compared to 94.4% and 87.6% in POBA group (p=0.043). Secondary patency rates were 94.3% at six months and 89.2% and 12 months in BMS group compared to 96.9% and 93.6% in POBA group (p=0.071). Freedom from TLR rates were 88.4% at six months and 81.8% at 12 months in BMS group compared to 94.1% and 89.9% in POBA group (p=0.01). There was a Rutherford classification improvement to intermittent claudication (excluding patients that need repeated TLR or major amputation) in 76.1% patients. There was a Rutherford classification improvement to

			intermittent claudication including patients that need repeated TLR in 82.7% patients. At 1 year, there was a complete wound healing in 82.7% patients. Limb salvage rates were 94.3% at six months and 92.9% at 12 months in BMS group compared to 96.8% and 96.8% in POBA group (p=0.21). Survival rates were 96.3% at six months and 91.1% at 2 months in BMS group compared to 90.1% and 85.8% in POBA group (p=0.32). There was no significant difference between nitinol stents, balloon-expandable stents and POBA in limb salvage or survival rates at 6 and 12 months in the subgroup analysis. Although, there was a significant inferiority in terms of primary and secondary patency rates in balloon-expandable stent (primary patency at six months: 94.1% in nitinol stent group versus 88.2% in balloon-expandable stent group versus 94.4% in POBA group, and at 12 months: 84.0% versus 77.4% versus 87.6% (p=0.012); secondary patency at six months: 97.1% versus 88.2% versus 94.4% and at 12 months: 93.0% versus 77.4% versus 87.6%, respectively (p=0.003)). The same occurring for freedom from TLR rates at six months: 87.4% versus 89.2% versus 94.1%, and at 12 months: 82.3% versus 81.2% versus 89.9%, respectively (p=0.04).
Schulte et al. (2015) – EXPAND study[44] Prospective, randomized trial.	92 Patients with more than 50 years and stenotic or occlusive *de novo* atherosclerotic disease at the infrapopliteal territory with severe intermittent claudication or CLI (Rutherford category 3-5).	<u>Stent arm:</u> 45 patients were treated with Astron Pulsar and Pulsar-18 self-expanding nitinol stents. <u>POBA arm:</u> 47 patients, four of these patients had bailout stenting.	At baseline, MLL was 34.1±28.3 mm in Stent group versus 39.5±34.9 mm in POBA group (p=0.49). Preprocedure diameter stenosis was 77.5±17.3% in Stent group versus 75.1±18.2% in POBA group (p=0.58). <u>12-month results:</u> There was no statistically significant difference between groups in terms of patency. Binary restenosis: 20.0% in stent group versus 33.3% in POBA group. Freedom from TLR was 76.6% in stent group versus 77.6% in POBA group. In nitinol stent group there was a mean Rutherford category improvement from 4.3±1.0 (95% CI 4.0 to 4.5) to 1.5±1.9 (95% CI 0.9 to 2.2) versus from 4.2±1.0 (95% CI 4.0 to 4.5) to 2.1±2.1 (95% CI 1.3 to 2.8) in POBA group. Freedom from MAE rates: 65.6% in stent group versus 60.9% in POBA group. Kaplan-Meier estimates of mortality were 7.4% in stent group compared to 2.1% in POBA group, and amputation rates were 8.9% (major amputation rate was 6.7%) in stent group compared to 13.2% (major amputation rate was 8.7%) in POBA group.

Table XVI - Drug-eluting stent studies, long version.

Femoropopliteal territory:

Study	Patients	Intervention	Outcomes
Kang et al. (2016)[45] Restrospective, single-arm study.	63 Patients with femoropopliteal lesions (Rutherford class 2-6), including ISR lesions.	Zilver PTX stent (a nitinol self-expanding stent with a polymer-free paclitaxel coating (3µg/mm^2 dose of paclitaxel)).	At baseline, MLL was 218.9±128.3 mm, there were 69.8% total occlusions, stenosis was 95.4±8.5%, moderate to severe calcification was identified in 27.0% of lesions, and there were 36.5% ISR lesions. At 12 months, primary patency (Kaplan-Meier estimate): 66.7%. There was a superiority of primary patency in cases of TASC II A and B lesions (TASC II A/B: 100% versus TASC II C/D: 59.3% (p=0.035)), treatment with complete coverage (77.7% versus incomplete coverage: 44.1% (p=0.007)), native vessel disease (79.2% versus ISR: 47.6% (p=0.008)), or lesions <200mm (79.3% versus 200≤length<400mm: 68.2% versus length ≥400mm: 16.7% (p<0.001)). Amputation rate was 3.2%. Mortality was 3.2%.
Muller-Hulsbeck et al. (2016) – MAJESTIC Trial[13] Prospective, single-arm study	57 Patients with chronic, symptomatic lower limb ischaemia (Rutherford category 2-4), and stenotic, restenotic (from non-drug-coated balloon angioplasty only), or occlusive lesion(s).	Eluvia stent (self-expanding nitinol coated with paclitaxel at a nominal concentration of 0.167 µg/mm^2).	At baseline, MLL was 70.8±28.1 mm, there was a 86.3%±16.2% of diameter stenosis, there was 46% occluded lesions and 65% severe calcified lesions. <u>12-month results:</u> Primary patency was 94% (51/54) at nine months and 96% (49/51) at 12 months. Improvement in Rutherford category was sustained through 12 months: 81% asymptomatic (category 0), 13% with mild claudication (category 1). There was an improvement in ABI from 0.73±0.22 at baseline to 1.02±0.20 at 12 months. Composite MAE rate: 4% (all were TLR). 0% major amputations. No device/procedure related death. There were no stent fractures.
Muller-Hulsbeck et al. (2017) – MAJESTIC trial[46]			<u>Three-year results of the previous study:</u> At 24 months, primary patency (Kaplan–Meier estimate) was 83.5%, and assisted primary patency was 88.9%. At 36 months, overall freedom from TLR was 85.3%. At 36 months, freedom from TLR: patients with diabetes 82.4%, patients with severe calcification 85.5%, and patients with occlusions 84.3%. At 24 months, there was an improvement by at least one Rutherford categories in 90.6% of patients without TLR and in 96.2% of patients including the ones with TLR. There was an improvement in mean ABI: at baseline 0.73 ± 0.22, at 12 months 1.02 ± 0.20, at 24 months 0.93 ± 0.26. There were no amputations.

			There were no stent fractures.
Yokoi et al. (2016)[47] Prospective, single-arm study	907 Patients/1075 lesions with symptomatic PAD involving femoropopliteal lesions, including ISR lesions.	Zilver PTX stent (a nitinol self-expanding stent with a polymer-free paclitaxel coating (3µg/mm^2 dose of paclitaxel)).	At baseline, MLL was 14.7 cm, 41.6% had total occlusions, there was 18.6% in-stent restenosis, and diameter stenosis was 91.9 ± 10.7%. <u>12-month results:</u> Primary patency rate (Kaplan-Meier estimate): 86.4%. There were no reports of paclitaxel-related adverse events. Freedom from TLR (Kaplan-Meier estimate): 91.0%. Freedom from thrombosis (Kaplan-Meier estimate): 97.0%. Clinical improvement of ≥ 1 Rutherford class occurred in 84.3% patients. There was a significant improvement in mean ABI from 0.63 at baseline to 0.86 at 12 months. Amputation rate was 0.8%. All-cause mortality: 5.1%. Device- or procedure-related deaths: 0. Fracture rate: 1.5%.
Infrapopliteal territory:			
Bosiers et al. (2017)[48] Prospective, single-arm study	70 Patients with CLI (Rutherford category 4-5, with stenotic or occlusive *de novo* lesions or restenosis after POBA.	Stentys Stent System (a nitinol, self-expanding, 3 µg/mm^2 paclitaxel-coated stent).	At baseline, MLL was 17.2 mm. Occlusion was identified in 14.3% of lesions and stenosis was present in 85.7%. Calcification was found in 61.4% lesions. <u>12-month results:</u> Primary patency: six months 87.6%, 12 months 72.6%. At 12 months, freedom from TLR: 79.1%. Limb salvage: 98.5%. At 12 months, there was an improvement of at least one level in Rutherford category in 79.6% patients. There was a mean ABI improvement of 0.33 compared with baseline. Nonhealing wounds were presente in 12 of 61 patients. Survival rate (Kaplan-Meier estimates): 89.4%. There were no stent fractures identified.
Bosiers et al. (2017)[49] Prospective, single-arm study	60 Patients with rest pain or minor tissue loss (Rutherford 4-5) and with *de novo* or restenosis after POBA longer lesions (lesion length 3-10 cm).	Xience Prime stent (a 1 µg/mm^2 everolimus-coated stent, embedded in a non-erodible polymer).	At baseline, MLL was 47.40±25.06 mm. There were 45.0% patients with stenosis and 53.3% with occlusions. Calcification was present in 45.0% of patients. <u>12-month results:</u> Primary patency: 75.4 %. Secondary patency: 98.1%. Limb-salvage rate: 96.6%. Freedom from TLR: 84.9%. Improvement of Rutherford classification by ≥ 1 class occurred in 85.7% patients.

