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Medical technology consultation supporting documentation

The enclosed documents were considered by the NICE medical technologies advisory committee (MTAC) alongside the assessment report and assessment report overview.

Documents included are:

1. Adoption scoping report – produced by the adoption team at NICE to provide a summary of levers and barriers to adoption of the technology within the NHS in England.

2. Sponsor submission of evidence – the evidence submitted to NICE by the notifying company.

3. Expert questionnaires – expert commentary gathered by the NICE team on the technology.

4. EAC correspondence log – a log of all correspondence between the external assessment centre (EAC) and the company and/or experts during the course of the development of the assessment report.

5. EAC additional work – during discussions at the committee meeting on 16 February 2018, the committee requested further information to support their decision-making. This work was then presented at the subsequent meeting on 23 March 2018.

Please use the bookmarks included in this PDF file to navigate to each of the above documents.

Medicines and Technologies Programme
Adoption Scoping Report MT 336
The IN.PACT drug-coated balloon for peripheral arterial disease

SUMMARY – for MTAC1 meeting

Adoption Levers

- Improved patency rates
- Reduced occurrence of restenosis
- Slower and less complicated occlusions in the event that restenosis does occur, than if a stent was used
- Reduced frequency and number of subsequent therapeutic interventions
- Noticeable longer term benefits

Adoption Barriers

- Cost: The cost of the technology is reported to be tenfold the cost of plain balloon PTA
- Commissioning: There is confusion amongst the clinical community about the inclusion of the technology on the high-cost medical device tariff
- Clinician acceptance: There is reported lack of knowledge and awareness of the technology

1. Introduction

The Adoption team has collated information from healthcare professionals working within NHS organisations who have experience of using the IN.PACT drug coated balloon (DCB).

This adoption scoping report includes some of the benefits and difficulties that may be faced by organisations when planning to adopt the technology into routine NHS use.

2. Contributing organisations

The adoption team spoke to 4 NHS clinicians, 3 consultant radiologists and 1 consultant vascular surgeon, all of whom have used IN.PACT as their DCB of choice

for more than 2 years. Three contributors work in the NHS in England, and one in Wales.

3. Use of IN.PACT drug-coated balloon (DCB) in practice

Organisation	Contributor	DCB used in organisation	First used IN.PACT	Annual usage (organisation)
A	Consultant Vascular and Endovascular Surgeon	IN.PACT & other DCBs	2014	40
B	Consultant Radiologist	Only IN.PACT	2015	54
C	Consultant Radiologist	Only IN.PACT	2014	24
D	Consultant Vascular and Interventional Radiologist	Only IN.PACT	2014	30

All contributors with experience of the device said that:

- this technology does not replace plain balloon percutaneous transluminal angioplasty (PTA)
- a plain balloon PTA is used initially and the decision to use an adjunct such as a stent, DCB or both is made during the procedure, by the individual clinician, following an angiogram
- there has been no change to the patient pathway with this technology
- the use of DCB is not widespread in the UK (mainly due to cost), unlike organisations throughout Europe where it is proactively encouraged,
- NHS organisations have developed local guides on which patients may require a DCB [see patient selection]
- there is national variation on post-surgery antiplatelet regime, for both DCB and stent
- there is anecdotal evidence that people who have DCB do better overall compared with those who have plain balloon angioplasty or stents

4. Reported benefits

The benefits of adopting IN.PACT as reported to the adoption team by the healthcare professionals using the technology are:

- improved patency rates compared with plain balloon angioplasty but equal to stents
- reduced occurrence of restenosis compared with plain balloon angioplasty and stents
- slower and less complicated occlusions in the event that restenosis does occur, than if a stent was used
- reduced frequency and number of subsequent therapeutic interventions required
- noticeable longer term benefits
- reduction in patients' 'resting pain'
- improved ulcer healing
- good alternative when stenting is not a viable option, such as severe critical ischaemia, severe tissue loss, or if there is an arteriovenous fistula
- long term cost saving due to reduced therapeutic interventions required however it is recognised by contributors that an actual financial benefit will not be realised by the organisation.

Contributors report that patients with complex presentations have had variable responses and in these situations there is uncertainty if the technology will be of benefit.

5. Levers and barriers to adoption

The key considerations for adoption highlighted through discussions with expert contributors are:

Cost

Cost was cited as the largest barrier to wide scale adoption by all contributors. The technology is reported to be of a similar cost to stents at £500 - £600. Contributors report this is tenfold the cost of plain balloon PTA which costs £40-£60.

One contributor reported that the company have agreed to refund the cost of the device if restenosis occurs within 2 years of the procedure.

There were varied reports in level of difficulty encountered when trying to implement or increase local usage of the technology. Contributors reported that the available clinical effectiveness evidence for IN.PACT aided this process but lack of clarity regarding the tariff for the technology is a barrier [see Commissioning].

The contributor from Wales reported the high cost and lack of a tariff as an adoption issue specific to organisations in Wales.

Some organisations have adopted IN.PACT as the only DCB used in order to provide uniformity in treatment and gain better negotiation on price. Other organisations stock a selection of DCBs to cater for individual clinician preferences.

Access to sufficient stock was compromised where there was reduced shelf space due to competing technologies. Liaison with the unit manager regarding the available evidence can support the decision to increase the stock of IN.PACT and reduce stocks of comparative technologies.

Commissioning

Contributors report that the device is paid for directly by their CCG or health board.

Confusion exists amongst the clinical community regarding the tariff and whether the technology is included as part of the new NHS England system for buying and supplying high-cost medical devices in specialised services.

The adoption team have identified that drug-eluting peripheral angioplasty balloons are listed on the National tariff payment system 2017/18 and 2018/19 high cost devices list (annexe a, tab 13A). All currently listed high cost devices are part of the new system for buying and supplying high-cost medical devices in specialised services. This is likely to be a lever to adoption.

Care pathway

All contributors advised that the technology is used as an adjunct to plain balloon PTA when additional therapeutic intervention is indicated. For patients with complex presentations clinicians may choose to use a stent in addition to a DCB such as IN.PACT.

One contributor reported this technology provides a final treatment option for patients with particularly complex presentations who are at risk of limb amputation.

Procedure time is reported to be up to 5 minutes longer than with plain balloon PTA alone, but remains shorter than when using a stent.

Patient selection

Contributors report that patients with complex presentations have had variable responses. This group are the most challenging and there is uncertainty when using the technology if it will be of benefit.

Contributors report some locally informal guidelines for patient selection. The final decision is made by the lead clinician during the procedure.

One contributor reported that young people, aged 50-60 years with PVD are a particular group which can benefit from this technology.

Examples provided by contributors of when a DCB would be used instead of a stent are:

- if there is a long sessile serrated adenoma (SSA) lesion or a popliteal lesion
- if there is severe or critical ischaemia or tissue loss and it is not feasible to stent
- if they have put in a stent and the stent has had a further lesion in it (in stent restenosis)
- if there is a recurrence of claudication
- if the patient has a complex presentation and no other vascular option the clinician may make a clinical decision to use both a stent and DCB. Factors influencing this decision would be disease diffusion and progression. This indication is as a last treatment option before amputation

Contributors reported that the majority of angioplasties are plain balloon PTA. One contributor reported doing 3 IN.PACT DCBs in a week out of approximately 23 angioplasties, another reported using IN.PACT 2-3 times a month but stated they would like to use it as first line for all angioplasties if cost wasn't an issue.

Although not reported as a barrier to adoption one contributor reported a failed procedure with IN.PACT potentially due to poor patient compliance with post

treatment exercise and antiplatelet regime, indicating patient compliance as important to the success of the technology.

Clinician confidence / acceptance

Clinician confidence in IN.PACT was not cited as a barrier by experienced users. Although in one organisation, some of the clinicians are continuing to do plain balloon PTA alone and do not use DCB for any patient group, indicating that clinician confidence may be a barrier.

One contributor cited awareness of the technology as a potential barrier however also noted that increasingly the referring clinicians are specifically requesting for a DCB to be used in angioplasty procedures, indicating increasing awareness.

Training

No additional training is required but the user has to be aware of, and comply with, some special considerations when handling the balloon and avoid touching the balloon as this could cause some of the drug to wash off. This information is easily available from the company.

In addition it is recommended that the time taken to insert the technology into the artery should be less than 3 minutes from getting it into the patient. This is because as soon as it enters the blood stream there is potential that the drug will be absorbed. This is reported as achievable and not an issue.

Other

Contributors report variation and lack of national guidelines in post-surgery antiplatelet therapy.

During interviews with contributors the following 4 regimes following angioplasty with DCB were identified, each subject to local clinical judgement and decision:

- 2 months dual antiplatelet, aspirin and clopidogrel, lifetime clopidogrel
- 6 months dual antiplatelet if clinically indicated due to level of risk
- 6 months dual antiplatelet, aspirin and clopidogrel, lifetime aspirin
- single-antiplatelet therapy, clopidogrel

6. Comparators

Contributors had previous experience of using the Lutonix 035 balloon and the Freeway 035. Whilst these technologies were reported to be cheaper reasons cited for changing to IN.PACT were availability of evidence and a greater range of sizes of the balloons for different guidewires.

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Medical Technologies Evaluation Programme

Sponsor submission of evidence

Evaluation title: The IN.PACT drug-coated balloon for femoro-popliteal peripheral arterial disease

Sponsor: Medtronic

Date sections A and B submitted: 4th October 2017

Date section C submitted: 1st November 2017

August 2011 (Version 1.1)

Contents

List of tables and figures

Glossary of terms

Term	Definition
PTA	Percutaneous Transluminal Angioplasty
TLR	Target Lesion Revascularization
PAD	Peripheral Arterial Disease
DCB	Drug-Coated Balloon
TVR	Target Vascular Revascularization
PVD	Peripheral Vascular Disease
ABI	Ankle–Brachial Index
6MWT	Six-Minute-Walking Test
ACD	Absolute Claudication Distance
BA	Balloon Angioplasty
BMS	Bare Metal Stent
BTK	Below -The-Knee (Lesion)
CAD	Cad: Coronary Artery Disease
CD-TLR	Clinically Driven Target Lesion Revascularization
CFA	Common Femoral Artery
CHF	Congestive Heart Failure
CI	Confidence Interval
CLI	Clinical Limb Ischemia
CTO	Chronic Total Occlusion
CVD	Cerebrovascular Disease
DCB	Drug-Coated Balloon Angioplasty
DEB	Drug-Eluting Balloon
DES	Drug-Eluting Stent
DUS	Duplex Ultrasound
EQ-5D	5-Dimension Health-Related Quality of Life Questionnaire
EVBT	Endovascular Brachytherapy
FP	Femoropopliteal
FPA	Femoropopliteal Artery
HIC	High-Income Countries
HTA	Health Technology Assessment
ISR	In-Stent Restenosis
LLL	Late Lumen Loss
LMIC	Low-Income or Middle-Income Countries
MAE	Major Adverse Events
MIB	Medtech Innovation Briefing
MLD	Minimum Lumen Diameter
MTG	Medical Technology Guidance
PA	Popliteal Artery
PEB	Paclitaxel-Eluting Balloon
POBA	Plain Old Balloon Angiography
PPA	Proximal Popliteal Artery
PSVR	Peak Systolic Velocity Ratio
QOL	Quality of Life
RBP	Rated Burst Pressure
RCT	Randomized Clinical Trial
SD	Standard Deviation
SFA	Superficial Femoral Artery
TER	Target Extremity Revascularisation
WIQ	Walking Impairment Questionnaire

Section A – Decision problem

Section A describes the decision problem, the technology and its clinical context. There is also information about ongoing studies, regulatory information and equality issues.

Sponsors should submit section A before the full submission (for details on timelines, see the NICE document 'Guide to the Medical Technologies Evaluation Programme process', available from www.nice.org.uk/mt

1 Statement of the decision problem

The decision problem is specified in the final scope issued by NICE. The decision problem states the key parameters that should be addressed by the information in the evidence submission. All statements should be evidence based and directly relevant to the decision problem.

Table A 1 Statement of the decision problem

	Scope issued by NICE	Variation from scope	Rationale for variation
Population	People with femoro-popliteal peripheral arterial disease undergoing revascularization for intermittent claudication.	None	N/A
Intervention	Percutaneous transluminal angioplasty (PTA) with IN.PACT drug coated balloon (Pacific or Admiral versions) (with or without bailout stenting)	None	N/A
Comparator(s)	Percutaneous transluminal angioplasty (PTA) with a non-drug coated balloon (with or without bailout stenting)	None	N/A
Outcomes	The outcome measures to consider include: • Intermittent claudication symptom severity (including scores) • Quality of life and functional capability • Rate of hospitalization • Target lesion revascularisation rates • Primary patency rates • Repeat intervention rates • Rates of vessel thrombosis • Angiographically determined late lumen loss • Device-related adverse events	None	N/A
Cost analysis	Costs will be considered from an NHS and personal social services perspective. The time horizon for the cost analysis will be sufficiently long to reflect any differences in costs and consequences between the technologies being compared. Sensitivity analysis will be undertaken to address uncertainties in the model parameters, which will include scenarios in which different numbers and combinations of devices are needed.	None	N/A
Subgroups to be considered	People presenting with in-stent restenosis People with restenosis or recurrence.	None	N/A
Special considerations, including issues related to equality	PAD is more common in older people and men and people with diabetes. Diabetes is more common in people from certain ethnic groups and race is a protected characteristic under the Equalities Act. Some people with PAD may have symptoms severe enough to limit their mobility and may be considered disabled under the Equalities Act.	None	N/A

2 Description of technology under assessment

2.1 Give the brand name, approved name and details of any different versions of the same device.

Brand Name: IN.PACT™ DCB

Approved name: IN.PACT™ Admiral – IN.PACT™ Pacific

Versions: IN.PACT™ Admiral – IN.PACT™ Pacific

The IN.PACT DCB Technology encompasses two DCBs, IN.PACT Admiral DCB and IN.PACT Pacific DCB. The primary difference between IN.PACT Admiral and IN.PACT Pacific is the guidewire compatibility: IN.PACT Admiral is compatible with a 0.035" guidewire and IN.PACT Pacific is compatible with a 0.018" guidewire. This difference provides the physician with expanded options to increase the likelihood of successfully reaching the targeted lesion without impacting the device performance or drug delivery at the target lesion. Thus, the clinical evidence generated with IN.PACT Admiral can be convincingly used to demonstrate the safety and effectiveness of IN.PACT Pacific to deliver paclitaxel to the target lesion in the peripheral artery. The below table details the similarities and differences between IN.PACT Admiral DCB and IN.PACT Pacific DCB.

Table A 2 Comparison of IN.PACT Admiral and IN.PACT Pacific

<table>
<tr><th></th><th>IN.PACT Admiral</th><th>IN.PACT Pacific</th></tr>
<tr><td>Indications for Use</td><td>The IN.PACT Admiral is indicated for percutaneous transluminal angioplasty (PTA) in patients with obstructive disease of peripheral arteries, including in-stent restenosis (ISR), and with obstructive lesions of native or synthetic arteriovenous dialysis fistulae.</td><td>Indicated for percutaneous transluminal angioplasty (PTA) in patients with obstructive disease of peripheral arteries.</td></tr>
<tr><td>Balloon Coating</td><td colspan="2">FreePac formulation (API - paclitaxel and Excipient – urea)</td></tr>
<tr><td>Paclitaxel Drug Dose</td><td colspan="2">2.5-5.0 µg/mm²</td></tr>
<tr><td>Balloon Diameters</td><td colspan="2">4.0, 5.0, 6.0, 7.0 mm</td></tr>
<tr><td>Balloon Working Lengths</td><td>20, 40, 60, 80, 120, 150 mm</td><td>20, 40, 60, 80, 120 mm</td></tr>
<tr><td>Balloon Wrap Configuration</td><td colspan="2">Ø 4.0 mm: 3-fold configuration
Ø 5.0 – 7.0 mm: 6-fold configuration</td></tr>
<tr><td>Catheter Useable Lengths</td><td>40, 80, and 130 cm</td><td>80 and 130 cm</td></tr>
<tr><td>Shaft Design</td><td>Over the Wire (Bilumen)</td><td>Over the Wire (Coaxial)</td></tr>
<tr><td>Guidewire Compatibility</td><td>0.035"</td><td>0.018"</td></tr>
<tr><td>Introducer Sheath Compatibility</td><td><table><tr><td>Ø 4.0 mm</td><td>5 F</td></tr><tr><td>Ø 5.0 – 6.0 mm</td><td>6 F</td></tr><tr><td>Ø 7.0 mm</td><td>7 F</td></tr><tr><td>Ø 8.0 mm</td><td>8 F</td></tr></table></td><td><table><tr><td>Ø 4.0 – 6.0 mm</td><td>5 F</td></tr><tr><td>Ø 7.0 mm</td><td>6 F</td></tr></table></td></tr>
<tr><td>Nominal Pressure</td><td>8 atm</td><td>7 bar[1]</td></tr>
<tr><td>Rated Burst Pressure</td><td>14 atm for all sizes</td><td><table><tr><td></td><td colspan="2">Balloon length [mm]</td></tr><tr><td>Balloon Ø [mm]</td><td>40</td><td>60/80/120</td></tr><tr><td>4.0</td><td>20 bar</td><td>14 bar</td></tr><tr><td>5.0</td><td>20 bar</td><td>14 bar</td></tr><tr><td>6.0</td><td>16 bar</td><td>14 bar</td></tr><tr><td>7.0</td><td>12 bar</td><td>12 bar</td></tr></table></td></tr>
<tr><td>Balloon Material</td><td colspan="2">Polyamide</td></tr>
<tr><td>Radiopaque Markers</td><td colspan="2">Platinum- Iridium Alloy marker bands</td></tr>
<tr><td>Sterilization Method</td><td colspan="2">EtO</td></tr>
</table>

[1] The conversion rate of bar to atm is: 1 bar = 0.9869 atm.

2.2 What is the principal mechanism of action of the technology?

The IN. PACT Drug Coated Balloon (DCB) catheter is a combination angioplasty device and acute drug delivery system engineered to treat peripheral artery disease through two modes of operation: 1) mechanical dilatation of the stenotic vessel by angioplasty, and 2) acute delivery of an anti-restenotic drug (paclitaxel) to the affected region (stenosis or occlusion) of a vessel. The components of the DCB include a balloon catheter coated with a drug matrix comprised of a drug and drug carrier (drug matrix FreePac®).

The primary mode of action is attributable to the balloon's mechanical dilatation of the vessel lumen while the secondary mode of action consists of drug delivery and application of the anti-proliferative drug paclitaxel to the vessel wall, which augments the effectiveness of the mechanical dilatation by preventing restenosis of the vessel. Paclitaxel is the ideal choice of anti-proliferative agent for a drug coated balloon as it is a potent cytotoxic agent that is hydrophobic and lipophilic, properties that lead to quick absorption of the drug by the vessel wall with prolonged duration of antiproliferation effects. Its hydrophobic properties prevent paclitaxel from being washed-out from the balloon surface during its transit through the vessel lumen until it is inflated and the balloon surface touches the vessel wall (to begin transfer of the drug to tissue). Its lipophilic properties facilitate rapid tissue absorption of the paclitaxel and sustained retention of low-levels of drug for extended and durable neointimal inhibition. The drug carrier (excipient) urea facilitates drug absorption (uptake) into the vessel wall to provide a single dose of antiproliferative therapy. Urea serves as a molecular spacer that increases paclitaxel surface exposure and facilitates its transfer to the vessel wall. Urea is one of the most common substances in human serum, is synthesized in the liver, used by the body to detoxify and excrete nitrogen derived from proteins and has very low toxicity and no hypersensitivity reactions. Therefore, paclitaxel with urea excipient is an ideal drug-carrier combination given its potency, quick absorption and retention in tissue - important characteristics since DCB angioplasty requires short-term and rapid deployment of drug in a single application.