			Amputation rate: rare; freedom from amputation: 94.4%. Survival rate: 89.3%. There were no stent fractures.

Table XVII - Plain old balloon angioplasty versus Drug-eluting stent studies, long version.

Femoropopliteal territory:

Study	Patients	Intervention	Outcomes
Dake et al. (2016)[50] Prospective, randomized controlled trial	474 patients with Rutherford category ≥2 with *de novo* or restenotic lesions were randomized.	DES arm: 236 patients were treated with Zilver PTX, a 3µg/mm^2 paclitaxel-coated nitinol drug-eluting stent. POBA arm: 238 patients. 120 patients of the POBA arm with acute POBA failure were subsequently randomly assigned to provisional DES (61 patients) or provisional BMS placement (59 patients).	A comparison is made between primary DES vs POBA, overall DES (primary and provisional) vs standard care (POBA and provisional Zilver BMS), and provisional DES vs provisional BMS. At baseline, MLL was 63.2±40.5 mm in POBA group vs 66.4±38.9 mm in primary DES group, p=0.31. Diameter stenosis was 78.4±17.1% in POBA group vs 79.8±17.0% in primary DES group, p=0.38. Occlusion was present in 27.4% in POBA group vs 32.8% in primary DES group, p=0.20. Severe calcification was present in 34.9% in POBA group vs 37.3% in primary DES group, p<0.01. 5-year results: Primary patency rate: 64.9% in primary DES group versus 19.0% in POBA group (p<0.01, log-rank); 66.4% in overall DES group versus 43.4% in standard care group (p<0.01, log-rank); 72.4% in provisional DES group versus 53.0% in provisional BMS group (p=0.03, log-rank). TLR was 16.1% in primary DES group vs 28.0% in POBA group (p<0.01). Freedom from CD-TLR rate was 83.1% in overall DES group versus 67.6% in standard care group (p<0.01). Freedom from TLR rate was 84.9% in provisional DES versus 71.6% in provisional BMS (p=0.06). There was a significant improvement (p<0.05) in Rutherford classification, ABI, and Walking Impairment Questionnaire score from baseline in overall DES group and in standard care group. Freedom from persistente/worsening symptoms of ischaemia (clinical benefit) was 81.8% in provisional DES group versus 63.8% in provisional BMS group (p=0.02). All-cause mortality rate was 13.6%: 16.9% in primary DES group versus 10.2% in POBA group (p=0.03). There were no procedure/device related deaths. Cumulative rate of stent fractures was 1.9%.
Femoropopliteal territory, In-Stent Restenosis Lesions:			
Murata et al. (2016)[51]	228 patients with femoropopliteal	DES arm: 112 patients/119	A stratification of patients for analysis was made: by lesions with and without in-stent