The IN.PACT DCB catheter has been specifically designed with an automated coating process to ensure uniform application of drug to the polyamide balloon surface, and adequate coating adhesion of the drug-excipient matrix, optimal drug release upon mechanical inflation of the balloon, and a specialised drug-excipient formulation that ensures that the drug is rapidly transferred to tissue within 60 seconds, optimizing function as a drug-based angioplasty device.

While there are many DCBs by different manufacturers in the marketplace, the designs of these devices are different in drug dose, drug solubility, as well as the excipient used in the drug coating formulation. As a result, the efficacy of these devices varies significantly, with some even proven to have no difference in efficacy in comparison to plain balloon angioplasty. Published clinical studies have demonstrated that DCB with urea-based excipient (IN.PACT DCB) has more favourable clinical and economic outcomes in comparison to other DCBs. This is due to a difference in target lesion revascularisation (TLR) rate for IN.PACT DCB in comparison to other DCBs (*Katsanos et al. 2016*[1]). It is therefore critical that each DCB is being assessed with its own clinical evidence as there is no class effects and all DCBs show different levels of clinical efficacy.

3 Clinical context

3.1 Provide a brief overview of the disease or condition for which the technology is being considered in the scope issued by NICE.

The target patient population for DCB treatment is similar to the target patient population for existing endovascular interventions including PTA with bail-out stenting, and comprises patients who satisfy the clinical and anatomic criteria/indications for endovascular treatment.

Peripheral arterial disease (PAD) results primarily from progressive narrowing of one or more arteries in the lower extremities resulting in decreased blood flow and oxygen to the affected tissues and muscles. The most common symptomatic presentation of chronic PAD is claudication /pain in legs, defined as exertional discomfort related to exercise-induced ischemia of the lower extremities. In the most severe form of the disease (critical limb ischemia), the disease is defined by ischemic pain at rest and breakdown of the skin resulting in ulceration or gangrene which may ultimately lead to amputation. PAD is associated with significant levels of morbidity and mortality. All individuals with PAD face a risk of progressive limb ischemic symptoms as well as 3-fold increase in risk of mortality and major cardiovascular events compared to those without PAD. PAD is also a major contributor to health care costs because of the high rates of morbidity and impairment in quality of life which require treatment to reduce symptoms and prevent or treat ischemic events. Symptomatic PAD is

associated with greater vascular-related hospitalisation rates and associated costs than even coronary artery disease (CAD) and cerebrovascular disease (CVD), largely due to high rates of recurrent rehospitalisation and repeat revascularization procedures. Symptomatic PAD has a major detrimental impact on patients' quality of life and ability to carry out daily activities, often with vocational or life-style limiting functional disability due to intermittent claudication, comparable to that of major diseases like congestive heart failure (CHF) and chronic lung disease.

In 2013, the global distribution of PAD was studied in a systematic review of population prevalence with the use of an ankle–brachial index (ABI) ≤0.9 as an indicator of disease (*Fowkes et al, 2013*[2]). Prevalence was compared between populations living in high-income countries (HIC) and those living in low-income or middle-income countries (LMIC). In high-income countries, the prevalence of PAD seemed to be similar in men and women, and to increase consistently with age from around 5% at age 45–49 years to 18% at age 85–89 years. Between 2000 and 2010 the number of cases worldwide was estimated to increase by around one-quarter to approximately 200 million, but with a higher relative increase in LMICs (29%) than in high-income countries (13%).

3.2 Give details of any relevant NICE or other national guidance or expert guidelines for the condition for which the technology is being used. Specify whether the guidance identifies specific subgroups and make any recommendations for their treatment. If available, these should be UK based guidelines.

The most recent HTA to include peripheral DCB was published in 2014, since which the evidence base has significantly improved as outlined in this submission.

In February 2014, NIHR published their Health Technology Assessment "Enhancements to angioplasty for peripheral arterial occlusive disease: systematic review, cost-effectiveness assessment and expected value of information analysis". This HTA concluded that the evidence showed a significant benefit to reducing restenosis rates for self-expanding and DESs, stent-graft, EVBT and DCBs. If it is assumed that patency translates into beneficial long-term clinical outcomes, then DCB and bail-out DES are most likely to be cost-effective enhancements to PTA.

In November 2014, this HTA was then reviewed as part of the 2-year surveillance review for CG 147: Lower limb peripheral arterial disease - diagnosis and management. The evidence updates concluded that "…drug coated balloons may reduce the need for revascularisation, after conventional angioplasty, but further research describing the impact on symptoms, quality of life and re-intervention is needed. Therefore, no impact on NICE CG147 is expected."

The most recent surveillance of CG147 in 2017 also concluded that the treatment section of the guideline would not be updated to include the use of drug-eluting technologies. Appendix-A-Summary of new evidence from surveillance stated that "Topic experts indicated that there is an increasing body of evidence which supports the use of drug eluting technologies in the management of femoropopliteal disease and it would be incorrect if NICE was to continue with the existing recommendations." However, the committee decided to await the results of the BASIL 3 Trial before updating this section of CG147. This indicates that there is wide variability in clinical evidence across different drug-eluting technologies in terms of efficacy, follow-up and study quality and therefore each technology should be reviewed in isolation.

There has also been a MIB published (MIB 72) for a DCB by a different manufacturer, Lutonix, however very limited economic evidence (one US conference presentation) is referenced within this briefing. Combined with IN.PACT DCB's superior evidence for clinical and patient outcomes, this submission looks more thoroughly at the UK-specific health system/economic benefits of IN.PACT DCB versus both the standard of care and other DCBs.

3.3 Describe the clinical pathway of care that includes the proposed use of the technology.

NICE guideline CG147 accurately describes the recommended clinical pathway of care for PAD patients. This submission recommends the primary use of IN.PACT DCB in place of PTA with or without bailout BMS, which is currently recommended within the treatment section of the clinical guideline.

3.4 Describe any issues relating to current clinical practice, including any uncertainty about best practice.

The clinical pathway of care is consistent with NICE CG147 however this submission recommends the primary use of IN.PACT DCB instead of PTA with or without bailout BMS as currently recommended.

3.5 Describe the new pathway of care incorporating the new technology that would exist if the technology was adopted by the NHS in England.

The clinical pathway of care is consistent with NICE CG147 however this submission recommends the primary use of IN.PACT DCB instead of PTA with bailout BMS as currently recommended.

3.6 Describe any changes to the way current services are organised or delivered as a result of introducing the technology.

Implementing IN.PACT™ DCB will not change the way current services are organised or delivered.

3.7 Describe any additional tests or investigations needed for selecting or monitoring patients, or particular administration requirements, associated with using this technology that are over and above usual clinical practice.

There are no additional tests or investigations needed for patient selection or monitoring. Current clinical practice will differentiate surgical candidates for treatment with IN.PACT™.

3.8 Describe any additional facilities, technologies or infrastructure that need to be used alongside the technology under evaluation for the claimed benefits to be realised.

Facility, technology and infrastructure requirements for IN.PACT™ DCB are consistent with other interventions currently in use in the NHS (eg. PTA).

3.9 Describe any tests, investigations, interventions, facilities or technologies that would no longer be needed with using this technology.

There will be no changes in tests, investigations, interventions, facilities and technologies.

3.10 Describe how the NHS in England can disinvest from tests, investigations, interventions, facilities or technologies described in section 3.9 that would no longer be needed with using this technology.

There will be no changes in tests, investigations, interventions, facilities and technologies.

4 Regulatory information

4.1 Provide PDF copies of the following documents:

- instructions for use
- CE mark certificate or equivalent UK regulatory approval such as EC declaration of conformity
- quality systems (ISO 13485) certificate (if required).

4.2 Does the technology have CE mark for the indication(s) specified in the scope issued by NICE? If so, give the date that authorisation was received. If not, state current UK regulatory status, with relevant dates (for example, date of application and/or expected approval dates).

The IN.PACT Admiral DCB has CE Mark as a class III medical device.
This CE Mark was received March 12, 2009.

The IN.PACT Pacific DCB has CE Mark as a class III medical device. This CE Mark was received in March 2011.

IN.PACT Admiral received expansion approval for in-stent restenosis on January, 09 2015 and for arteriovenous (AV) fistula on January, 04 2016.

4.3 Does the technology have regulatory approval outside the UK? If so, please provide details.

The IN.PACT™ Admiral is approved in Australia, Belarus, Bolivia, Bosnia-Herzegovina, Brazil, Canada, Colombia, Costa Rica, Ecuador, Egypt, European Economic Area and Switzerland, Guatemala, Hong Kong, India, Indonesia, Israel, Japan, Jordan, Macedonia, Mexico, New Zealand, Perú, Philippines, Russia, Saudi

Arabia, Singapore, Serbia, South Korea, Syria, Taiwan, Thailand, Turkey, Turkmenistan, Ukraine, Uruguay, USA, Venezuela.

The IN.PACT™ Pacific is approved in Belarus, Bolivia, Bosnia-Herzegovina, Colombia, Costa Rica, Ecuador, Egypt, European Economic Area and Switzerland, Guatemala, Hong Kong, Israel, Macedonia, New Zealand, Perú, Philippines, Russia, Saudi Arabia, Singapore, Serbia, Syria, Taiwan, Thailand, Turkey, Ukraine.

4.4 If the technology has not been launched in the UK provide the anticipated date of availability in the UK.

IN.PACT DCB was launched in the UK in March 2009.

4.5 If the technology has been launched in the UK provide information on the use in England.

UK sales records indicate that [redacted] procedures were performed using IN.PACT DCB from 1st May 2016 to 31st April 2017.

5 Ongoing studies

5.1 Provide details of all completed and ongoing studies on the technology from which additional evidence relevant to the decision problem is likely to be available in the next 12 months.

- IN.PACT Global Full Clinical Cohort at 12 months
- IN.PACT Global Long Lesion Imaging Cohort at 12 months
- IN.PACT Global ISR Imaging Cohort at 12 months
- IN.PACT Global CTO Imaging Cohort at 12 months
- IN.PACT Global Severe Calcium Cohort at 12 months
- IN.PACT Global Standard vs. Wider Use at 12 months
- IN.PACT SFA at 36 months

5.2 If the technology is, or is planned to be, subject to any other form of assessment in the UK, please give details of the assessment, organisation and expected timescale.

There are no additional planned assessments of the IN.PACT™ DCB in the UK.

6 Equality

NICE is committed to promoting equality of opportunity and eliminating unlawful discrimination on the grounds of age, disability, gender reassignment, race, religion or belief, sex, and sexual orientation, and to comply fully with legal obligations on equality and human rights.

Equality issues require special attention because of NICE's duties to have due regard to the need to eliminate unlawful discrimination, promote equality and foster good relations between people with a characteristic protected by the equalities legislation and others.

Any issues relating to equality that are relevant to the technology under assessment should be described. This section should identify issues described in the scope and also any equality issues not captured in the final scope.

Further details on equality may be found in section 11.3 of this document.

6.1.1 Describe any equality issues relating to the patient population and condition for which the technology is being used.

There are no equality issues related to the use of the IN.PACT™ DCB in any appropriately selected, clinically qualified patient.

6.1.2 Describe any equality issues relating to the assessment of the technology that may require special attention.

There are no known equality issues relating to the assessment of the technology that may require special attention.

6.1.3 How will the submission address these issues and any equality issues raised in the scope?

There are no issues related to equality.

Section B – Clinical evidence

7 Published and unpublished clinical evidence

Section B requires sponsors to present published and unpublished clinical evidence for their technology.

Sponsors should read section 6 of the Medical Technologies Evaluation Programme methods guide on published and unpublished evidence, available from www.nice.org.uk/mt

All statements should be evidence-based and directly relevant to the scope. Reasons for deviating from the scope should be clearly stated and explained in table A1.

Sponsors are required to submit section B in advance of the full submission (for details on timelines, see the NICE document 'Guide to the Medical Technologies Evaluation Programme process', available from www.nice.org.uk/mt

7.1 Identification of studies

Published studies

7.1.1 Describe the strategies used to retrieve relevant clinical data from the published literature. Exact details of the search strategy used should be provided in section 10, appendix 1.

A manual and electronic research has been performed. The literature search has been limited to published studies, available in full- text and only publications in English has been considered.

The search terms that have been used individually or combined include "Percutaneous Transluminal Angioplasty", "popliteal", "femoral", "balloon", "IN.PACT", "paclitaxel" and a string of words previously proposed. To enhance the sensibility of our search, we will not include words related to the outcomes of interest. In addition, previously published relevant systematic reviews were identified for reference lists which were hand searched to verify if all publications of interest had been included from the database searches.

The search strategy used is shown in Section 1, Appendix 1.

Unpublished studies

7.1.2 Describe the strategies used to retrieve relevant clinical data from unpublished sources.

A manual search was carried out to include conference presentations that reported on 3-year data from the IN.PACT SFA RCT. This data is yet to be published in manuscript format. Additionally, unpublished data from the IN.PACT Global registry is reported in this submission as a result of a second manual search for any conference presentations that reported data from this registry.

7.2 Study selection

Published studies

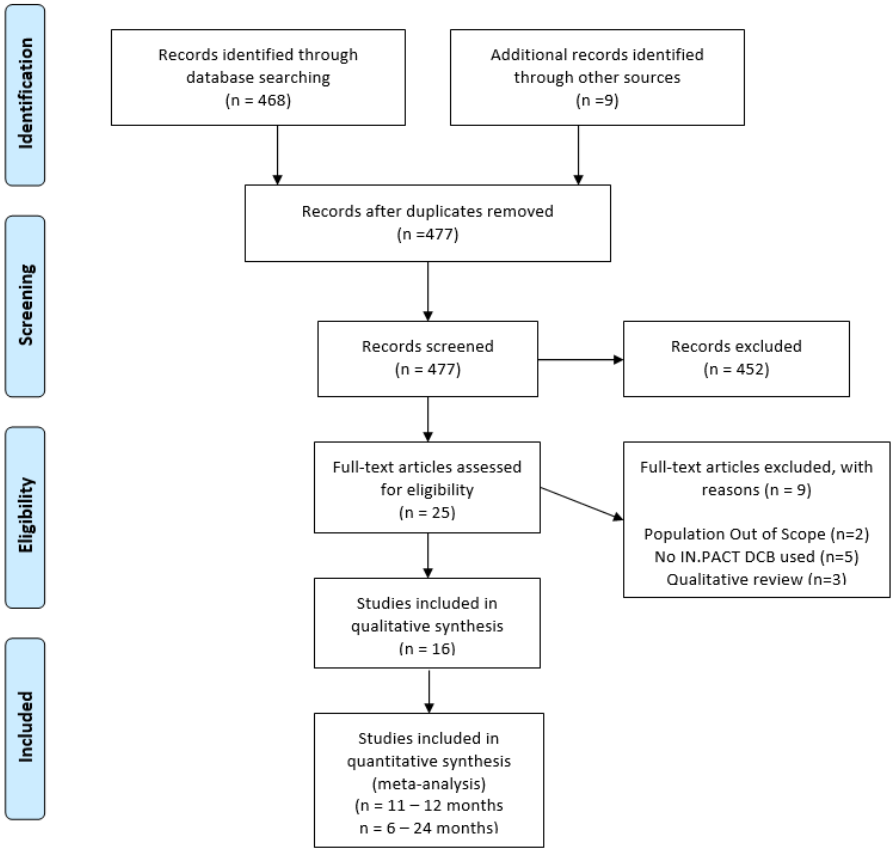
7.2.1 Complete table B1 to describe the inclusion and exclusion criteria used to select studies from the published literature. Suggested headings are listed in the table below. Other headings should be used if necessary.

Table B 1 Selection criteria used for published studies

Inclusion criteria	
Population	Patients with peripheral arterial disease with intermittent claudication as an indication for invasive treatment.
Interventions	Percutaneous Transluminal Angioplasty (PTA) with IN.PACT™ Admiral™ or IN.PACT™ Pacific™ Paclitaxel-coated Balloon Catheter
Outcomes	The outcome measures to consider include: • Primary Patency • Target Lesion Revascularization (TLR) • Target Vessel Revascularization (TVR) • Thrombosis • Restenosis • Target limb major amputation • Procedure or device-related adverse events • Survival
Study design	Randomized Clinical Trials (RCTs) Observational Studies Case series
Language restrictions	English only
Search dates	1995 – July 2017
Exclusion criteria	
Population	• Patients without Peripheral Artery Disease • Patients with below-the-knee lesion (BTK)
Interventions	• Patients NOT treated with DCB or • Patients treated with DCB but not with IN.PACT™ Admiral or IN.PACT™ Pacific • Mixed population
Outcomes	None of the following are reported: • Primary Patency • Target Lesion Revascularization (TLR) • Target Vessel Revascularization (TVR) • Thrombosis • Restenosis • Target limb major amputation • Procedure or device-related adverse events • Survival
Study design	Case report, in-vitro studies, not human studies
Language restrictions	Non-English
Search dates	Prior to 1995

7.2.2 Report the numbers of published studies included and excluded at each stage in an appropriate format.

Figure 1 – PRISMA Flow-chart – Published studies



Unpublished studies

7.2.3 Complete table B2 to describe the inclusion and exclusion criteria used to select studies from the unpublished literature. Suggested headings are listed in the table below. Other headings should be used if necessary.

Table B 2 Selection criteria used for unpublished studies

Inclusion criteria	
Population	Patients with peripheral arterial disease with intermittent claudication as an indication for invasive treatment.
Interventions	Percutaneous Transluminal Angioplasty (PTA) with IN.PACT™ Admiral™ or IN.PACT™ Pacific™ Paclitaxel-coated Balloon Catheter
Outcomes	The outcome measures to consider include: • Primary Patency • Target Lesion Revascularization (TLR) • Target Vessel Revascularization (TVR) • Thrombosis • Restenosis • Target limb major amputation • Procedure or device-related adverse events • Survival
Study design	Randomized Clinical Trials (RCTs) Observational Studies
Language restrictions	English only
Search dates	2009 – July 2017
Exclusion criteria	
Population	• Patients without Peripheral Artery Disease • Patients with below-the-knee lesion (BTK)

Interventions	• Patients NOT treated with DCB or • Patients treated with DCB but not with IN.PACT™ Admiral or IN.PACT™ Pacific • Mixed population
Outcomes	None of the following are reported: • Primary Patency • Target Lesion Revascularization (TLR) • Target Vessel Revascularization (TVR) • Thrombosis • Restenosis • Target limb major amputation • Procedure or device-related adverse events • Survival
Study design	Case report, in-vitro studies, not human studies
Language restrictions	Non-English
Search dates	No exclusion

7.2.4 Report the numbers of unpublished studies included and excluded at each stage in an appropriate format.

7 conference presentations were identified, of which all were included.

Complete list of relevant studies

The sponsor should provide a PDF copy of all studies included in the submission if the sponsor is either the copyright owner or has adequate copyright clearance to permit the intended use by NICE. If the sponsor does not have sufficient copyright clearance, they are asked to submit references or links only, or details of contacts for unpublished studies. For unpublished studies for which a manuscript is not available, provide a structured abstract about future journal publication. If a structured abstract is not available, the sponsor must provide a statement from the authors to verify the data provided.

7.2.5 Provide details of all published and unpublished studies identified using the selection criteria described in tables B1 and B2.

Table B 3 List of relevant published studies

Primary study reference	Study name (acronym)	Population	Intervention	Comparator
Tepe et al 2015[3]– 12 Months results	IN.PACT SFA Trial	Patients with symptomatic SFA and/or proximal popliteal artery disease and moderate to severe intermittent claudication or ischemic rest pain (Rutherford 2–4), stenosis of 70% to 99% with lesion lengths between 4 and 18 cm or occlusion with lengths 10 cm involving the superficial femoral and proximal popliteal arteries.	IN.PACT Admiral DCB	Standard PTA balloon
Laird et al 2015[4] – 24 Months results	IN.PACT SFA Trial	Same as above	Same as above	Same as above
Bague et al 2017[5]	PLAISIR Trial	Symptomatic patients with femoropopliteal in-stent restenosis.	IN.PACT Admiral DCB	No comparator group

Krankenberg et al 2015[6]	FAIR Trial	Patients with SFA ISR of up to 20 cm in length.	IN.PACT Admiral DCB	Admiral Xtreme PTA balloon
Liistro et al 2013[7]	DEBATE-SFA Trial	Patients with either intermittent claudication or critical limb ischemia (CLI)	IN.PACT Admiral DCB	Standard PTA balloon
Micari et al 2012[8]- 12 Months results	Multicentre Italian Registry	Adult patients diagnosed with peripheral artery disease for claudication or rest pain as per Rutherford classes 2 through 4.	IN.PACT Admiral DCB	No comparator group
Micari et al 2013[9]- 24 Months results	Multicentre Italian Registry	Same as above	Same as above	Same as above
Micari et al 2016[10]- 12 Months results	SFA-Long study	Adult patients diagnosed with peripheral artery disease for claudication or rest pain (Rutherford class 2 to 4).	IN.PACT Admiral DCB	No comparator group
Micari et al 2017[11]- 24 Months results	SFA-Long study	Same as above	Same as above	Same as above
Schmidt et al 2016[12]	Real-world Registry	Patients undergoing treatment of complex femoropopliteal lesions (defined as de novo atherosclerotic lesions ≥10 cm or restenosis after previous endovascular treatment for de novo disease) using DCBs.	IN.PACT Pacific or IN.PACT Admiral DCB	No comparator group
Stabile et al 2012[13] – 12 months results	-	Patients undergoing percutaneous transluminal angioplasty (PTA) for the treatment of superficial-femoral artery in-stent restenosis (SFA-ISR).	IN.PACT DEB	No comparator group
Virga et al 2014[14] – 24 months results	-	Same as above	Same as above	Same as above
Grotti et al 2016[15]	DEBATE-ISR Study	Symptomatic diabetic patients with claudication or critical limb ischemia (CLI) undergoing treatment for femoropopliteal in-stent restenosis (ISR).	IN.PACT Admiral DEB	Conventional balloon angioplasty (BA)
Werk et al 2012[17]	PACIFIER Trial	Patients with symptomatic femoro popliteal atherosclerotic disease undergoing percutaneous transluminal angioplasty.	IN.PACT Pacific DEB	Uncoated Pacific Xtreme balloon
Debing et al 2016[18]	Belgian diabetic IN.PACT Trial	Diabetic patients with symptomatic peripheral arterial disease (PAD)	IN.PACT Pacific or IN.PACT Admiral DCB	Plain old balloon angiography (POBA)

Fanelli et al 2012[19]	DEBELLUM Trial	Patients with symptomatic PAD undergoing percutaneous transluminal angioplasty	IN.PACT Admiral DEB	Conventional balloon angioplasty (BA)

Table B 4 List of relevant unpublished studies

Data source	Study name (acronym)	Population	Intervention	Comparator
Drug-Coated Balloon Treatment for Patients with Intermittent Claudication: Insights from the IN.PACT Global Full Clinical Cohort Presented by M. Jaff at VIVA 2016 Estimated Completion date: December 2020	IN.PACT Global Full Clinical Cohort at 12 months	Rutherford Class 2,3 and 4 Lesion(s) in SFA/PA Single or multiple stenosis or occlusions of any lesion length ≥2cm De novo or restenotic (including ISR) At least one infrapopliteal run-off vessel	IN.PACT Admiral DCB	N/A
Drug Coated Balloon Treatment for Patients with Intermittent Claudication: New Insights from the IN.PACT Global Study Long Lesion (≥15cm) Imaging Cohort Presented at EuroPCR 2015 by D. Scheinert Estimated Completion date: December 2020	IN.PACT Global Long Lesion Imaging Cohort at 12 months	Patients with long lesions in SFA and/or popliteal artery (≥15cm) (Average lesion length 26.40cm ±8.61cm)	IN.PACT Admiral DCB	N/A
Drug-coated Balloon treatment for patients with lifestyle limiting claudication: New insights from the IN.PACT Global Study in-stent restenosis imaging cohort Presented at VIVA 2015 by M. Brodmann Estimated Completion date: December 2020	IN.PACT Global ISR Imaging Cohort at 12 months	De novo In-stent Restenosis Imaging Cohort with pure ISR lesions.	IN.PACT Admiral DCB	N/A
IN.PACT Global Drug-Coated Balloon for Treatment of Chronic Total Occlusions in the SFA Presented at Charing Cross 2014 by G.Tepe Estimated Completion date: December 2020	IN.PACT Global CTO Imaging Cohort at 12 months	Patients with chronic total occlusion (CTO ≥5 cm) in SFA and/or popliteal artery (Mean lesion length 22.83 ± 9.76 cm)	IN.PACT Admiral DCB	N/A

DCB in Calcification: An Assessment of Complex Lesions (long lesions, chronic occlusions & severe calcium) from the IN.PACT Global Study Presented by F. Fanelli at Charing Cross 2017 Estimated Completion date: December 2020	IN.PACT Global Severe Calcium Cohort at 12 months	Post-hoc analysis of patients with complex lesions including severe calcium	IN.PACT Admiral DCB	N/A
12-month Outcomes of Standard versus Wider Usage of Drug-Coated Balloons: IN.PACT Global Study Presented by Ansel, G at Charing Cross 2017 Estimated Completion date: December 2020	IN.PACT Global Standard vs. Wider Use at 12 months	Substantiate consistent and durable performance of the IN.PACT Admiral DCB in a real-world population with complex lesions by comparing results from an ad-hoc analysis of IN.PACT Global Clinical Cohort Standard DCB use vs Wider DCB use	IN.PACT Admiral DCB	N/A
Drug-coated balloons show superior three-year outcomes vs. angioplasty: Results from IN.PACT SFA randomized trial. Presented by Krishan P at VIVA 2016	IN.PACT SFA at 36 months	Patients with symptomatic SFA and/or proximal popliteal artery disease and moderate to severe intermittent claudication or ischemic rest pain (Rutherford 2–4), stenosis of 70% to 99% with lesion lengths between 4 and 18 cm or occlusion with lengths 10 cm involving the superficial femoral and proximal popliteal arteries.	IN.PACT Admiral DCB	Standard PTA balloon

7.2.6 State the rationale behind excluding any of the published studies listed in tables B3 and B4.

None of the above-mentioned studies have been excluded.

7.3 Summary of methodology of relevant studies

7.3.1 Describe the study design and methodology for each of the published and unpublished studies using tables B5 and B6 as appropriate. A separate table should be completed for each study.

Table B 5 Summary of methodology for randomised controlled trials

Study name	**INPACT SFA** [Tepe et al 2015[3] (12 months); Laird et al 2015[4] (24 Months); Krishan 2016 (36 months - Unpublished)]
Objectives	To investigate the longer-term outcomes of a paclitaxel-eluting DCB compared to PTA for femoropopliteal lesions.
Location	INPACT SFA I: Europe INPACT STA II: United States
Design	**Multicentre, single blinded, randomized, controlled trial** The trial was prospectively designed to be conducted in 2 phases: IN.PACT SFA I (in Europe) and IN.PACT SFA II (in the United States), which are jointly referred to as IN.PACT SFA. The 2 phases occurred sequentially in time with enrollment completed in the IN.PACT SFA I phase before the initiation of the IN.PACT SFA II phase. The IN.PACT SFA Trial was prospectively analyzed according to a single statistical analysis plan
Duration of study	**Enrollment**

	• Phase I: between September 2010 and April 2011; • Phase II: between April 2012 and January 2013; **Follow-up** • Up to 5 years
Sample size	331 (150 IN.PACT SFA I + 181 IN.PACT SFA II)
Inclusion criteria	***Key* Inclusion Criteria include the following:** • Documented ischemia with Rutherford classification 2, 3, or 4; • Life expectancy, in the Investigator's opinion, of at least 12 months; • Target lesion is in the superficial femoral artery and/or proximal popliteal artery above the knee, located in the arterial segment starting at least 1 cm beyond the Common Femoral Artery (CFA) bifurcation between the superficial and profunda femoral arteries (proximal anatomical landmark) to the distal P1 segment of the popliteal artery at the level of the proximal edge of the patella (distal anatomical landmark); • Angiographic evidence that target lesion consists of a single *de novo* or non-stented restenotic lesion (or tandem lesions or a combination lesion as defined) that is: --70% - 99% occluded with total lesion length ≥40 mm and **≤180 mm** (by visual estimate); or --100% occluded with total lesion length **≤100 mm** (by visual estimate). ***NOTES:*** I. Combination lesions (a non-occlusive lesion that includes a totally occluded segment along its length) will be eligible *provided that* (1) the combined lesion length is≥ 40 mm and ≤180 mm **and** (2) *the totally occluded segment is not greater than 100 mm in length.* II. Tandem (or "adjacent") lesions may be enrolled providing they meet all of the following criteria: ▪ Separated by a gap of ≤ 30 mm (3 cm); ▪ Total combined lesion length meets requirements (including 30 mm gap); ▪ Able to be treated as a single lesion. Minor differences between the IN.PACT SFA I phase and the IN.PACT SFA II phase eligibility criteria exist and include subtle variations in concomitant inflow and contralateral limb treatment, along with differences in predilatation requirements.
Exclusion criteria	**Key Exclusion Criteria include the following:** • Contralateral SFA/PPA disease requiring treatment in the same setting as index procedure; • Any major (e.g., cardiac, peripheral, abdominal) intervention (including in the contralateral SFA/PPA) performed within 30 days prior to enrollment, or planned within 30 days post index procedure; • Presence of a second lesion in the target vessel that requires treatment but does not meet the definition of "tandem lesions"; • Failure to successfully cross the target lesion with a guide wire (successful crossing means tip of the crossing device is distal to the target lesion in the absence of flow-limiting dissections or perforations); • Target lesion is an in-stent restenosis, a post-DEB restenosis, or has been previously treated with bypass surgery; • Pre-randomization dilatation resulted in a major (≥Grade D) flow-limiting dissection (observed on 2 orthogonal views) or residual stenosis >70% and translesional peak gradient > 10mm Hg
Method of randomisation	2:1 randomized DCB:PTA (An Interactive Voice Response System with the use of a method of permuted blocks was used).
Method of blinding	The patients and the trial sponsor were blinded to the treatment assignments through the completion of all 12-month follow-up evaluations. The independent core laboratories and clinical events committee will remain blinded to the treatment assignments throughout the 60-month follow-up duration.

<table>
<tr><td></td><td>Because of the visual difference between the IN.PACT DCB and standard PTA balloon, treating physicians, research coordinators, and catheterization laboratory staff were not blinded to the treatment assignment. Treating physicians, research coordinators, and catheterization laboratory staff received detailed and specific instructions and training on how to preserve the patients' blinded status.</td></tr>
<tr><td>Intervention(s) (n =) and comparator(s) (n =)</td><td>IN.PACT DCB (n=220) – Standard PTA (n=111)</td></tr>
<tr><td>Baseline differences</td><td>The following patients and lesions' characteristics were different between the two groups:
<table>
<tr><th>Characteristic</th><th>DCB</th><th>PTA</th><th>P-value</th></tr>
<tr><td colspan="3">No. of patent runoff vessels, % (m/n)</td><td rowspan="5">0.042</td></tr>
<tr><td>0</td><td>3.3 (7/212)</td><td>4.5 (5/112)</td></tr>
<tr><td>1</td><td>13.7 (29/212)</td><td>26.8 (30/112)</td></tr>
<tr><td>2</td><td>41.5 (88/212)</td><td>33.0 (37/112)</td></tr>
<tr><td>3</td><td>41.5 (88/212)</td><td>35.7 (40/112)</td></tr>
<tr><td>Predilatation, % (m/n)</td><td>96.4 (212/220)</td><td>85.6 (95/111)</td><td><0.001</td></tr>
<tr><td># of treated balloons/pt,</td><td>1.4±0.7</td><td>1.1±0.3</td><td><0.001</td></tr>
</table></td></tr>
<tr><td>Duration of follow-up, lost to follow-up information</td><td>1 Y [Tepe et al 2015[3]]:
DCB: 10 patients withdrawn the consent before 1Y FU and 3 patients were Lost to Follow-Up (total at 1Y: 207)
PTA: 1 patient withdrawn the consent before 1Y FU and 3 patients were Lost to Follow-Up (total at 1Y: 107)

2 Y [Laird et al 2015[4]]:
DCB: 17 patients withdrawn the consent, 16 patients died and 17 patients were Lost to Follow-Up (total at 2Y: 170)
PTA: 6 patients withdrawn the consent, 1 patient died and 10 patients were Lost to Follow-Up (total at 2Y: 94)</td></tr>
<tr><td>Statistical tests</td><td>Continuous variables are described as mean±standard deviation and were compared by Student t tests. Dichotomous and categorical variables were described as counts and proportions and were compared by the Fisher exact test or Cochran-Mantel-Haenszel modified scores, respectively.
Time-to-event data for primary patency and CD-TLR were analyzed by the Kaplan-Meier method. The difference in the survival curves between groups was assessed by using log-rank statistics.
For all endpoints, the level of statistical significance was set at $p < 0.05$ with no correction for multiple comparisons.</td></tr>
<tr><td>Primary outcomes (including scoring methods and timings of assessments)</td><td>1 Y [Tepe et al 2015[3]]:
Primary patency at 12 months following the index procedure, defined as freedom from clinically driven target lesion revascularization (CD-TLR) and restenosis as determined by a duplex ultrasonography–derived peak systolic velocity ratio of ≤2.4.
Safety end points included 30-day device- and procedure-related death, all-cause death, major target limb amputation, and target vessel thrombosis.

2 Y [Laird et al 2015[4]]:
Primary patency, defined as freedom from CD-TLR or freedom from restenosis as determined by duplex ultrasonography-derived peak systolic velocity ratio #2.4; and CD-TLR, defined as reintervention at the target lesion due to symptoms or decrease in ankle brachial index (ABI) ≥20% or >0.15 when compared with post-procedure baseline ABI. In addition, primary patency at 24 months plus the 30-day follow-up window was analyzed. The primary composite safety endpoint was freedom from device- and procedure-related death through 30 days and freedom</td></tr>
</table>

	from target limb major amputation and clinically driven target vessel revascularization (CD-TVR) through 24 months. **3 Y [unpublished but presented at VIVA 2016]:** Primary patency, defined as freedom from CD-TLR or freedom from restenosis as determined by duplex ultrasonography-derived peak systolic velocity ratio #2.4; and CD-TLR, defined as reintervention at the target lesion due to symptoms or decrease in ankle brachial index (ABI) ≥20% or >0.15 when compared with post-procedure baseline ABI. In addition, primary patency at 36 months plus the 30-day follow-up window was analyzed. The primary composite safety endpoint was freedom from device- and procedure-related death through 30 days and freedom from target limb major amputation and clinically driven target vessel revascularization (CD-TVR) through 36 months.
Secondary outcomes (including scoring methods and timings of assessments)	**1 Y [Tepe et al 2015[3]]:** Acute procedural success, target vessel revascularization at 12 months, and primary sustained clinical improvement (defined as freedom from target limb amputation, target vessel revascularization, and increase in Rutherford class at 12 months). Functional assessments included general appraisal through administration of a 5-dimension (EQ-5D) health-related quality-of-life questionnaire and specific evaluation of walking capacity by using a Walking Impairment Questionnaire. A Six-Minute Walk Test was additionally conducted in the IN.PACT SFA II phase only. **2 Y [Laird et al 2015[4]]:** The major adverse event rate (death from any cause, CD-TVR, major target limb amputation, and thrombosis at target lesion site) at 24 months. Cumulative binary restenosis, the individual components of the major adverse event composite, and primary sustained clinical improvement (defined as freedom from target limb amputation, freedom from target vessel revascularization, and increase in Rutherford class at 24 months). Functional assessments included general appraisal through administration of the EuroQOL (EQ)-5D, a 5-dimension generic health status questionnaire, and specific evaluation of walking capacity using the Walking Impairment Questionnaire. A 6-min walk test was additionally conducted in the IN.PACT SFA II. **3 Y [unpublished but presented at VIVA 2016]:** The major adverse event rate (death from any cause, CD-TVR, major target limb amputation, and thrombosis at target lesion site) at 36 months. Cumulative binary restenosis, the individual components of the major adverse event composite, and primary sustained clinical improvement (defined as freedom from target limb amputation, freedom from target vessel revascularization, and increase in Rutherford class at 36 months). Functional assessments included general appraisal through administration of the EuroQOL (EQ)-5D, a 5-dimension generic health status questionnaire, and specific evaluation of walking capacity using the Walking Impairment Questionnaire. A 6-min walk test was additionally conducted in the IN.PACT SFA II.
Study name	**FAIR Trial** [Krankenberg et al 2015[6]]
Objectives	To compare drug-coated balloon angioplasty (DCB) and standard balloon angioplasty (POBA) in terms of restenosis prevention for superficial femoral artery (SFA) in-stent restenosis (ISR).
Location	Germany
Design	Prospective, multicentre, block-randomized, nonblinded trial
Duration of study	Enrollment: between January 2010 and November 2012 Follow-up: 12 months