Retrospective study	ISR were included.	lesions were treated with Zilver PTX stent (a nitinol self-expanding stent with a polymer-free paclitaxel coating (3µg/mm^2 dose of paclitaxel). POBA arm: 116 patients/133 lesions were treated with POBA.	occlusion (an independent predictor for recurrent ISR after POBA). To minimize the differences between groups at baseline study population was matched by lesion length for comparison between groups. At baseline, after extracting a matched population, in no in-stent occlusion group MLL was 11±7 cm in both arms (p=0.965); in in-stent occlusion group MLL was 21±7 cm in both arms (p=0.907). Chronic total occlusion was 40%. 12-month results: There were no significant differences between POBA and DES arms in non-occlusive ISR group in terms of MALE (24 in POBA group vs 33 in DES group, p=0.405) and recurrent restenosis (39 in POBA group vs 39 in DES group, p=0.996). In groups with in-stent occlusion, MALE rates were 29 in DES group versus 62 in POBA group (p=0.024) and recurrent restenosis was 86 in POBA group vs 51 in DES group (p=0.014).
Infrapopliteal territory:			
Study	**Patients**	**Intervention**	**Outcomes**
Spreen et al. (2016) – PADI trial[52] Randomized controlled trial	133 Patients/144 limbs with CLI (Rutherford category ≥4).	DES arm: 73 patients/74 limbs/121 lesions were treated with TAXUS Liberté, a balloon expandable paclitaxel-eluting stainless steel coronary stents (with a 1 µg/mm^2 dose of paclitaxel). POBA±BMS arm: 64 patients/66 limbs/91 lesions were treated with POBA and if necessary bail-out stenting with BMS.	At baseline, MLL was 23.1±21.8 mm in POBA±BMS group vs 21.1±19.3 mm in DES group. Preprucedure stenosis was 83.1±16.7% in POBA±BMS group vs 83.2±15.3% in DES group. 12-month results: Six months, patency rates in the modified-intention-to-treat (MITT) were 48.0% in DES group versus 35.1% in POBA±BMS group (p=0.096), and in the per-protocol analysis were 51.9% in DES group versus 35.1% in POBA±BMS group (p=0.037). At six months, DES group had a better composite clinical and morphological outcome when compared to POBA group in MITT (p=0.041) and per-protocol analysis (p=0.009). At six and 12 months there was a significant improvement from baseline (comparable between groups) in mean Rutherford category, ABI and toe pressure in both groups (p≤0.005). Mean Rutherford score at 6/12 months was 2.81/1.81 in POBA±BMS group vs 3.11/1.87 in DES group, p=0.49/p=0.90. Mean ABI at 6/12 months was 0.83/0.91 in POBA±BMS group vs 0.85/0.94 in DES group, p=0.74/p=0.74. Major amputation rate was 11.4% in DES group versus 20.5% in POBA±BMS group, p=0.066. Death occurred in 25.1% in POBA±BMS arm vs 23.3% in DES arm, p=0.52. At 12 months survival rate was 76.7% in DES group compared to 74.9% in POBA±BMS group.

Spreen et al. (2017) – PADI trial[53]			<u>Five-year results of the previous study:</u> Primary patency rates were significantly superior in DES group when compared to POBA±BMS group at one, three and four years of follow-up. Amputation- and event-free survival rates were 31.8% in DES group versus 20.4% in POBA±BMS group (p=0.043), and 26.2% in DES group versus 15.3% in POBA±BMS group (p=0.041), respectively. Amputation rate was 7.8% in POBA±BMS group vs 2.7% in DES group. Diabetes mellitus, higher Rutherford category, age and high or unmeasurable ankle-brachial index are factors associated with an increased risk of major amputation. 5-year survival rate was 37.0% in POBA±BMS group vs 37.7% in DES group (p=0.45). Death at five years was 48.4% in POBA±BMS group vs 43.8% in DES group.
Katsanos et al. (2016) – ACHILLES Trial[54] Prospective, randomized controlled trial Seeks to report the results of health-related quality of life, QALYs gain and wound healing.	200 Patients with symptomatic PAD (Rutherford class 3-5) with *de novo* and restenotic lesions.	<u>DES arm:</u> 99 patients/113 lesions were were treated with Cypher Select Sirolimus-Eluting Stent (coated with 1.4 µg/mm^2 of sirolimus). <u>POBA arm:</u> 101 patients/115 lesions.	At baseline, MLL was 26.9 ± 20.9 mm in DES group vs 26.8 ± 21.3 mm in POBA group, p=0.913. Chronic total occlusions were 81.3% in DES group vs 71.4% in POBA group, p=0.334. Pre-prucedure stenosis was 68.8 ± 19.3% in DES group vs 74.0 ± 19.0% in POBA group, p=0.039. <u>12-month results:</u> None of the rates of closed wounds were statistically significant, however a trend was identified in favor of DES group. There were similar differences that favor DES group at six weeks and at six months in termos of percentage of wound healing. At six months there was a significant superiority of DES group: 95% versus 60% in POBA group (p=0.048). At 12 months, DES group showed higher complete wound closure rates: 72.9% versus 55.6% in POBA group (p=0.088). There was an improvement in calculated weighted EQ-5D scores (to assess health-related quality of life) in both groups, but this was statistically significant only in DES group (p<0.0001). DES had a significant improvement in recorded weighted EQ-5D score (p<0.0001), the same not occurring for POBA group. DES placement produced statistically significant QALY gains at six weeks, six months, and 12 months, but POBA group only had significant QALY gains up to six months. In DES group 0.13 QALYs were gained at 12 months versus 0.03 QALYs gained in POBA group.