Sample size	119 patients
Inclusion criteria	Patients were eligible for enrolment if they had an SFA ISR of up to 20 cm in length. Diameter stenosis had to be at least 70% by duplex ultrasound (DUS). At baseline, the popliteal artery and 1 of the infrapopliteal (below the knee) vessels had to be patent (≤50% stenosis) for sustained distal runoff. Clinically, the patients had to suffer from chronic limb ischemia of Rutherford category 2 to 4.
Exclusion criteria	Major exclusion criteria were an untreated ipsilateral iliac artery stenosis, ongoing dialysis treatment, and treatment with oral anticoagulants other than antiplatelet agents.
Method of randomisation	After a parallel-group, block randomization with a block size of 10 and an allocation ratio of 1:1, patients were assigned to either DCB or POBA.
Method of blinding	The trial had a nonblinded design
Intervention(s) (n =) and comparator(s) (n =)	DCB (n=62); POBA (n=57)
Baseline differences	No baseline characteristic difference was statistically significant (p<0.05).
Duration of follow-up, lost to follow-up information	The patients were followed for 12 months, during which 2 patients from DCB group (3.2%) and 3 patients from POBA group (5.3%, p=0.67) died. At 12 months follow-up, data from 45 patients of the DCB and 44 patients of the POBA group, were available.
Statistical tests	Differences between continuous variables were assessed with the Student t test or Kolmogorov-Smirnov test. Differences between categorical variables were assessed with the Fisher exact test, χ2 test, and Kruskal-Wallis test. Kaplan-Meier analysis was performed to estimate freedom from TLR. The Mantel-Cox log-rank test was run to test whether the survival functions differ. A value of P<0.05 indicated statistical significance. Statistical analyses were performed with SPSS 16.0.
Primary outcomes (including scoring methods and timings of assessments)	The primary study endpoint was the cumulative incidence of binary recurrent ISR at 6 months.
Secondary outcomes (including scoring methods and timings of assessments)	Secondary procedural end points were primary angiographic success, cumulative incidence of binary recurrent restenosis at 12 months, and Kaplan- Meier estimate of freedom from TLR based on recurrent restenosis ≥50%/re-occlusion and clinical signs through the 6- and 12-month follow-up (not including procedural bailout). Secondary hemodynamic end points were ankle-brachial index at 6 and 12 months and immediate and sustained hemodynamic success (ankle-brachial index improvement of ≥0.15 from baseline to discharge and to 6 and 12 months without the need for TLR). Secondary clinical end points were sustained clinical improvement by ≥1 Rutherford category, relative and absolute claudication distance at 6 and 12 months, and major adverse vascular events, defined as all-cause death, myocardial infarction, major amputation, major bleeding, and thrombosis or surgical intervention related to the target limb.
Study name	**DEBATE-SFA Trial** [Liistro et al 2013[7]]
Objectives	To investigate the safety and efficacy of Paclitaxel-eluting balloon (PEB) angioplasty compared with pre-dilation with conventional uncoated balloon catheters (PTA) before systematic implantation of a self-expanding nitinol bare-metal stent (BMS) in terms of reduction of restenosis in a population with FPA artery stenosis or occlusion.
Location	Italy
Design	Prospective, single-centre, randomized, parallel-group, open-label involving the blinded evaluation of endpoints trial.
Duration of study	Enrollment: between November 2010 and November 2011 Follow-up: 12 months

Sample size	104 patients (110 lesions in 110 limbs)
Inclusion criteria	• Age ≥ 18 years; • De novo stenosis ≥ 50% or occlusion of at least 40 mm in length located in the superficial femoral artery or popliteal artery; • Presence of a clear healthy segment between the lesion in the superficial femoral artery and common femoral artery and between the popliteal and tibioperoneal trunk; • Presence of at least 1 patent tibial vessel with distal runoff (below-the-knee; • Artery was considered patent if free from obstructive lesions determining angiographic stenosis >70%).
Exclusion criteria	• Life expectancy <1 year; • Contraindication for combined antiplatelet therapy; known allergy to nickel or paclitaxel; • Need for major amputation at the time of enrolment; • Failure to recanalize intended below-the-knee arteries in CLI patients at risk of major amputation.
Method of randomisation	1:1 randomization was performed by block randomization (blocks of 10 patients).
Method of blinding	Post-operative evaluation was deferred to physicians who were unaware of the assigned intervention.
Intervention(s) (n =) and comparator(s) (n =)	PEB+BMS (n=53 patients, 55 lesions) PTA+BMS (n=51 patients, 55 lesions)
Baseline differences	No baseline characteristic difference was statistically significant (p<0.05).
Duration of follow-up, lost to follow-up information	Overall, 104 patients were enrolled between November 2010 and November 2011. At 12 months 3 deaths (2 in the PEB+BMS group, and 1 in the PTA+BMS group) had occurred.
Statistical tests	Continuous data are expressed as mean values ± SD. Categorical variables were compared with the use of the $\chi 2$ test or Fisher exact test. Student t tests for independent samples were used to compare groups on continuous variables. Kaplan-Meier curves (log-rank [Mantel-Cox] test) were used to compare freedom from TLR between the 2 study groups.
Primary outcomes (including scoring methods and timings of assessments)	The primary endpoint of the study was the comparison of 12-month binary restenosis rate, by either angiography or DUS.
Secondary outcomes (including scoring methods and timings of assessments)	The key secondary endpoint was the incidence of TLR. TLR was only performed if clinically indicated (reoccurrence of symptoms, either claudication or CLI), and when a target lesion diameter stenosis of ≥ 50% was present. Major amputation at 12 months, defined as unplanned amputation of the target limb where prosthesis was required for standing or walking, was another secondary endpoint.
Study name	**PACIFIER Trial** [Werk et al 2012[17]]
Objectives	To evaluate the anti-restenotic effect of this DEB technology in comparison with standard PTA.
Location	Germany
Design	Investigator-initiated multicentre randomized trial
Duration of study	Enrolment: not reported Follow-up: 12 months
Sample size	85 patients, 91 lesions
Inclusion criteria	• claudication or critical limb ischemia (Rutherford 2, 3, 4, or 5);

	• atherosclerotic disease involving the superficial femoral artery or the popliteal artery; lesion length between 3 and 30 cm; • an occlusion or a grade of stenosis ≥70%; • absence of contraindications to dual antiplatelet therapy.
Exclusion criteria	• acute thrombus or aneurysm in the target vessel; • failure to cross the target lesion with a guidewire; • inflow lesions that cannot be successfully pretreated; • significant disease of all 3 infrapopliteal vessels; • renal failure (serum creatinine >2.0 mg/dL); • known intolerance or allergy to study medications; • life expectancy <2 years.
Method of randomisation	The randomization sequence was computer generated, in blocks of 10 patients each, and allocation concealment was guaranteed by the use of numbered, opaque, sealed envelopes, which were only opened after the decision was made that the patient had to be treated according to the protocol. The patients were randomized 1:1 to DEB or non-DEB group.
Method of blinding	The trial had a nonblinded design
Intervention(s) (n =) and comparator(s) (n =)	DEB (n=41 patients, 44 lesions); BA (n=44 patients, 47 lesions)
Baseline differences	No clinically relevant differences were found comparing the 2 groups in the prognostically relevant variables.
Duration of follow-up, lost to follow-up information	Before, immediately after the intervention, and 6 months later, angiography of the target vessel was performed in identical projections (2 orthogonal planes for each treated lesion). These images were compared with follow-up angiograms. Patients were followed clinically with direct patient visits at 24 hours, 6, and 12 months. In those refusing 6-month angiographic control, magnetic resonance angiography or duplex ultrasound were recommended to document vessel patency. **Evaluable cases at 6-month follow-up:** • DEB: 35 patients (79.5%) • Non-DEB: 34 patients (72.7%) **Evaluable cases at 12-month follow-up:** • DEB: 42 patients (95.5%) • Non-DEB: 43 patients (91.5%)
Statistical tests	Continuous values are reported as means with SD for non-repeated measurements. For repeated measurements of continuous variables, results were estimated in mixed linear models and shown as means with 95% CI. For nonrepeated continuous data, t tests or Wilcoxon rank sum tests were used for treatment group comparisons as appropriate. Categorical data are shown as relative and absolute frequencies. For categorical data, a Fisher exact test or a χ^2 test was used for treatment group comparisons for nonrepeated measurements. For analyses of multiple observations per patient (i.e., multiple lesions), mixed models were used for continuous data, multinomial regression analysis based on generalized estimation equations for categorical data, and logistic regression analysis based on generalized estimation equations for binary data. Independence was used as working correlation matrix to account for the correlation of multiple observations per patient (the correlation applies for all lesions only). The P values for the categorical and binary data are drawn from the Type3 likelihood ratio test for the factor treatment when using PROC GENMOD in SAS. For the end points, MAE and TLR, survival analysis was performed on the days from randomization to first event using proportional hazard Cox regression and log-rank tests. Data were displayed by Kaplan-Meier curves. If no event was reported, the days to event were censored at the last visit with reports on the end point of interest. Correlations between continuous variables were computed with Spearman rho correlation coefficient. Statistical significance was set at the 2-tailed 0.05 level. Computations were performed with SAS 9.2 (SAS Institute, Cary, NC).

Primary outcomes (including scoring methods and timings of assessments)	The primary study end point was LLL, defined as the difference in minimum lumen diameter of the target lesion between the time points immediately postintervention and the 6-month follow-up angiography or at the time of a clinically driven target lesion revascularization (TLR).
Secondary outcomes (including scoring methods and timings of assessments)	Secondary end points were binary angiographic restenosis and change in Rutherford class at 6 months, and TLR plus major adverse events (MAE, defined as death, target limb amputation, or TLR), at 6 and 12 months.
Study name	**Belgian diabetic IN.PACT Trial** [Debing et al 2016[18]]
Objectives	To demonstrate the efficacy of the IN.PACT Pacific and Admiral DCB versus POBA to inhibit restenosis of SFA and PA in a diabetic population.
Location	Belgium
Design	Principal investigator initiated, prospective, multicentre, randomized (1:1) and controlled trial.
Duration of study	Enrolment: Between September 2012 and December 2014 Follow-up: 6 months
Sample size	106 patients
Inclusion criteria	Diabetic, non-pregnant patients older than 18 years with severe claudication (Rutherford stage 3), ischemic pain while at rest (Rutherford stage 4), or minor ischemic tissue loss (Rutherford stage 5). Lesion criteria for enrollment included: • ≥50% de novo or restenotic SFA lesions with a length of ≤10 cm or ≤ 5 cm occlusion of the SFA; • ≥50% de novo or restenotic lesions or occlusion of PA artery with a length of ≤10 cm; • reference vessel diameter ≥2 mm and ≥7 mm.
Exclusion criteria	Exclusions included life expectancy of ≤1 year, in stent restenosis, previous surgical distal revascularization, contra-indication for anticoagulant therapy or included in other studies.
Method of randomisation	Patients were randomized at a ratio of 1:1 to POBA or IN.PACT DCB. The allocation sequence was concealed by means of sealed and consecutive envelops.
Method of blinding	The trial had a nonblinded design
Intervention(s) (n =) and comparator(s) (n =)	DCB (n=52 patients) ; POBA (n=54 patients)
Baseline differences	Most baseline characteristics were well matched between the groups, except for incidence of cerebrovascular disease (15% POBA versus 8% DCB, p=0.04). There was not significant difference in terms of lesion characteristics between the two groups, neither in arterial calcification.
Duration of follow-up, lost to follow-up information	Patients were clinically re-evaluated at 1 and 6 months after the procedure, and their Rutherford classification was reassessed. At 6-month follow-up data from 91 patients (DCB=44; POBA=47) were available. Death: 6 patients (DCB=3; POBA=3); Withdrawal: 4 patients ((DCB=2; POBA=2); Lost to follow-up: 4 patients (DCB=2; POBA=2); Major amputation: 1 DCB patient.

Statistical tests	Distribution of continuous variables are teste for normality by use of the one-sample Kolmogorov-Smirnov test. Continuous variables with normal distribution are expressed as mean ± standard deviation and compared with the independent-sample T test. Continuous variables with a skewed distribution are expressed as the median and compared with Mann-Whitney test. Categorical variables are compared with χ^2 test or Fisher's exact test. For all endpoints, the level of statistical significance was set at $p<0.05$.
Primary outcomes (including scoring methods and timings of assessments)	The primary endpoint of the study was primary patency, mean diameter restenosis and binary restenosis at 6 months without re-intervention in the interim. Patency of the SFA was assessed by duplex and considered lost when no flow could be detected at the treated lesion, or an increase in the peak systolic velocity ratio (PVSR) ≥2.5 suggested a ≥50% reduction in luminal diameter. The patency of the PA artery was assessed by CT-or conventional angiography and considered lost if the treated segment appeared occluded, or likewise showed a ≥50% reduction in lumen diameter. The binary restenosis was defined as ≥50% diameter stenosis at 6-months follow-up.
Secondary outcomes (including scoring methods and timings of assessments)	The secondary endpoint was the clinically driven target lesion revascularization (cdTLR) rate at 6 months. A reintervention was allowed in case of ≥50% diameter stenosis (confirmed by duplex, CT or conventional angiography) within ± mm proximal and/or distal to the target lesion after documentation of recurrent clinical symptoms. An improved clinical outcome was defined as an improvement of baseline symptoms by at least 1 Rutherford stage that was sustained through follow-up with no additional intervention. Major adverse clinical events were defined as death, myocardial infarction (MI), and minor or major imputation.
Study name	**DEBELLUM Trial** [Fanelli et al 2012[19]]
Objectives	To compare DEBs to conventional angioplasty balloons (ABs) in terms of late lumen loss 6 months after treatment of occlusive disease in the femoropopliteal and infrapopliteal arteries.
Location	Italy
Design	Single-centre randomized controlled trial (RCT).
Duration of study	Enrollment: between September 2010 and March 2011 Follow-up: 6 months
Sample size	50 patients (including SFA and BTK lesions), 92 lesions (SFA), 33 limbs (including SFA and BTK lesions).
Inclusion criteria	Patients with single or multiple lesions (stenosis or occlusion between 3 and 30 cm in length) in the native SFA, the popliteal artery (PA).
Exclusion criteria	In-stent restenosis, aneurysms, acute thrombosis, pregnancy, life expectancy, 1 year, and absence of a patent crural artery.
Method of randomisation	Patients were randomized (1:1) without stratification using computer-generated assignments when they entered the angiographic suite.
Method of blinding	Patients, but not operators, were blinded to the assigned intervention
Intervention(s) (n =) and comparator(s) (n =)	DEB: n=25 patients (including SFA and BTK lesions), 42 lesions, 33 limbs (including SFA and BTK lesions); AB: n=25 patients, 46 lesions (including SFA and BTK lesions), 38 limbs (including SFA and BTK lesions).
Baseline differences	No baseline characteristic difference was statistically significant ($p<0.05$).

Duration of follow-up, lost to follow-up information	Six-month assessment involved clinical evaluation to determine the ABI and the Fontaine stage and imaging to measure late lumen loss (duplex ultrasound. Follow-up evaluation was also planned at 12 and 24 months after intervention.
Statistical tests	Continuous variables were reported as the mean ± standard deviation or the median and range as appropriate; differences were compared using the Student t test. For categorical variables, the absolute and relative proportions were calculated and compared using the Fisher exact test. Significance was assumed at $p< 0.05$.
Primary outcomes (including scoring methods and timings of assessments)	The primary endpoint was the late lumen loss at 6 months as determined by duplex ultrasound. Late lumen loss was the difference in millimetres between the minimum lumen diameter (MLD) immediately after the procedure and the MLD during follow-up.
Secondary outcomes (including scoring methods and timings of assessments)	The secondary endpoints were: • binary restenosis (>50%); • acute thrombotic occlusion of an artery within 48 hours of the procedure as determined by ultrasound, angiography, or clinical evidence; • any reintervention performed for thrombosis or restenosis (>50% diameter stenosis) of the target lesion after documentation of recurrent ischemic symptoms (target lesion revascularization, TLR); • amputation at 6, 12, and 24 months.

Table B 6 Summary of methodology for observational studies

Study name	**PLAISIR Trial** [Bague et al 2017[5]]
Objective	To assess 18-month outcomes of the paclitaxel eluting balloon (PEB) in patients with femoropopliteal (FP) in-stent restenosis (ISR).
Location	France
Design	Multicentre, prospective, cohort study
Duration of study	**Enrollment**: between January 2012 and June 2013 **Follow-up:** 18 months
Patient population	Symptomatic patients with femoropopliteal in-stent restenosis
Sample size	53 patients (55 limbs)
Inclusion criteria	• Age ≥18 years old. • Symptomatic patient according to Rutherford Class 1, 2, 3, 4 or 5. • Clinical degradation by at 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. • The target ISR lesion is fully contained between the origin of the SFA and distally the femoropopliteal crossover (crossing by SFA of medial rim of femur in the PA projection). • Adequate SFA inflow and outflow either pre-existing or successfully re-established (outflow defined as patency of at least one infragenicular artery). • The target lesion must not extend beyond the stent margin. • Successful crossing of the target lesion, inflow and outflow lesions with a guidewire. • Patient belongs to the French health care system. • Written informed consent.
	• No atheromatous disease. • Asymptomatic lesion. • Known allergies to heparin, aspirin, other anti-coagulant/ antiplatelet therapies, and/or paclitaxel. • Acute limb ischemia. • Patient on oral anticoagulation therapy. • Target lesion requires/has been pretreated with alternative therapy such as: DES, laser, atherectomy, cryoplasty, cutting/scoring balloon, etc. • Life expectancy < 1 year.

	• Patient involved in another trial. • Refusing patient. • Pregnancy. • Patients receiving anticoagulation.
Intervention(s) (n =) and comparator(s) (n =)	No comparator group was provided.
Baseline differences	No comparator group was provided.
How were participants followed-up (for example, through pro-active follow-up or passively). Duration of follow-up, participants lost to follow-up	Patients were prospectively followed up on an outpatient Basis. Follow-up included medical examination, ankle brachial index (ABI) measurements, and duplex scan at 1, 3, 6, 9, 12, and 18 months. The median follow-up was 17 months (range 1e19 months). Three patients were lost of follow-up at 1 year after the procedure.
Statistical tests	Results were reported prospectively on an intention-to treat basis. TLR, TER, clinical sustained improvement and patency data were calculated on a per limb basis. Survival rate curves for outcomes were plotted and calculated using the Kaplan-Meier method. Wilcoxon tests were used to analyse quality of life assessment by EQ-5D questionnaire and ABI during follow-up. A $p < 0.05$ was considered statistically significant. Data were analysed using the SPSS software.
Primary outcomes (including scoring methods and timings of assessments)	The primary endpoint was clinically driven target lesion revascularisation (TLR) rate at 1 year. TLR was considered clinically driven in case of clinical degradation by at least 1 Rutherford stage or absence of healing of all skin lesions associated with a stenosis ≥50% at the stented site and/or a peak systolic velocity ratio (PSVR) < 2.4. The angiographic patterns of ISR were defined according to the classification proposed by Tosaka as follows: class I (focal or multifocal restenosis < 5 cm), class II (diffuse restenosis > 5 cm) and class III (total occlusion).
Secondary outcomes (including scoring methods and timings of assessments)	Secondary endpoints were target extremity revascularisation (TER), major adverse cardiovascular events, primary and secondary sustained clinical improvement (primary and secondary sustained clinical improvement was defined as a sustained upward shift of ≥1 category of the Rutherford classification for claudicants and by wound healing and rest pain resolution for patients in CLI, with or without the need for repeated TLR in surviving patients), primary and secondary patency, quality of life assessment by the EQ-5D questionnaire,20 device success, technical success, duration of hospital stay, Rutherford classification, and measurement of ABI at 1 year.
Study name	**Multicentre Italian Registry** [Micari et al 2012[8], 2013[9]]
Objective	To prospectively evaluate the safety and effectiveness of the IN.PACT Admiral PEB when used in routine practice with a strict provisional stenting strategy, for treatment of patients with symptoms of claudication and rest pain due to femoropopliteal ischemic vascular disease.
Location	Italy
Design	Multicentre Registry
Duration of study	**Enrollment**: Not reported **Follow-up:** 27 ± 3 months
Patient population	Adult patients diagnosed with peripheral artery disease for claudication or rest pain as per Rutherford classes 2 through 4
Sample size	105 patients (114 treated lesions)
Inclusion criteria	• SFA and first 2 segments of the proximal popliteal target vessel with reference diameter between 3 and 7 mm; • Lesion and/or occlusion length ≤15 cm; • Adequate runoff with evidence of at least 1 patent crural vessel to the foot either pre-existing or re-established;

	• Good inflow in the aortic-iliac and common femoral districts (either pre-existing or re-established); • Patients presenting with shorter (≤15 cm) stenosis (≤50%) and occlusions were eligible if these inflow lesions could be successfully treated before the target SFA lesion.
Exclusion criteria	• Long (>15 cm) stenosis (>50%) or occlusions in the aortic-iliac and common femoral districts; • Patients with a previously implanted stent in the target lesion, aneurysm in the target vessel, or acute thrombus in the target limb ; • failure to cross the target lesion with a guidewire, and use of alternative therapies, such as atherectomy, cutting balloon, or laser or radiation therapy as part of the index procedure
Intervention(s) (n =) and comparator(s) (n =)	No comparator group was provided.
Baseline differences	No comparator group was provided.
How were participants followed-up (for example, through pro-active follow-up or passively). Duration of follow-up, participants lost to follow-up	All endpoints were assessed at baseline and at 3, 6, and 12 and 24 months after the procedure. At 12-month follow-up, 92 of 105 (87.6%) enrolled patients were evaluable and duplex ultrasonography was performed on 77 (73.3%) patients. Patients who did not return for follow-up appointments were contacted by phone. One patient death occurred before the 3-month follow-up due to cardiovascular causes with acute pulmonary oedema and the second patient death, between 6 and 12 months after procedure, was of non-cardiovascular causes (pulmonitis) and unrelated to the device or procedure.
Statistical tests	Descriptive statistics were used to present baseline and follow-up variables. The Kaplan- Meier estimate was used for presentation of primary patency. Inferential statistics were used as follows: Rutherford classification and the categorical variables of QOL were compared using the Kruskal-Wallis test; continuous variables (visual analogue scale, walking impairment questionnaire, ABI, ACD, and PSVR) were compared within group at different time points using the Student t test. There was no correction for multiple comparisons. Primary patency was calculated from the hierarchical composite of TLR, binary restenosis (PSVR >2.4 by duplex ultrasonography), and occlusion (PSVR = 0). The Euro QoL-5D levels were dichotomized into “no problems” and “problems” for graphical presentation. The data underwent inferential analysis using the Kruskal-Wallis test to determine any statistical difference between the study visits.
Primary outcomes (including scoring methods and timings of assessments)	The primary endpoint after intervention was the primary patency rate defined as freedom from the combined endpoints of target lesion revascularization (TLR), occlusion, and >50% restenosis in the treated lesion. Rates of TLR, death, and amputation were also analysed.
Secondary outcomes (including scoring methods and timings of assessments)	Secondary endpoints were: secondary patency, major adverse events (composite of death, amputation, or TLR), change in Rutherford class and ankle-brachial index (ABI) from baseline to 12 and 24 months. Walking capacity and absolute claudication distance (ACD) were evaluated as functional capacity measures. Walking capacity was measured using a validated 5-point walking impairment questionnaire that assessed walking distance, speed, ability to climb stairs, and symptoms with walking. ACD was defined as the distance at which the patient could no longer ambulate based on the 6-min walking test. The impact of treatment on health-related QOL was assessed using the Euro QoL-5D Questionnaire.
Study name	**SFA-Long Study** [Micari et al 2016[10], 2017[11]]
Objective	To appraise outcomes after femoropopliteal PTA with the IN.PACT Admiral PCB.
Location	Italy
Design	Independent, prospective, multicentre, single-arm study.
Duration of study	**Enrollment**: Not reported **Follow-up:** 24 months

Patient population	Adult patients diagnosed with peripheral artery disease for claudication or rest pain (Rutherford class 2 to 4), due to femoropopliteal lesions >15 cm long.
Sample size	105 patients (105 femoropopliteal lesions).
Inclusion criteria	• Atherosclerotic disease of the superficial femoral and popliteal artery, with reference vessel diameter between 4 and 7 mm, having stenotic lesions or occlusions for a total length ≤150 mm. • Multiple adjacent lesions without angiographic evidence of healthy segments 3 cm or greater were cumulatively considered and treated as single lesions. • Patients were required to have adequate runoff, with evidence of at least 1 patent crural vessel to the foot either pre-existing or re-established (patients were eligible if an impaired outflow vessel [>50% diameter stenosis] was successfully treated during the index procedure). • Unhindered inflow in the aortic-iliac and common femoral districts (either pre-existing or re-established). • Patients presenting <150 mm inflow lesions which could be successfully treated before the target femoropopliteal lesion.
Exclusion criteria	• Patients presenting >150 mm inflow lesions. • In-stent restenosis, aneurysm in the target vessel. • Acute thrombus in the target limb failure to cross the target lesion with a guidewire and concomitant (intentional or accidental) use of alternative therapies in the target vessel, including atherectomy, excimer laser, or cutting balloon during the index procedure.
Intervention(s) (n =) and comparator(s) (n =)	No comparator group was provided.
Baseline differences	No comparator group was provided.
How were participants followed-up (for example, through pro-active follow-up or passively). Duration of follow-up, participants lost to follow-up	Follow-up after 12 months was obtained in 101 patients, while the 24-month follow-up data were available in 93 patients.
Statistical tests	Descriptive statistics (absolute frequencies and percentages for categorical variables, mean ± SD and medians and interquartile ranges for continuous variables) were used to summarize the values and changes from baseline at follow-up. Comparisons for continuous variables were performed by means of the Wilcoxon signed rank sum test applied on the difference between baseline and follow-up data for completers. Qualitative variables were compared using the McNemar test. For the statistical analysis of primary and main secondary endpoints, 95% exact Cis are reported. The Kaplan-Meier estimate was used to estimate the probability of primary patency persistence, together with an approximated 95% CI. The EQ- 5D levels were dichotomized into “no problems” and “problems” for graphical presentation, and change in quality of life between baseline and 12-month follow-up was analysed by means of the McNemar test. In addition, change in quality of life was described in the categories of “no change,” “improved” (from “problems” to “no problems”), and “worsened” (from “no problems” to “problems”). A Cox proportional hazards multivariate regression analysis was also performed including the following known and potential prognostic factors related to outcomes: age, sex, diabetes, lesion length (<25 vs. >25 mm), calcification, and impaired versus unimpaired outflow. Statistical significance was set at a 2-tailed level of 0.05, and p values unadjusted for multiplicity are reported throughout.
Primary outcomes (including scoring methods and timings of assessments)	Primary patency rate at 12 months, defined as freedom from the combined endpoints of clinically driven target lesion revascularization (TLR), occlusion, and >50% restenosis in the treated lesion as appraised by duplex ultrasound (peak systolic velocity ratio >2.4); clinically driven TLR was defined as any reintervention

	within the target lesion due to symptoms or drop in ankle-brachial index of ≥20% or >0.15 compared with post-procedure.
Secondary outcomes (including scoring methods and timings of assessments)	Major adverse events (the composite of death of any cause, major target limb amputation, thrombosis at the target lesion site, or non–target lesion target vessel revascularization), change in Rutherford class, and quality of life.
Study name	**Real-world Registry** [Schmidt et al 2016[12]]
Objective	To investigate whether DCB would improve patency for complex femoropopliteal lesions and to assess the durability of results over an extended time, beyond 1 year.
Location	Germany
Design	Retrospective cohort study
Duration of study	**Enrolment**: between May 2009 and January 2012 **Follow-up:** 24 months
Patient population	Patients undergoing treatment of complex femoropopliteal lesions (defined as de novo atherosclerotic lesions ≥10 cm or restenosis after previous endovascular treatment for de novo disease).
Sample size	260 patients, 288 limbs
Inclusion criteria	No formal inclusion criteria were applied, but patients had to be treated for symptomatic peripheral arterial disease classified as Rutherford stage ≥1.
Exclusion criteria	Nonatherosclerotic disease such as aneurysm, vasculitis, entrapment, and treatment of restenosis/re-occlusion of surgical bypass.
Intervention(s) (n =) and comparator(s) (n =)	No comparator group was provided.
Baseline differences	No comparator group was provided.
How were participants followed-up (for example, through pro-active follow-up or passively). Duration of follow-up, participants lost to follow-up	Before discharge, all patients underwent clinical examination, ABI measurement, and duplex ultrasound to determine interventional success. The same information was captured at each follow-up visit, which was routinely performed at 6, 12, and 24 months after the intervention. In patients who did not return for follow-up, their status was confirmed after 1 and 2 years by telephone contact. At 1-year data from 245 treated lesions are available. At 2 years data from 233 treated lesions are available.
Statistical tests	Descriptive statistics were used to present continuous data as mean ± SD or median (range) as appropriate. Categorical variables were expressed as numbers and percentages. Group comparisons were performed either by the Student t test, analysis of variance or chi-square test as appropriate. Patency rates, freedom from TLR, and patient survival were described using Kaplan-Meier analyses, and the log-rank test was used to compare survival curves between groups.
Primary outcomes (including scoring methods and timings of assessments)	The primary endpoint was vessel patency, defined as freedom from >50% restenosis as determined by either duplex ultrasound (peak systolic velocity ratio <2.4) or digital subtraction angiography, and freedom from TLR.
Secondary outcomes (including scoring methods and timings of assessments)	Secondary endpoints were freedom from TLR, Rutherford class, ABI, and safety endpoints, including amputation rate and death. Any adverse events potentially related to the use of DCBs were captured.
Study name	**Prospective Registry** [Stabile et al 2012[13], Virga et al 2014[14]]
Objective	To evaluate the safety and efficacy of the use of drug-eluting balloon (DEB) for the treatment of in-stent restenosis (ISR).
Location	Italy
Design	Prospective cohort

Duration of study	Enrolment: between December 2009 and December 2010 Follow-up: 24 months
Patient population	Patients undergoing percutaneous transluminal angioplasty (PTA) for the treatment of superficial-femoral artery in-stent restenosis (SFA-ISR)
Sample size	39 patients
Inclusion criteria	• Diabetes; • Femoropopliteal in-stent restenosis (ISR).
Exclusion criteria	Not reported
Intervention(s) (n =) and comparator(s) (n =)	No comparator group was provided.
Baseline differences	No comparator group was provided.
How were participants followed-up (for example, through pro-active follow-up or passively). Duration of follow-up, participants lost to follow-up	Patients were evaluated through hospital discharge; at 30 days; and at 3, 6, and 12,15, 18, 21, and 24 months post-procedure. Clinical follow-up was performed by clinical examination and duplex ultrasonography scan.
Statistical tests	**1 year [Stabile, 2012[13]]** Nominal and categorical variables were presented as contingency tables with frequencies and percentages. Continuous variables were reported as the mean with SD or median and interquartile ranges. Variables were compared by t test for normally distributed values ($p < 0.05$ was considered statistically significant). **2 years [Virga 2014[14]]** Continuous variables are presented as mean ± standard deviation, whereas categorical variables are given as count (percentage). Survival and patency rates were estimated using a Kaplan-Meier time-to-event model; curves were compared using the log-rank test. Differences were considered significant at $p<0.05$.
Primary outcomes (including scoring methods and timings of assessments)	The primary endpoint was primary patency defined as PVR of <2.4 documented by duplex ultrasound at 12 months without target lesion revascularization (TLR).
Secondary outcomes (including scoring methods and timings of assessments)	The secondary endpoints included: **Phase I-12 months** • freedom from TLR at 1 year; • secondary patency at 1 year documented by duplex (patency defined as a PVR <2.4); • clinical success as defined by >1 category improvement in the Rutherford scale from baseline (or 2 categories if there was pre-existing tissue loss) at 1 year; • hemodynamic success, defined by a 0.1 improvement in the ankle-brachial index during the period from baseline to 30 days post-procedure and no deterioration >0.15 from the maximum early post-procedure level at 1 year. **Phase II-24 months** • freedom from TLR at 24 months; • secondary patency at 2 years documented by duplex (patency defined as a PVR <2.4).
Study name	**DEBATE-ISR Study** [Grotti et al 2016[15]]
Objective	To compare 3-years outcomes of symptomatic diabetic patients with femoropopliteal ISR undergoing reintervention with DEBs compared with historical controls treated with BA.

Location	Italy
Design	Single-centre prospective cohort
Duration of study	**Enrolment:** between January 2010 and December 2011 **Follow-up:** 36 months
Patient population	Symptomatic diabetic patients with femoropopliteal ISR
Sample size	86 patients
Inclusion criteria	Not reported
Exclusion criteria	Not reported
Intervention(s) (n =) and comparator(s) (n =)	DEB (n=44); BA (n=42)
Baseline differences	No baseline characteristic difference was statistically significant (p<0.05).
How were participants followed-up (for example, through pro-active follow-up or passively). Duration of follow-up, participants lost to follow-up	After hospital discharge, patients were asked to return to the outpatient clinic at 1, 6, 12, 24, and 36 months for clinical and duplex ultrasound evaluation. During the 3-year follow-up, 9 patients per group died, while 1 patient per group underwent major amputation.
Statistical tests	Continuous data are expressed as mean values ± standard deviation. Categorical variables were compared with the use of the chi-square test or Fisher exact test; p<0.05 was considered statistically significant. Kaplan-Meier curves (log-rank test) were used to compare freedom from TLR between the 2 study groups and according to the class of ISR.
Primary outcomes (including scoring methods and timings of assessments)	The primary endpoint of the study was the 3-year incidence of target lesion revascularization (TLR), which was performed only if clinically indicated (recurrence of symptoms) and when a ≥50% target lesion stenosis was present.
Secondary outcomes (including scoring methods and timings of assessments)	A post hoc sub analysis was performed for major adverse events (MAEs), defined as death from any cause, major amputation, and clinically driven TLR.
UNPUBLISHED	
Study name	IN.PACT Global Study – Full cohort and sub-cohort analyses: • IN.PACT Global Full Clinical Cohort at 12 months • IN.PACT Global Long Lesion Imaging Cohort at 12 months • IN.PACT Global ISR Imaging Cohort at 12 months • IN.PACT Global CTO Imaging Cohort at 12 months • IN.PACT Global Severe Calcium Cohort at 12 months • IN.PACT Global Standard vs. Wider Use at 12 months
Objective	The purpose of this study is to collect safety and efficacy data on the IN.PACT Admiral™ Drug Eluting Balloon (DEB) in treatment of atherosclerotic disease in the superficial femoral and/or popliteal arteries in a "real world" patient population.
Location	64 sites in Canada, South America, Europe, Australia, North America, Africa and Asia
Design	Cohort Study (Prospective Observational Study)
Duration of study	5 years
Patient population	Patients 18 years of age or older with PAD in the femoropopliteal region and Rutherford category 2 through 4
Sample size	• Total Enrollment (n = 1535) • Full Clinical Cohort (n = 1416) (M. Jaff, VIVA 2016)

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ITT (n=1406)
150mm DCB Cohort (n = 119)
De Novo ISR (n = 131) (M Brodmann, VIVA 2015)
Long Lesion (≥15 cm) (n = 157) (D. Scheinert, EuroPCR 2015)
CTO (≥5 cm) (n = 126) (G.Tepe, Charing Cross 2016)

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<tr><td>Inclusion criteria</td><td>

Rutherford Class 2,3 and 4
Lesion(s) in SFA and/or popliteal artery
Single or multiple stenosis or occlusions of any lesion length ≥2cm
De novo or restenotic (including ISR)
At least one infrapopliteal run-off vessel

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<tr><td>Exclusion criteria</td><td>

Rutherford Class 5 and 6
Acute or sub-acute thrombus in the target vessel
Previous surgical bypass to the target lesion
Failure to successfully cross the target lesion with a guidewire

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<tr><td>Intervention(s) (n =) and comparator(s) (n =)</td><td>

Total Enrollment (n = 1535)
Full Clinical Cohort (n = 1416) (M. Jaff, VIVA 2016)
150mm DCB Cohort (n = 119)
De Novo ISR (n = 131) (M Brodmann, VIVA 2015)
Long Lesion (≥15 cm) (n = 157) (D. Scheinert, EuroPCR 2015)
CTO (≥5 cm) (n = 126) (G.Tepe, Charing Cross 2016)

</td></tr>
<tr><td>Baseline differences</td><td>
Apart from the Standard vs Wider Use presentation, analyses did not report a comparator. However, because comparisons are likely to be made between groups, the baseline characteristics for each cohort has been outlined below:
<table>
<tr><th rowspan="2">Characteristic</th><th rowspan="2">Jaff, VIVA 2015</th><th rowspan="2">Scheinert EuroPCR 2015</th><th rowspan="2">Brodmann, VIVA 2015</th><th rowspan="2">Tepe, Charing Cross 2014</th><th rowspan="2">Fanelli, Charing Cross 2017</th><th colspan="2">Ansel, Charing Cross 2017</th></tr>
<tr><th>Standard Use</th><th>Wider Use</th></tr>
<tr><td>Age (Y)</td><td>68.6</td><td>69.5</td><td>67.8</td><td>67.5</td><td>73.6</td><td>67.2</td><td>68.9</td></tr>
<tr><td>Male (%)</td><td>67.8</td><td>66.2</td><td>69.5</td><td>69.0</td><td>68.1</td><td>63.3</td><td>68.9</td></tr>
<tr><td>Diabetes (%)</td><td>39.9</td><td>41.0</td><td>35.1</td><td>29.6</td><td>45.8</td><td>36.6</td><td>40.8</td></tr>
<tr><td>Hypertension (%)</td><td>70.5</td><td>87.9</td><td>81.5</td><td>82.3</td><td>87.5</td><td>76.7</td><td>85.1</td></tr>
<tr><td>Hyperlipidemia (%)</td><td>70.5</td><td>76.7</td><td>72.1</td><td>64.5</td><td>80.0</td><td>68.8</td><td>70.9</td></tr>
<tr><td>Current Smoker (%)</td><td>31.8</td><td>34.4</td><td>35.9</td><td>49.2</td><td>19.4</td><td>38.1</td><td>30.2</td></tr>
<tr><td>Obesity (BMI≥30kg/m^2) (%)</td><td>20.5</td><td>22.1</td><td>17.6</td><td>20.2</td><td>23.6</td><td>18.6</td><td>21.0</td></tr>
<tr><td>Coronary Heart Disease (%)</td><td>40.5</td><td>52.3</td><td>36.5</td><td>24.1</td><td>55.7</td><td>33.1</td><td>42.4</td></tr>
<tr><td>Carotid Artery Disease (%)</td><td>20.2</td><td>22.4</td><td>19.8</td><td>19.2</td><td>24.6</td><td>17.2</td><td>20.9</td></tr>
<tr><td>Renal Insufficiency[1] (%)</td><td>11.2</td><td>14.4</td><td>9.9</td><td>10.0</td><td>12.3</td><td>8.6</td><td>11.8</td></tr>
<tr><td>Previous Peripheral Revasc. (%)</td><td>52.4</td><td>55.4</td><td>100</td><td>33,3</td><td>58.3</td><td>37.7</td><td>56.1</td></tr>
<tr><td>Concomitant BTK Disease (%)</td><td>45.3</td><td>47.5</td><td>43.3</td><td>41.0</td><td>58.5</td><td>42.4</td><td>46.1</td></tr>
<tr><td>ABI</td><td>0.678</td><td>0.669</td><td>0.667</td><td>0.593</td><td>0.689</td><td>0.695</td><td>0.674</td></tr>
<tr><td>RCC2 (%)</td><td>31</td><td>21.8</td><td>33</td><td>25.4</td><td>29</td><td>38</td><td>29</td></tr>
<tr><td>RCC3 (%)</td><td>58</td><td>61.5</td><td>58</td><td>63.5</td><td>51</td><td>54</td><td>59</td></tr>
<tr><td>RCC4 (%)</td><td>8</td><td>10.3</td><td>8</td><td>8.7</td><td>10</td><td>8</td><td>9</td></tr>
<tr><td>RCC5 (%)</td><td>3</td><td>6.4</td><td>2</td><td>2.4</td><td>10</td><td>0</td><td>3</td></tr>
</table>
</td></tr>
</table>