Table XVIII - Stent versus Drug-eluting stent studies, long version.

Femoropopliteal territory:

Study	Patients	Intervention	Outcomes
Jeon-Slaughter et al. (2018)[55] Retrospective study	958 patients with PAD were included (including ISR lesions)	DES arm: 174 patients were treated with Zilver PTX stent (a nitinol self-expanding stent with a polymer-free paclitaxel coating (3µg/mm^2 dose of paclitaxel). BMS arm: 784 patientes (the unmatched data) were treated with BMS, the propensity-score matched data of patients treated with BMS consisted of 174 patients.	At baseline, in the unmatched cohort, MLL was 162.5±118.7 mm in DES group vs 156.5±93.7 mm in Stent group, p=0.93. In the propensity-score matched data, MLL was 164.8±97.97 mm in the Stent group, p=0.50. In the unmatched cohort, chronic total occlusions were present in 63.79% in DES group vs 63.65% in Stent group, p=0.97. In the propensity-score matched data, chronic total occlusions were present in 63.79% in Stent group, p>0.99. In the unmatched cohort, there were 32.18% heavily calcified lesion in DES group vs 53.57% in Stent group, p<0.001. In the propensity-score matched data, 32.76% in Stent group, p=0.91. In the unmatched cohort, there were 26.44% ISR lesions in DES group vs 10.97% in Stent group, p<0.001. In the propensity-score matched data, there were 27.59% ISR lesions in Stent group, p=0.81. 12-month results: Unmatched cohort: there were no significant differences in procedures in both groups – TLR was 9.2% in DES group versus 13.8 in stent group (p=0.10), TVR was 9.8% in DES group versus 13.8% in stent group (p=0.16). Propensity-score matched data: DES group had significantly inferior TLR and TVR versus stent group – TLR was 9.2% in DES group versus 18.4% in stent group (p=0.01), TVR was 9.8% in DES group versus 18.4% in stent group (p=0.02). Propensity-score matched data: there was a statistically significant inferior risk of TLR in DES group versus BMS group (p=0.03), and an inferior TVR risk in DES group with an attenuated statistical significance (p=0.08), there wasn't a significantly inferior risk of target-limb revascularization in DES group compared to stent group at one year (p=0.29). There was a significantly superior all-cause mortality rate in DES group versus stent group in both unmatched (5.3% compared to 1.8%; p=0.03) and propensity-score matched data (5.3% compared to 1.3%; p=0.04).
Femoropopliteal territory, In-Stent Occlusion lesions:			
Tomoi et al. (2016)[56] Retrospective, nonrandomized, observational study	1433 patients/1851 limbs underwent endovascular therapy with provisional self-expanding nitinol stent implantation for	DES arm: 21 of these 123 patients were treated with a 3 µg/mm^2 paclitaxel DES. BMS arm: 79 of these 123 patients were	At baseline, MLL was 221.5±83.9 mm in Stent group vs 254.8±61.2 mm in DES group, p=0.09. 24-month results: Freedom from recurrent ISR rate (Kaplan-Meier estimated): 79.3% in DES group vs 20.2% in stent group (p<0.001). There was an inferior likelihood of recurrent ISR with the use of DES.

	de novo femoropopliteal lesions, during follow-up ISO was observed in 123 patients/154 lesion.	treated with BMS.	Freedom from recurrent TLR was 85.7% in DES group versus 27.1% in stent group (p<0.001). Freedom from reocclusion was 85.9% in DES group versus 42.5% in stent group (p=0.006). Freedom from MALE was 85.7% in DES group versus 25.3% in stent group (p<0.001). ABI at baseline was 0.41±0.22 in stent group vs 0.45±0.29 in DES group, p=0.45, and postprocedure was 0.76±0.16 in stent group vs 0.90±0.17 in DES group, p<0.001.