	<table><tr><th>Lesion Characteristic</th><th>Jaff, VIVA 2015</th><th>Scheinert EuroPCR 2015</th><th>Brodmann, VIVA 2015</th><th>Tepe, Charing Cross 2014</th><th>Fanelli, Charing Cross 2017</th><th colspan="2">Ansel, Charing Cross 2017</th></tr><tr><th></th><th></th><th></th><th></th><th></th><th></th><th>Standard Use</th><th>Wider Use</th></tr><tr><td>De novo (%)</td><td>74.4</td><td>83.2</td><td>0.0</td><td>92.1</td><td>81.5</td><td>92.5</td><td>70.8</td></tr><tr><td>Restenotic (non-stented) (%)</td><td>7.7</td><td>16.8</td><td>0.0</td><td>7.9</td><td>18.5</td><td>7.5</td><td>7.7</td></tr><tr><td>In-stent Restenosis</td><td>18.0</td><td>0.0</td><td>100.0</td><td>0.0</td><td>0.0</td><td>0.0</td><td>21.4</td></tr><tr><td>Lesion Length (cm ± SD)</td><td>12.09</td><td>26.40</td><td>17.17</td><td>22.83</td><td>24.73</td><td>7.86</td><td>12.88</td></tr><tr><td>Total Occlusions %</td><td>35.5</td><td>60.4</td><td>34.0</td><td>100</td><td>60.3</td><td>34.2</td><td>35.7</td></tr><tr><td>Calcification %</td><td>68.7</td><td>71.8</td><td>59.1</td><td>71.0</td><td>100</td><td>54.8</td><td>71.3</td></tr><tr><td>Severe Calcification %</td><td>10.2</td><td>19.6</td><td>8.3</td><td></td><td>56.4</td><td>0.0</td><td>12.1</td></tr><tr><td>RVD (mm ± SD)</td><td>51.86</td><td>4.594</td><td>5.222</td><td>5.049</td><td>5.180</td><td>5.157</td><td>5.191</td></tr><tr><td>Diameter Stenosis (% ± SD)</td><td>88.8</td><td>90.9</td><td>84.8</td><td>100.0</td><td>90.9</td><td>89.1</td><td>88.7</td></tr><tr><td>Dissections 0</td><td>56.8</td><td>37.9</td><td>69.1</td><td>32.3</td><td>46.9</td><td>49.1</td><td>58.2</td></tr><tr><td>Dissections A-C</td><td>35.4</td><td>47.2</td><td>26.2</td><td>44.1</td><td>40.7</td><td>41.6</td><td>34.2</td></tr><tr><td>Dissections D-F</td><td>7.8</td><td>14.9</td><td>4.7</td><td>23.6</td><td>12.4</td><td>9.3</td><td>7.6</td></tr></table><table><tr><th>Procedural Characteristic</th><th>Jaff, VIVA 2015</th><th>Scheinert EuroPCR 2015</th><th>Brodmann, VIVA 2015</th><th>Tepe, Charing Cross 2014</th><th>Fanelli, Charing Cross 2017</th><th colspan="2">Ansel, Charing Cross 2017</th></tr><tr><th></th><th></th><th></th><th></th><th></th><th></th><th>Standard Use</th><th>Wider Use</th></tr><tr><td>Device Success</td><td>99.4</td><td>99.5</td><td>99.6</td><td>99.3</td><td>99.0</td><td>100.0</td><td>99.3</td></tr><tr><td>Procedure Success</td><td>99.3</td><td>99.4</td><td>99.2</td><td>100</td><td>98.6</td><td>100.0</td><td>99.1</td></tr><tr><td>Clinical Success</td><td>98.8</td><td>99.4</td><td>98.5</td><td>99.2</td><td>98.6</td><td>99.6</td><td>98.6</td></tr><tr><td>Pre-dilatation (%)</td><td>78.0</td><td>89.8</td><td>64.1</td><td>94.4</td><td>90.3</td><td>69.4</td><td>80.2</td></tr><tr><td>Post-dilatation</td><td>35.1</td><td>39.1</td><td>26.0</td><td>50.0</td><td>36.1</td><td>30.0</td><td>36.4</td></tr><tr><td>Provisional stent (%)</td><td>25.3</td><td>40.4</td><td>14.5</td><td>46.8</td><td>51.4</td><td>16.1</td><td>27.6</td></tr></table>
How were participants followed-up (for example, through pro-active follow-up or passively). Duration of follow-up, participants lost to follow-up	Patients were pro-actively followed up at 6, 12, 24 and 36 (in-hospital visits), 48, and 60 months (telephone FU)
Statistical tests	Not described in the presentations
Primary outcomes (including scoring methods and timings of assessments)	**Primary Endpoint Clinical Cohort [Time Frame: 12 months]** Freedom from clinically-driven target lesion revascularization (TLR) within 12 months post-index procedure, which is defined as: • Any re-intervention within the target lesion(s) due to symptoms or drop of ABI ≥ 20% or > 0.15 when compared to post-index procedure baseline ABI. **Primary Endpoint Imaging Cohort [Time Frame: 12 months]** Primary Patency within 12 months post-index procedure, which is defined as: Freedom from clinically-driven TLR and • Freedom from restenosis as determined by DUS Peak Systolic Velocity Ratio (PSVR) ≤ 2.4 Restenosis determined by either PSVR >2.4 as assessed by an independent DUS core lab or >50% stenosis as assessed by an independent angiographic core lab **Primary Safety Endpoint [Time Frame: 12 months]** A composite of freedom from device- and procedure-related mortality through 30 days, freedom from major target limb amputation and TLR within 12 months post-index procedure.
Secondary outcomes (including scoring methods and timings of assessments)	**MAEs [Time Frame: 30 days, 6, 12, 24, 36, 48 and 60 months]** MAE (Major Adverse Events)is defined as all-cause mortality, clinically-driven TVR (Target Vessel Revascularization), major target limb amputation, thrombosis at the target lesion site. **All-cause mortality [Time Frame: 30 days, 6, 12, 24, 36, 48 and 60 months]** **Clinically-driven TLR [Time Frame: 30 days, 6, 24, 36, 48 and 60 months]** **Clinically-driven TVR [Time Frame: 30 days, 6, 12, 24, 36, 48 and 60 months]**

	Clinically-driven TVR is defined as any re-intervention within the target vessel due to symptoms or drop of ABI of ≥ 20% or > 0.15 when compared to post-index procedure baseline ABI. **TLR [Time Frame: 6, 12, 24, 36, 48 and 60 months]** **TVR [Time Frame: 6, 12, 24, 36, 48 and 60 months]** **Major target limb amputation [Time Frame: 30 days, 6, 12, 24, 36, 48 and 60 months]** **Time to first clinically-driven TLR [Time Frame: through 60 months post-index procedure]** **Time to all-cause mortality [Time Frame: through 60 months post-index procedure]** **Primary sustained clinical improvement [Time Frame: 6, 12, 24, 36 months]** Primary sustained clinical improvement is defined as sustained upward shift of at least 1 category on Rutherford classification as compared to baseline without the need for repeated TLR or surgical revascularization in amputation-free surviving subjects. **Secondary sustained clinical improvement [Time Frame: 6, 12, 24, 36 months]** Secondary sustained clinical improvement is defined as sustained upward shift of at least 1 category on Rutherford classification as compared to baseline including the need for repeated TLR or surgical revascularization in amputation-free surviving subjects. **Immediate hemodynamic improvement [Time Frame: post-index procedure]** Immediate hemodynamic improvement is defined as an ABI improvement of ≥ 0.1 or to an ABI ≥ 0.9. **Sustained hemodynamic improvement [Time Frame: 6, 12, 24, 36 months]** Sustained hemodynamic improvement is defined as persistent improvement of ABI-values with ≥ 0.1 as compared to baseline values or to an ABI ≥ 0.9 throughout follow-up without the need for repeated TLR or surgical revascularization in amputation-free surviving subjects. **Walking impairment evaluation by Walking Impairment Questionnaire (WIQ) [Time Frame: 6, 12, 24, 36 months]** **Walking distance as measured by 6 Minute Walk Test [Time Frame: 6, 12, 24, 36 months]** **Health related Quality of life scores (EQ5D) [Time Frame: 6, 12, 24, 36 months]** **Device success [Time Frame: Index-procedure]** Device success is defined as successful delivery, balloon inflation and deflation and retrieval of the intact study device without burst below the rated burst pressure (RBP) **Clinical success [Time Frame: prior to discharge]** Clinical success is defined as procedural success without procedural complications (mortality, major target limb amputation, thrombosis of the target lesion, or TVR) prior to discharge **Imaging cohort: Duplex-defined binary restenosis (PSVR > 2.0) of the target lesion [Time Frame: at 12 months, or at the time of re-intervention]** **Imaging cohort: 21. Duplex-defined binary restenosis (PSVR > 3.4) of the target lesion [Time Frame: at 12 months, or at the time of re-intervention]**

7.3.2 Provide details on data from any single study that have been drawn from more than one source (for example a poster and unpublished report) and/or when trials are linked this should be made clear (for example, an open-label extension to randomised controlled trial).

The IN.PACT SFA trial has been referenced several times. Results from the 12 month and 24 months publications are included in this document as well as results at 36 months not yet published but presented at VIVA, 2016. Section 7.4.1, table B5 describes the methodology for the IN.PACT SFA based on all three publications/presentation (12, 24 and 36 months).

The Multicentre Italian Registry has been referenced two times. Both results at 12 and 24 months have been published by Micari et al [8,9] and included in this document. Section 7.4.1, table B6 describes the methodology of the registry based on both publications (12 and 24 months).

The SFA-Long Study has been referenced two times. Both results at 12 and 24 months have been published by Micari et al [10,11] and included in this document. Section 7.4.1, table B6 describes the methodology of the SFA-Long Study based on both publications (12 and 24 months).

Stabile et al, 2012[13] and Virga et al, 2014[14] presented the 12 months and 24 months results of a registry conducted in Italy. Section 7.4.1, table B6 describes the methodology of the registry based on both publications (12 and 24 months).

The methodology and results, not yet published, of the IN.PACT Global Study have been reported in the document considering the full cohort of patients and sub-cohort analyses:

- IN.PACT Global Full Clinical Cohort at 12 months
- IN.PACT Global Long Lesion Imaging Cohort at 12 months
- IN.PACT Global ISR Imaging Cohort at 12 months
- IN.PACT Global CTO Imaging Cohort at 12 months
- IN.PACT Global Severe Calcium Cohort at 12 months
- IN.PACT Global Standard vs. Wider Use at 12 months

Section 7.4.1, table B6 (UNPUBLISHED section) describes the methodology of the IN.PACT Global Study.

7.3.3 Highlight any differences between patient populations and methodology in all included studies.

Regarding the seven RCTs, all included patients with superior femoral or popliteal artery lesions. Krankenberg et al[6], Laird et al[4], Tepe et al[3] and Werk et al[17] included patients with a Rutherford classification 2 to 4 (2 to 5 for Werk et al[17]) while Debing et al[18] and Liistro et al[7] included only patients with Rutherford ≥ 3. Krankenberg et al[6] included patients with In-stent restenosis while Debing et al[18] only diabetic patients.

Among the registries or cases series, Bague et al[5] and Schmidt et al[12] included also patients with Rutherford class 1. Among the ten publications, 5 included ISR and three focused on diabetic patients.

7.3.4 Provide details of any subgroup analyses that were undertaken in the studies included in section 7.4.1. Specify the rationale and state whether these analyses were pre-planned or post-hoc.

In Laird et al[4], a post-hoc subgroup analysis demonstrated outcomes in favour of DCB across a variety of clinical and anatomic subgroups. Except for patients having ischemic rest pain (Rutherford Category 4), all subgroups showed better results with DCB. Longer and more complex lesions, including total occlusions, had significantly better primary patency following treatment with DCB. A strong treatment effect was also observed for diabetic patients and women (Figure 1). Importantly, primary patency was significantly better for diabetic patients treated with DCB compared with PTA (73.3% vs. 45.8%; $p < 0.001$). Female patients in the DCB group outperformed their PTA-treated counterparts (Figure 1). Primary patency for female patients treated with DCB was 76.7% compared with 42.3% for those treated with PTA ($p < 0.001$).

In Liistro et al[7], a post hoc exploratory comparisons were performed between long (≥100 mm) versus shorter lesions and true lumen versus subintimal recanalization. Finally, as a confirmatory analysis, late lumen loss (LLL), defined as the difference in minimum lumen diameter of the target lesion between the time points immediately following intervention and the 12-month follow-up angiography or at the time of a clinically driven TLR was calculated by quantitative angiography and compared between the PTA + BMS and PEB + BMS groups.

Long lesions (≥100 mm) showed a reduced restenosis rate in the PEB + BMS versus PTA + BMS groups (21% vs. 62%, p=0.01). Restenosis rate was significantly lower in the PEB + BMS than in the PTA + BMS group, irrespective of the recanalization approach (true lumen vs. subintimal). LLL was significantly lower in the PEB + BMS group compared with the PTA + BMS group.

In Bague et al[5], a sub-group analysis was performed to compare the 10 patients defined as protocol violation with the others; there was no statistically significant difference in terms of TLR (90.5 ± 4.5% vs. 88.9 ± 10.5%; p = .42), TER (90.5 ± 4.6% vs. 88.9 ± 0.5%; p = .42), survival (95.1 ± 3.4% vs. 100%; p = .49), primary (83.6 ± 5.7% vs. 77.8 ± 0.45%; p = .45), or secondary (92.7 ± 4.1% vs. 88.9 ± 10.5%; p = 0.52) clinical improvement. Tosaka class I (25 lesions) and class II lesions (29 lesions) were compared in terms of freedom from TLR at 1 year. There was no significant difference between these groups (87.1 ± 7.0% versus 92.7 ± 5.0%; p = .44)

In Micari et al 2012[8], 2013[9], no statistically significant difference in patency rates was noted in stented patients compared with nonstented (69.2% vs. 75.4%, p = 0.426), in patients presenting with occlusive versus nonocclusive stenosis and in patients with severe calcified lesions versus non-severely calcified lesions.

In Micari et al 2016[10], 2017[11], patency was evaluated in patients with occlusive versus stenotic lesions.
The rate at 360 days was 88.4% (95% CI: 78.6% to 98.2%) versus 91.5% (95% CI: 83.5% to 99.5%), respectively, with no statistically significant difference (log-rank p = 0.1649). The rate of clinically driven TLR was 4% (95% CI: 0.2% to 7.8%). No statistically significant association with the primary endpoint in the multivariate analysis was revealed in the Cox proportional hazards model for any of the considered covariates. The proportion of asymptomatic (Rutherford class 0) patients increased from 0% at baseline to 58% at 12 months. In addition, no difference was observed, as to primary patency at 2-years, between patients with diabetes and patients without diabetes.

Significant differences of survival curves for primary patency were found in several subgroups, including male versus female, diabetic versus nondiabetic, smokers versus nonsmokers, lesions with heavy calcification versus non/mild/moderate calcification, lesion location (SFA only vs. popliteal involvement), and ISR versus in-stent reocclusion. De novo and nonstented restenosis showed a trend toward better patency versus ISR in Schmidt et al 2016[12].
Significant differences of survival curves for TLR were found in male versus female and de novo/ nonstented restenosis versus ISR lesions. To identify independent predictors of restenosis after 2 years, stepwise logistic regression was performed including all factors associated with significant differences in patency rates and factors that are thought to be associated with a higher restenosis rate (female sex, lesion length ≥24 cm, ISR, involvement of the PA, severe calcification, TASC C and D lesions, percutaneous transluminal angioplasty without prior atherectomy/thrombectomy, residual stenosis ≥30%, diabetes mellitus, smoking, obesity, and chronic.

In Grotti et al 2016[15], a post hoc sub-analysis was performed for major adverse events (MAEs), defined as death from any cause, major amputation, and clinically driven TLR. During the 3-year follow-up, 9 patients per group died, while 1 patient per group underwent major amputation.

In Werk et al 2012[17], subgroup analyses for the primary end point confirmed the significant superiority of DEB in the following lesion subtypes: de novo versus restenotic, nonocclusive versus occlusive, relatively short versus long lesions.
Further exploration of the association between postprocedural angiographic features and LLL showed that lesions with higher postprocedural residual stenosis were more likely to exhibit lower LLL values or even late lumen gain which constitutes an expression of plaque regression. Finally, angiographic analysis for safety up to 6 months showed freedom from aneurismal changes, ectasia, persistent dissection or thrombosis in all cases.

In Debing et al 2016[18], a subgroup analysis of stenosis treated with dilation only vs. those treated with stenting followed by postdilation demonstrated better results using DEB (p<0.05).
Considering both SFA and BTK non-stented lesions, a late lumen loss of 0.5±0.9 mm in the DEB group vs. 1.5±0.6 mm in the AB group (p<0.01) was showed. In those patients who had angioplasty performed after stent implantation, late lumen loss was 0.51±0.7 mm using DEB and 1.7±0.2 mm with AB (p<0.01).
Considering SFA non-stented lesions only, a late lumen loss of 0.38±0.4 mm in the DEB group vs. 1.54±1.1 mm in the AB group (p<0.05) was showed, while in patients who had angioplasty performed after stent implantation, late lumen loss was 0.51±0.7 mm using DEB and 1.7±0.2 mm with AB (p<0.05).
Moreover, patients who received treatment with DEB alone (considering both SFA and BTK lesions) were analysed to correlate results with the amount of calcium on the arterial wall estimated from CTA axial images

and stratified into 4 categories (grade 4 represented the highest calcium burden). Late lumen loss was 0.49±0.2 mm in grade 1 patients, 0.63±0.3 mm in grade 2, 0.7±0.2 mm in grade 3, and 0.75±0.2 mm in grade 4. TLR was more frequent in patients with grades 3 (1 case) and 4 (1 case) calcification; the previously mentioned thrombotic event occurred in a patient with significant (grade 4) calcification, as did the only major amputation.

7.3.5 If applicable, provide details of the numbers of patients who were eligible to enter the study(s), randomised, and allocated to each treatment in an appropriate format.

Study flowcharts provided within the appendix.

7.3.6 If applicable provide details of and the rationale for, patients that were lost to follow-up or withdrew from the studies.

When applicable, the patient withdrawals and patients lost to follow-up are listed in the flow-charts mentioned in section 7.4.5 or in table B5 and B6.

7.4 Critical appraisal of relevant studies

7.4.1 Complete a separate quality assessment table for each study. A suggested format for the quality assessment results is shown in tables B7 and B8.

Table B 7 Critical appraisal of randomised control trials

Study name	**INPACT SFA** [Tepe et al 2015[3] (12 months); Laird et al 2015[4] (24 Months); Krishan, 2016 (unpublished)]	
Study question	**Response (yes/no/not clear/N/A)**	**How is the question addressed in the study?**
Was randomisation carried out appropriately?	Yes	Subjects were randomly assigned by an Interactive Voice Response System with the use of a method of permuted blocks to ensure that a 2:1 ratio was maintained across sites
Was the concealment of treatment allocation adequate?	Yes	The patients were blinded to the treatment assignments through the completion of all 12-month follow-up evaluations.
Were the groups similar at the outset of the study in terms of prognostic factors, for example, severity of disease?	Yes	The treatment groups were well matched at baseline with similar demographics, comorbidities, and lesion characteristics.
Were the care providers, participants and outcome assessors blind to treatment allocation? If any of these people were not blinded, what might be the likely impact on the risk of bias (for each outcome)?	No	The patients and the trial sponsor were blinded to the treatment assignments through the completion of all 12-month follow-up evaluations. The independent core laboratories and clinical events committee will remain blinded to the treatment assignments throughout the 60-month follow-up duration. Because of the visual difference between the IN.PACT DCB and standard PTA balloon, treating physicians, research coordinators, and catheterization laboratory staff were not blinded to the treatment assignment.
Were there any unexpected imbalances in drop-outs between groups? If so, were they explained or adjusted for?	No	No unexpected imbalances (See table B 5)
Is there any evidence to suggest that the authors measured more outcomes than they reported?	No	

Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Yes	**All analyses were based on the intention-to-treat principle.** Multiple imputation was performed by using the logistic regression approach for patients with missing primary endpoint data. The following variables were included in the imputation model as covariates: age, sex, diabetes mellitus, lesion length, total occlusion, and Rutherford class at baseline. Five data sets were imputed from these covariates that mimic different realizations of the missing data. Within each imputed data set for the endpoint, the proportion experiencing the endpoint was statistically compared between treatment groups by using the 2-sample Z test. From these, an overall test statistic for the endpoint and its associated P value were calculated for the imputed data. The imputed difference (95% confidence interval) and P value are reported along with the as-observed numerator and denominator. A sensitivity analysis of the as-observed rates revealed a similar highly significant - P value (P<0.001).
Study name	**DEBATE-SFA Trial** (Liistro et al 2013[7])	
Study question	**Response (yes/no/not clear/N/A)**	**How is the question addressed in the study?**
Was randomisation carried out appropriately?	Yes	Lesions were randomly assigned 1:1 to undergo either PEB (paclitaxel-eluting balloon) followed by nitinol bare-metal stent (BMS) implantation (PEB + BMS group) or standard PTA (percutaneous transluminal angioplasty) followed by nitinol stent implantation (PTA + BMS group) according to a computer-generated random series of numbers. Randomization was performed by block randomization (blocks of 10 patients).
Was the concealment of treatment allocation adequate?	Not clear	No details regarding the concealment of treatment allocation are provided
Were the groups similar at the outset of the study in terms of prognostic factors, for example, severity of disease?	Yes	There were no significant differences in any demographic or clinical characteristics at baseline between the 2 groups.
Were the care providers, participants and outcome assessors blind to treatment allocation? If any of these people were not blinded, what might be the likely impact on the risk of bias (for each outcome)?	No	Due to differences in technique between PEB and PTA it was not possible to blind participants, treating physicians and other staff members. Only outcome assessment operators were blinded (without knowledge of clinical status and randomization group).
Were there any unexpected imbalances in drop-outs between groups? If so, were they explained or adjusted for?	No	No unexpected imbalances in drop-outs between groups.
Is there any evidence to suggest that the authors measured more outcomes than they reported?	No	
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate	Yes	No cross-over or dropouts (only 2 patients in the PEB + BMS group died before lesion evaluation).

methods used to account for missing data?		
Study name	**FAIR Trial** (Krankenberg et al 2015[6])	
Study question	**Response (yes/no/not clear/N/A)**	**How is the question addressed in the study?**
Was randomisation carried out appropriately?	Yes	After a parallel-group, block randomization with a block size of 10 and an allocation ratio of 1:1, patients were assigned to either DCB (Drug-Coated Balloon Angioplasty) or POBA (Plain Old Balloon Angioplasty).
Was the concealment of treatment allocation adequate?	Yes	Allocation sequence was concealed from the investigators by sequentially numbered, opaque, sealed envelopes.
Were the groups similar at the outset of the study in terms of prognostic factors, for example, severity of disease?	Yes	Patients groups were well matched with respect to risk factors and lesion characteristics.
Were the care providers, participants and outcome assessors blind to treatment allocation? If any of these people were not blinded, what might be the likely impact on the risk of bias (for each outcome)?	No	Due to differences in technique between DCB and POBA it was not possible to blind participants, treating physicians and other staff members. The core-laboratory that confirmed restenosis assessment done at study sites was blinded.
Were there any unexpected imbalances in drop-outs between groups? If so, were they explained or adjusted for?	No	No unexpected imbalances in drop-outs between groups.
Is there any evidence to suggest that the authors measured more outcomes than they reported?	No	
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Not clear	Analyses were performed for all enrolled cases. No details are provided regarding the methods used to account for missing data.
Study name	**DEBELLUM Trial** (Fanelli et al 2012[19])	
Study question	**Response (yes/no/not clear/N/A)**	**How is the question addressed in the study?**
Was randomisation carried out appropriately?	Yes	Patients were randomized (1:1) without stratification using computer-generated assignments.
Was the concealment of treatment allocation adequate?	Yes	Randomization occurred after the patients entered the angiographic suite.
Were the groups similar at the outset of the study in terms of prognostic factors, for example, severity of disease?	Yes	There were no significant differences in any demographic or clinical characteristics at baseline between the 2 groups.
Were the care providers, participants and outcome assessors blind to treatment allocation? If any of these people were not blinded, what might	No	Patients, but not operators, were blinded to the assigned intervention (drug-eluting balloons vs conventional angioplasty balloons) but it is not

be the likely impact on the risk of bias (for each outcome)?		specified whether they remained blinded for the whole follow-up duration. Postoperative evaluation was deferred to different physicians not informed about the assigned intervention.
Were there any unexpected imbalances in drop-outs between groups? If so, were they explained or adjusted for?	No	No unexpected imbalances in drop-outs between groups.
Is there any evidence to suggest that the authors measured more outcomes than they reported?	No	
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Yes	All data were analysed according to the intention-to-treat principle. No need to account for missing data as no dropouts nor cross-overs occurred.
Study name	**PACIFIER** (Werk et al 2012[17])	
Study question	**Response (yes/no/not clear/N/A)**	**How is the question addressed in the study?**
Was randomisation carried out appropriately?	Yes	The randomization sequence was computer generated, in blocks of 10 patients each.
Was the concealment of treatment allocation adequate?	Yes	Allocation concealment was guaranteed using numbered, opaque, sealed envelopes, which were only opened after the decision was made that the patient had to be treated according to the protocol.
Were the groups similar at the outset of the study in terms of prognostic factors, for example, severity of disease?	Yes	No clinically relevant differences were found comparing the 2 groups in the prognostically relevant variables; treatment groups differed slightly in respect of mean baseline diameter stenosis and a lower rate of postprocedural dissections.
Were the care providers, participants and outcome assessors blind to treatment allocation? If any of these people were not blinded, what might be the likely impact on the risk of bias (for each outcome)?	No	The operators could not be blinded to the assigned treatment because of the different appearance of coated and uncoated balloons. Angiographic analyses were performed by an independent core-laboratory blinded to treatment assignment.
Were there any unexpected imbalances in drop-outs between groups? If so, were they explained or adjusted for?	No	No unexpected imbalances in drop-outs between groups.
Is there any evidence to suggest that the authors measured more outcomes than they reported?	No	
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Not clear	Analyses were performed for all enrolled cases. No details are provided regarding the methods used to account for missing data.
Study name	**Belgian diabetic IN.PACT Trial** (Debing et al 2016[18])	
Study question	**Response**	**How is the question addressed in the study?**

	(yes/no/not clear/N/A)	
Was randomisation carried out appropriately?	Yes	Patients were randomized at a ratio of 1:1 to POBA (Plain Old Balloon Angioplasty) or IN.PACT DCB (Drug-coated balloon).
Was the concealment of treatment allocation adequate?	Yes	The allocation sequence was concealed by means of sealed and consecutive envelops.
Were the groups similar at the outset of the study in terms of prognostic factors, for example, severity of disease?	Yes	Most characteristics were well matched between the groups, except for incidence of cerebrovascular disease.
Were the care providers, participants and outcome assessors blind to treatment allocation? If any of these people were not blinded, what might be the likely impact on the risk of bias (for each outcome)?	No	Neither the patient, the investigator, the independent angiographic nor the ultrasound laboratories were blinded.
Were there any unexpected imbalances in drop-outs between groups? If so, were they explained or adjusted for?	No	No unexpected imbalances in drop-outs between groups.
Is there any evidence to suggest that the authors measured more outcomes than they reported?	No	
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Not clear	Analyses were performed for all enrolled cases. No details are provided regarding the methods used to account for missing data.
Adapted from Centre for Reviews and Dissemination (2008) Systematic reviews. CRD's guidance for undertaking reviews in health care. York: Centre for Reviews and Dissemination		

Table B 8 Critical appraisal of observational studies

Study name: PLAISIR Trial (Bague et al 2017[5])		
Study question	**Response yes/no/not clear/N/A)**	**How is the question addressed in the study?**
Was the cohort recruited in an acceptable way?	Yes	Prospective study, inclusion and exclusion criteria are well defined. Not specified if patients were consecutive.
Was the exposure accurately measured to minimise bias?	Yes	Multicentre study, blinded review of patients, no groups. All major cardiovascular adverse events recorded.
Was the outcome accurately measured to minimise bias?	Yes	Objective and validated measures have been used for primary and secondary endpoint.
Have the authors identified all important confounding factors?	Yes	Potential confounding factors discuss in a specific section of the article.
Have the authors taken account of the confounding factors in the design and/or analysis?	No	This study was not designed to analyse confounding factors (acknowledged by authors). Only a sub-group analysis for 10 patients identified as not respecting inclusion criteria has been performed.

Was the follow-up of patients complete?	Yes	53 patients enrolled. At 12-months follow-up (primary endpoint): 3 lost to follow-up at 12 months, 1 death right after the procedure.
How precise (for example, in terms of confidence interval and p values) are the results?	Yes	P values and confidence intervals reported. Continuous measures reported as mean ± standard deviation
Study name*:* Real-world Registry (Schmidt et al 2016[12])		
Study question	**Response yes/no/not clear/N/A)**	**How is the question addressed in the study?**
Was the cohort recruited in an acceptable way?	Yes	Retrospective analysis. Only exclusion criteria are defined. No inclusion criteria were applied.
Was the exposure accurately measured to minimise bias?	Yes	All adverse events have been recorded. Single centre.
Was the outcome accurately measured to minimise bias?	Yes	Objective and validated measures have been used for primary and secondary endpoint. No groups.
Have the authors identified all important confounding factors?	Yes	Potential confounding factors (single technique analysed, ultrasound performed in different centres, dropout) discussed in a specific section of the article. Clinical, angiographic and procedural variables have been also identified.
Have the authors taken account of the confounding factors in the design and/or analysis?	Yes	The possible influence of clinical, angiographic and procedural variables on restenosis has been evaluated. A stratified analysis has been conducted for primary endpoint.
Was the follow-up of patients complete?	Yes	288 lesions (260 patients) at baseline. 245 lesions (85.1%) at 12-month follow-up. 233 lesions (80.9%) at 24-month follow-up.
How precise (for example, in terms of confidence interval and p values) are the results?	Yes	P values reported. Other measures reported as mean ± standard deviation
Study name: **Drug-eluting balloons for the treatment of the superficial femoral artery in-stent restenosis: 2-year follow-up** (Virga et al 2014[14])		
Study question	**Response yes/no/not clear/N/A)**	**How is the question addressed in the study?**
Was the cohort recruited in an acceptable way?	Yes	Prospective registry, inclusion criteria are defined, patients were consecutive. Exclusion criteria not specified.
Was the exposure accurately measured to minimise bias?	No	Single centre registry. Only cardiac and cerebrovascular adverse events recorded.
Was the outcome accurately measured to minimise bias?	Yes	Objective and validated measures have been used for primary and secondary endpoint.
Have the authors identified all important confounding factors?	Yes	Several possible predictors of restenosis have been identified.

Have the authors taken account of the confounding factors in the design and/or analysis?	Yes	An exploratory analysis has been undertaken to identify predictors of restenosis.
Was the follow-up of patients complete?	Yes	At 24-months follow-up (primary endpoint): 70.3% of enrolled patients.
How precise (for example, in terms of confidence interval and p values) are the results?	Yes	P values reported. Measures reported as mean ± standard deviation
Study name: SFA-Long Study (Micari et al 2016[10], 2017[11])		
Study question	**Response yes/no/not clear/N/A)**	**How is the question addressed in the study?**
Was the cohort recruited in an acceptable way?	Yes	Prospective analysis. Inclusion and exclusion criteria are defined, consecutive patients.
Was the exposure accurately measured to minimise bias?	Yes	Multicentre study, all adverse events have been recorded.
Was the outcome accurately measured to minimise bias?	Yes	Objective and validate measures have been used for primary and secondary endpoint. No groups.
Have the authors identified all important confounding factors?	Yes	Known prognosis factors have been considered. Also, possible limitations of the study (focus on single treatment strategy and on patients with claudication, 50% of sites enrolled 86% of patients) discussed in a specific section.
Have the authors taken account of the confounding factors in the design and/or analysis?	Yes	The influence of potential prognosis factors has been evaluated with Cox proportional hazards multivariate regression analysis.
Was the follow-up of patients complete?	Yes	12-month follow-up: 96.2% of enrolled patients 24-month follow-up: 93.3% of enrolled patients
How precise (for example, in terms of confidence interval and p values) are the results?	Yes	95% Confidence Intervals reported for results of primary and secondary objectives. P-values reported.
Study name: Multicentre Italian Registry (Micari et al 2012[8], 2013[9]).		
Study question	**Response yes/no/not clear/N/A)**	**How is the question addressed in the study?**
Was the cohort recruited in an acceptable way?	Yes	Prospective registry, consecutive patients, inclusion and exclusion criteria are well defined.
Was the exposure accurately measured to minimise bias?	Yes	Multicentre registry. All adverse events recorded.
Was the outcome accurately measured to minimise bias?	Yes	Objective and validated measures have been used for primary and secondary endpoint.
Have the authors identified all important confounding factors?	Yes	Focus on single treatment strategy and on patients without severe critical limb ischemia acknowledged by authors.

Have the authors taken account of the confounding factors in the design and/or analysis?	No	Exploratory analysis to identify predictors of restenosis from baseline characteristics.
Was the follow-up of patients complete?	Yes	12-month follow-up: 87.6% of enrolled patients 24-month follow-up: 93.3% of enrolled patients
How precise (for example, in terms of confidence interval and p values) are the results?	Yes	P values and confidence interval reported. Measures reported as mean ± standard deviation
Study name: DEBATE-ISR Study (Grotti et al 2016[15])		
Study question	**Response yes/no/not clear/N/A)**	**How is the question addressed in the study?**
Was the cohort recruited in an acceptable way?	Yes	Prospective study. Consecutive patients, inclusion criteria are defined.
Was the exposure accurately measured to minimise bias?	Yes	All major adverse events have been reported. Control group selected.
Was the outcome accurately measured to minimise bias?	Yes	Objective and validated measures have been used for primary and secondary endpoint.
Have the authors identified all important confounding factors?	Yes	Authors acknowledged: - No propensity score matching between treatment and control group - Lack of external data adjudication and core laboratory
Have the authors taken account of the confounding factors in the design and/or analysis?	Yes	Exploratory regression analysis to identify possible predictors of restenosis, then included in multivariate models.
Was the follow-up of patients complete?	Yes	1-6-12-24-36-month follow-ups.9 patients per group died, 1 patient per group underwent amputation.
How precise (for example, in terms of confidence interval and p values) are the results?	Yes	P values reported. Continuous variables reported as mean ± standard deviation
Study name: Drug-eluting balloon for treatment of superficial femoral artery in-stent restenosis (Stabile et al 2012[13])		
Study question	**Response yes/no/not clear/N/A)**	**How is the question addressed in the study?**
Was the cohort recruited in an acceptable way?	Yes	Prospective registry. Inclusion and exclusion criteria are defined, consecutive patients.
Was the exposure accurately measured to minimise bias?	No	Single centre study. Only cardiovascular or cerebrovascular events related to the procedure have been recorded.
Was the outcome accurately measured to minimise bias?	Yes	Objective and validate measures have been used for primary and secondary endpoint.
Have the authors identified all	Yes	Baseline clinical characteristics of patients are described and lesions classified.

important confounding factors?		
Have the authors taken account of the confounding factors in the design and/or analysis?	No	No stratified or sensitivity analysis.
Was the follow-up of patients complete?	Yes	12-month follow-up: 92.1% of enrolled patients (3 patients lost to follow-up, 1 death).
How precise (for example, in terms of confidence interval and p values) are the results?	Yes	P-values reported. Continuous variables reported as mean ± standard deviation

7.5 Results of the relevant studies

7.5.1 Complete a results table for each study with all relevant outcome measures pertinent to the decision problem. A suggested format is given in table B9.