Table XIX - Drug-eluting balloon versus Drug-eluting stent studies, long version.

Infrapopliteal territory:

Study	Patients	Intervention	Outcomes
Siablis et al. (2014) – IDEAS trial[57] Prospective randomized controlled trial	50 patients with Rutherford classification of 3-6 with long infrapopliteal lesions (>70 mm in length) were randomized.	<u>DEB arm:</u> 25 patients/25 arteries/25 limbs were treated with IN.PACT Amphirion DEB (coated with 3.5 µg/mm^2 of paclitaxel). <u>DES arm:</u> 25 patients/30 arteries/27 limbs were treated with zotarolimus-eluting stent (Resolute stent, with 1.6 µg/mm^2 of zotarolimus), sirolimus-eluting stent (Cypher stent, with 1.4 µg/mm^2 of sirolimus), or everolimus-eluting stent (Promus stent, with 1 µg/mm^2 of everolimus).	At baseline, MLL was 127 ± 46.5 mm in DES group vs 148 ± 56.7 mm in DEB group, p=0.14. Chronic total occlusions were present in 23% in DES group vs 12% in DEB group, p=0.31. Baseline stenosis was 86.8 ± 10.1% in DES group vs 85.3 ± 8.9% in DEB group, p=0.58. Severe calcification was identified in 50% in DES group vs 44% in DEB group, p=0.64. <u>Six-month results:</u> Total vessel reocclusion occurred in 15.8% in DEB group compared to 20.0% in DES group (p=0.72). Binary restenosis was significantly inferior in DES group (28% versus 57.9% in DEB; p=0.0457). LLL was similar: 1.35 ± 0.2 mm in DES group compared to 1.15 ± 0.3 mm in DEB group (p=0.62). TLR wasn't significantly different (7.7% in DES group versus 13.6% in DEB group; p=0.65). Median Rutherford class at baseline was 4.5 in both groups (p=0.69) and at six months was 1 in both groups, p=0.87. At six months complete, partial and unchanged wound healing were similar in both groups. Major amputation occurred in one limb in DEB group (1 of 25) vs two in DES group (2 of 27; p=1.00). Two deaths (2 of 25) in DEB group vs 3 in DES group (3 of 25; p=1.00). There were no stent fractures in DES group.

Table XX - Drug-coated devices versus Non-drug-coated devices studies, long version.

Femoropopliteal territory:

Study	Patients	Intervention	Outcomes
Secemsky et al. (2019)[58] Retrospective, cohort study Seek to evaluate differences in all-cause mortality between patients who were treated with drug-coated devices vs non–drug-coated devices for femoropopliteal artery revascularization.	16560 Patients were enrolled.	Non-drug-coated devices arm: 10571 of these patients were treated with BMS or POBA. Drug-coated devices arm: 5989 patients were treated with DES or DEB.	Median follow-up: 389 days. Cumulative incidence of all-cause mortality was inferior in drug-coated devices versus non–drug-coated devices through 600 days postprocedure (32.5% compared to 34.3%, respectively; p=0.007). Survival was identical for DEB versus POBA (p=0.06) and for DES versus BMS (p=0.56), when stratified by type of device. Patients with CLI: cumulative incidence of mortality through 600 days was inferior in drug-coated devices group (38.1% compared to 40.1% in non–drug-coated devices group; p=0.04) (there was no difference in survival between device). Patients without CLI: a statistical difference was not observed in cumulative incidence of survival between drug-coated devices and non–drug-coated devices groups (26.5% compared to 29.0%, respectively; p=0.07). A relationship between drug-coated devices and all-cause mortality wasn't identified (with multivariable adjustment) (adjusted HR, 0.97; p=0.43); adjusted mortality risk showed no difference between DEBs alone treatment (p=0.17) or DES with/without DEB treatment (p=0.48); and among patients with CLI (p=0.09) and without CLI (p=0.20).