Table B 9 Outcomes from published studies

Study name		**IN.PACT SFA** [Tepe et al 2015[3], Laird et al 2015[4], Krishan, 2016 (unpublished)]
Size of study groups	**Treatment**	DCB (n=220)
	Control	PTA (n=111)
Study duration	**Time unit**	**Enrollment** • Phase I: between September 2010 and April 2011; • Phase II: between April 2012 and January 2013. **Follow-up** • Up to 5 years
Type of analysis	**Intention-to - treat/per protocol**	Intention-to-treat
Outcome	**Name**	Procedural success, % (m/n)
	Unit	Residual diameter stenosis of ≤50% for no stented patients or ≤30% for stented patients
Effect size	**Value**	DCB **99.5%;** PTA **98.2%**
	95% CI	Not reported
Statistical test	**Type**	Z test 1-sided
	p value	0.1
Other outcome	**Name**	Freedom from clinically driven TLR or freedom from restenosis
	Unit	Phase I 12 months: DCB **82.2%**; PTA **52.4%** Phase II 24 months: DCB **78.9%**; PTA **50.1%** Phase III 36 months: DCB **69.5%**; PTA **45.1%**
Effect size	**Value**	Not reported
	95% CI	12 months: z test 24 Months: Kaplan Meier by using log rank test 36 Months: Kaplan Meier by using log rank test
Statistical test	**Type**	Phase I 12 months: **<0.001** Phase II 24 months: **<0.001** Phase III 36 months: **<0.001**
	p value	Freedom from clinically driven TLR or freedom from restenosis
Other outcome	**Name**	Efficacy - Clinically driven target lesion revascularization

	Unit	Proportion rate of clinically driven TLR – number of subjects with TLR over number of evaluable subjects at each annual visit
Effect size	**Value**	Phase I 12 months: DCB **2.4%**; PTA **20.6%** Phase II 24 months: DCB **9.1%**; PTA **28.3%** Phase III 36 months: DCB **15.2%**; PTA **31.1%**
	95% CI	Not reported
Statistical test	**Type**	Phase I 12 months: Z test 1-sided Phase II 24 months: Student t test Phase III 36 months: Fisher exact test, 2-sided
	p value	Phase I 12 months: **<0.001** Phase II 24 months: **<0.001** Phase III 36 months: **0.002**
Other outcome	**Name**	Efficacy- restenosis
	Unit	Binary restenosis rate
Effect size	**Value**	Phase I 12 months: not assessed Phase II 24 months: DCB **19.8%**; PTA **46.9%**
	95% CI	Not reported
Statistical test	**Type**	Kaplan-Meier by using log rank test
	p value	**<0.001**
Other outcome	**Name**	Efficacy -Primary sustained clinical improvement
	Unit	Proportion rate – number of subjects with freedom from target limb amputation, target vessel revascularization, and increase in Rutherford class over number of evaluable subjects at each annual visit
Effect size	**Value**	Phase I 12 months: DCB **85.2%**; PTA **68.9%** Phase II 24 months: DCB **76.9%**; PTA **59.2%** Phase III 36 months: DCB **68.7%**; PTA **52.6%**
	95% CI	Not reported
Statistical test	**Type**	Fisher exact test, 2-sided
	p value	Phase I 12 months: **<0.001** Phase II 24 months: **0.003** Phase III 36 months: **0.012**
Other outcome	**Name**	ABI/TBI at each annual visit
	Unit	mean ABI/TBI
Effect size	**Value**	Phase I 12 months: DCB=**0.951 ± 0.221**; PTA=**0.886 ± 0.169** Phase II 24 months: DCB=**0.924 ± 0.261**; PTA=**0.938 ± 0.184** Phase III 36 months: DCB=**0.917 ± 0.231**; PTA=**0.894 ± 0.194**
	95% CI	See SD above
Statistical test	**Type**	T-test 2-sided
	p value	Phase I 12 months: **0.002** Phase II 24 months: 0.611 Phase III 36 months: 0.429
Other outcome	**Name**	Functional outcomes - Improvement in quality of life
	Unit	Mean change from baseline by EQ-5D index
Effect size	**Value**	Phase I 12 months: DCB=**0.106 ± 0.209**; PTA=**0.073 ±0.195** Phase II 24 months: DCB=**0.096 ± 0.216**; PTA=**0.055 ± 0.229** Phase III 36 months: DCB= **0.083 ± 0.229**; PTA=**0.066 ± 0.198**
	95% CI	See SD above
Statistical test	**Type**	T-test 2-sided
	p value	Phase I 12 months: 0.095 Phase II 24 months: 0.151 Phase III 36 months: 0.556
Other outcome	**Name**	Functional outcomes - Walking impairment
	Unit	Walking Impairment %
Effect size	**Value**	Phase I 12 months: DCB=**72.7 ± 31.4**; PTA=**73.6 ± 29.5** Phase II 24 months: DCB=**72.5 ± 34.1**; PTA=**67.2 ± 33.6**

		Phase III 36 months: DCB= **71.8 ± 34.2**; PTA=**74.7 ± 29.2**
	95% CI	See SD above
Statistical test	**Type**	T-test 2-sided
	p value	Phase I 12 months: 0.590 Phase II 24 months: 0.228 Phase III 36 months: 0.499
Other outcome	**Name**	Functional outcomes - Improvement in walking distance
	Unit	Mean change in 6MWT from baseline
Effect size	**Value**	Phase I 12 months: DCB=**38.7 ± 92.1**; PTA=**59.1 ± 102.3** Phase II 24 months: DCB=**30.9 ± 87.7**; PTA=**60.5 ± 97.6** Phase III 36 months: DCB= **9.0 ± 119.1**; PTA=**56.0 ± 101.4**
	95% CI	See SD above
Statistical test	**Type**	T-test 2-sided
	p value	Phase I 12 months: 0.878 Phase II 24 months: 0.117 Phase III 36 months:0.075
Other outcome	**Name**	Primary safety endpoint
	Unit	Proportion rate – number of subjects with freedom from 30-day device- and procedure-related death, target limb major amputation and clinically driven TLR over number of evaluable subjects at each annual visit
Effect size	**Value**	Phase I 12 months: DCB=0; PTA=0 (incidence rate) Phase II 24 months: DCB=87.4%; PTA=69.8% (freedom from event) Phase III 36 months: DCB= 81.2%; PTA=64.1% (freedom from event)
	95% CI	Not reported
Statistical test	**Type**	Phase I 12 months: Chi-square test 1-sided Phase II 24 months: Fisher exact test, 2-sided Phase III 36 months: Fisher exact test, 2-sided
	p value	Phase I 12 months: **<0.001** Phase II 24 months: **<0.001** Phase III 36 months: **0.002**
Other outcome	**Name**	Safety outcome - Target limb major amputation
	Unit	Proportion rate – number of subjects with target limb major amputation over number of evaluable subjects at each annual visit
Effect size	**Value**	Phase I 12 months: DCB=0; PTA=0 Phase II 24 months: DCB=0; PTA=0 Phase III 36 months: DCB=0; PTA=0
	95% CI	Not reported
Statistical test	**Type**	Fisher exact test, 2-sided
	p value	**>0.999**
Other outcome	**Name**	Safety outcome – Survival
	Unit	All-cause death
Effect size	**Value**	Phase I 12 months: DCB=**1.9%**; PTA=**0%** Phase II 24 months: DCB=**8.1%**; PTA=**0.9%** Phase III 36 months: DCB=**10.7%**; PTA=**1.9%**
	95% CI	Not reported
Statistical test	**Type**	Fisher exact test, 2-sided
	p value	Phase I 12 months: 0.930 Phase II 24 months: **0.008** Phase III 36 months: **0.006**
Other outcome	**Name**	Safety outcome- Thrombosis
	Unit	% of patients with thrombosis
Effect size	**Value**	Phase I 12 months: DCB=**1.4%**; PTA=**3.7%** Phase II 24 months: DCB=**1.5%**; PTA=**3.8%** Phase III 36 months: DCB=**2.0%**; PTA=**4.9%**

	95% CI	Not reported
Statistical test	**Type**	Fisher exact test, 2-sided
	p value	Phase I 12 months: 0.100 Phase II 24 months: 0.243 Phase III 36 months: 0.283
Comments		
Study name		**DEBATE SFA** [Liistro et al 2013[7]]
Size of study groups	**Treatment**	PEB + BMS = 53 patients (55 lesions)
	Control	PTA + BMS = 51 patients (55 lesions)
Study duration	**Time unit**	**Enrollment:** between November 2010 and November 2011 **Follow-up:** 12 months
Type of analysis	**Intention-to - treat/per protocol**	Intention-to-treat
Outcome	**Name**	Comparison of 12-month binary restenosis rate
	Unit	Number of binary restenosis/number of lesions
Effect size	**Value**	PEB + BMS= **17%**; PTA + BMS= **47%**;
	95% CI	Not reported
Statistical test	**Type**	X^2, Fisher exact test
	p value	**0.008**
Other outcome	**Name**	TLR incidence
	Unit	Freedom from TLR at 12 months
Effect size	**Value**	PEB + BMS= **83%**; PTA + BMS= **67%**;
	95% CI	Not reported
Statistical test	**Type**	Kaplan-Meier analysis by using log-rank test
	p value	**0.07**
Other outcome	**Name**	Major amputation at 12 months
	Unit	Number of major amputation occurred
Effect size	**Value**	PEB + BMS= 0; PTA + BMS= 0;
	95% CI	Not applicable
Statistical test	**Type**	Not applicable
	p value	Not applicable
Comments		
Study name		**Plaisir Trial** [Bague et al 2017[5]]
Size of study groups	**Treatment**	IN.PACT DCB 53 patients (55 limbs)
	Control	Not applicable
Study duration	**Time unit**	**Enrollment:** between January 2012 and June 2013 **Follow-up:** 18 months
Type of analysis	**Intention-to - treat/per protocol**	Intention-to-treat
Outcome	**Name**	Freedom from TLR rates at 12 and 18 months
	Unit	Survival rate
Effect size	**Value**	Both **90.2** ± **4.2%**

	95% CI	Not reported
Statistical test	**Type**	Kaplan Meier
	p value	Not applicable
Other outcome	**Name**	Freedom from TER rates at 12 and 18 months
	Unit	Survival rate
Effect size	**Value**	**85 ± 5%** and **76.6 ± 6.2%**, respectively
	95% CI	Not reported
Statistical test	**Type**	Kaplan Meier
	p value	Not applicable
Other outcome	**Name**	Survival at 18 months
	Unit	Survival rate
Effect size	**Value**	**96% ± 2.7%**
	95% CI	Not reported
Statistical test	**Type**	Kaplan-Meyer curves
	p value	Not applicable
Other outcome	**Name**	Primary and secondary sustained clinical Improvements at 1 year
	Unit	Sustained upward shift of ≥ 1 category of the Rutherford classification for claudicants and by wound healing and rest pain resolution for patients in CLI, with or without the need for repeated TLR in surviving patients.
Effect size	**Value**	**78.6 ± 5.7%** and **92.0 ± 3.8%**
	95% CI	Not reported
Statistical test	**Type**	Not applicable
	p value	Not applicable
Other outcome	**Name**	Primary and secondary sustained clinical Improvements at 18 months
	Unit	As above
Effect size	**Value**	**63.2 ± 6.7%** and **79.2 ± 5.9%**
	95% CI	Not reported
Statistical test	**Type**	Not applicable
	p value	Not applicable
Other outcome	**Name**	Primary patency rates at 12 months
	Unit	Patency without any re-intervention and with PSVR < 2.4.
Effect size	**Value**	**83.7%**
	95% CI	Not reported
Statistical test	**Type**	Not applicable
	p value	Not applicable
Other outcome	**Name**	Primary patency rates at 12 months (with reintervention)
	Unit	Patency with PSVR < 2.4 with the assistance of reintervention.
Effect size	**Value**	**78.1%**
	95% CI	Not reported
Statistical test	**Type**	Not applicable
	p value	Not applicable
Other outcome	**Name**	Mean ABI increase from baseline at 12 and 18 months
	Unit	Increase in ABI respect to baseline levels of 0.54 ± 0.37

Effect size	**Value**	12 months: **0.96 ± 0.54** 18 months: **0.92 ± 0.23**
	95% CI	Not reported
Statistical test	**Type**	Wilcoxon tests
	p value	12 months: **<0.001** 18 months: **0.01**
Other outcome	**Name**	Improvement in quality of life self-evaluation at 12 and 18 months
	Unit	Improvement in quality of life from baseline value 65.8 ± 14.1
Effect size	**Value**	12 months: **76.2 ± 16.3** 18 months: **72.3 ± 17.7**
	95% CI	Not reported
Statistical test	**Type**	Wilcoxon tests
	p value	12 months: 0.10 18 months: 0.14
Comments		
Study name		**FAIR Trial** [Krankenberg et al 2015[6]]
Size of study groups	**Treatment**	DCB (n=62)
	Control	POBA (n=57)
Study duration	**Time unit**	**Enrollment:** between January 2010 and November 2012 **Follow-up:** 12 months
Type of analysis	**Intention-to - treat/per protocol**	Intention-to-treat
Outcome	**Name**	Binary recurrent restenosis at 6 months
	Unit	Restenosis assessed by DUS (peak systolic velocity ratio ≥2.4)
Effect size	**Value**	DCB **15.4%** (8 of 52); POBA **44.7%** (21 of 47)
	95% CI	Not reported
Statistical test	**Type**	Fisher exact test, χ^2 test, and Kruskal-Wallis test
	p value	**0.002**
Other outcome	**Name**	Primary angiographic success
	Unit	Successful access and deployment of the device with ≤50% diameter residual stenosis without bailout procedures
Effect size	**Value**	DCB **95.1%** (51 of 61); POBA **78.9%** (45 of 57)
	95% CI	Not reported
Statistical test	**Type**	Fisher exact test, χ^2 test, and Kruskal-Wallis test
	p value	0.102
Other outcome	**Name**	Cumulative incidence of binary recurrent restenosis at 12 months
	Unit	Restenosis assessed by DUS (peak systolic velocity ratio ≥2.4).
Effect size	**Value**	DCB **29.5%** (13 of 44); POBA **62.5%** (25 of 40)
	95% CI	Not reported
Statistical test	**Type**	Fisher exact test, χ^2 test, and Kruskal-Wallis test
	p value	**0.004**
Other outcome	**Name**	Freedom from TLR at 6 and 12 months
	Unit	Recurrent restenosis ≥50% /re-occlusion and clinical signs
Effect size	**Value**	6 months: DCB **96.4%**; POBA **81.0%** 12 months: DCB **90.8%**; POBA **52.6.0%**
	95% CI	Not reported

Statistical test	**Type**	Kaplan – Meier by using log rank test
	p value	6 months: **0.011** 12 months: **<0.001**
Other outcome	**Name**	Hemodynamic success
	Unit	Ankle-brachial index (ABI) increase from baseline to discharge
Effect size	**Value**	DCB: from **0.63±0.27** to **0.94±0.30** POBA: from **0.64±0.25** to **0.81±0.22**
	95% CI	Not reported
Statistical test	**Type**	Student t test or Kolmogorov-Smirnov Test
	p value	Not reported
Other outcome	**Name**	Sustained clinical improvement at 6 and 12 months
	Unit	Increase by ≥1 Rutherford category
Effect size	**Value**	6 months: DCB **64.7%** (33 of 51); POBA **53.2%** (25 of 47) 12 months: DCB **66.7%** (30 of 45); POBA **70.5%** (31 of 44)
	95% CI	Not reported
Statistical test	**Type**	Fisher exact test, χ^2 test, and Kruskal-Wallis test
	p value	6 months: 0.413 12 months: 0.820
Other outcome	**Name**	Survival
	Unit	Rate of death at 12 months
Effect size	**Value**	DCB **3.2%** (n=2); POBA **5.3%** (n=3)
	95% CI	Not reported
Statistical test	**Type**	Kaplan-Meier by using log rank test
	p value	0.67
Comments		
Study name		**Multicentre Italian Registry** [Micari et al 2012[8], 2013[9]]
Size of study groups	**Treatment**	105 patients, 114 treated lesions
	Control	Not applicable
Study duration	**Time unit**	**Enrollment:** Not reported **Follow-up:** 27 ± 3 months
Type of analysis	**Intention-to - treat/per protocol**	N/A
Outcome	**Name**	Primary patency
	Unit	Freedom from the combined endpoints of TLR, occlusion rate and >50% restenosis in the treated lesion
Effect size	**Value**	6 Months: **87.8%** 1 Year: **83.7%** 2 Years: **72.4%**
	95% CI	Not reported
Statistical test	**Type**	Kaplan Meier
	p value	Not applicable
Other outcome	**Name**	Incidence of TLR
	Unit	Rate of TLR
Effect size	**Value**	6 Months: **4.4%** 1 Year: **7.6%** 2 Years: **7.1%**
	95% CI	Not reported
Statistical test	**Type**	Kaplan- Meier

	p value	Not applicable
Other outcome	**Name**	Secondary patency
	Unit	Freedom from the combined endpoints TLR, occlusion rate, and >50% restenosis in the treated lesion
Effect size	**Value**	1 Year: **90.2%** 2 Years: **84.7%**
	95% CI	Not reported
Statistical test	**Type**	Kaplan- Meier
	p value	Not applicable
Other outcome	**Name**	Major adverse events
	Unit	Composite of: death, amputation, TLR rates
Effect size	**Value**	1 Year: **9.8%** 2 Years: **17.5%**
	95% CI	Not reported
Statistical test	**Type**	Not applicable
	p value	Not applicable
Other outcome	**Name**	Change in Rutherford class
	Unit	Reduction in number of patients with RC 2,3 and 4 from baseline to 1 and 2 years
Effect size	**Value**	*
	95% CI	Not reported
Statistical test	**Type**	Kruskal-Wallis test
	p value	**<0.001**
Other outcome	**Name**	Change in ankle-brachial index (ABI)
	Unit	Change in ABI from baseline (0.56)
Effect size	**Value**	1 Year: **0.86** 2 Years: **0.88**
	95% CI	Not reported
Statistical test	**Type**	Student t test
	p value	**<0.001**
Other outcome	**Name**	Change in walking capacity at 12 months
	Unit	5-point walking impairment questionnaire that assessed walking distance, speed, ability to climb stairs, and symptoms with walking.
Effect size	**Value**	From baseline **40.3** to **86.1** at 12 months
	95% CI	Not reported
Statistical test	**Type**	Student t test
	p value	Not reported
Other outcome	**Name**	Change in absolute claudication distance (ACD) at 12 months
	Unit	Distance at which the patient could no longer ambulate based on the 6-min walking test.
Effect size	**Value**	Baseline: **111m** 1 year: **361m** 2 years: **418m**
	95% CI	Not reported
Statistical test	**Type**	Student t test
	p value	**<0.001**
Comment		*Please refer to the diagram in the paper.
Study name		**SFA-Long Study** [Micari et al 2016[10], 2017[11]]
	Treatment	105 patients 105 femoropopliteal lesions.

Size of study groups	**Control**	Not applicable
Study duration	**Time unit**	**Enrollment:** Not reported **Follow-up:** 24 months
Type of analysis	**Intention-to - treat/per protocol**	N/A
Outcome	**Name**	Primary patency
	Unit	Freedom from the combined endpoint of clinically driven TLR and >50% restenosis.
Effect size	**Value**	1 Year: **89.3%** 2 Years: **71 ± 5%**
	95% CI	1 Year: Not reported 2 Years: See SD above
Statistical test	**Type**	Kaplan- Meier
	p value	Not applicable
Other outcome	**Name**	Clinically driven TLR (incidence)
	Unit	TLR incidence rate
Effect size	**Value**	1 Year: **4%** 2 Years: **15.3%**
	95% CI	1 Year: **0.2%-7.8%** 2 Years: **9.2%-22.4%**
Statistical test	**Type**	Not applicable
	p value	Not applicable
Other outcome	**Name**	Clinically driven TLR (freedom)
	Unit	Freedom from clinically driven TLR
Effect size	**Value**	1 Year: **96%** 2 Years: **84.7%**
	95% CI	1 Year: **90.2%-98.9%** 2 Years: **77.6%-90.8%**
Statistical test	**Type**	Not applicable
	p value	Not applicable
Other outcome	**Name**	Major adverse events
	Unit	Composite of death of any cause, major target limb amputation, thrombosis at the target lesion site, or non–target lesion target vessel revascularization
Effect size	**Value**	1 Year: **6.9%** 2 Years: **10.2%**
	95% CI	1 Year: **2.8%-13.7%** 2 Years: not reported
Statistical test	**Type**	Not applicable
	p value	Not applicable
Other outcome	**Name**	Improve in Rutherford class
	Unit	Increase in proportion of asymptomatic patients from 0% at baseline
Effect size	**Value**	1 Year: **58%** 2 Years: **51%**
	95% CI	Not reported
Statistical test	**Type**	Not applicable
	p value	Not applicable
Other outcome	**Name**	Functional status
	Unit	Increase in ankle-brachial index (ABI) from baseline (0.63)
Effect size	**Value**	1 Year: **0.95** 2 Years: not reported

	95% CI	Not reported
Statistical test	**Type**	1 Year: Wilcoxon tests
	p value	1 Year: **<0.001**
Comment		
Study name		**Real-world registry** [Schmidt et al 2016[12]]
Size of study groups	**Treatment**	260 patients, 288 limbs
	Control	Not applicable
Study duration	**Time unit**	**Enrolment:** between May 2009 and January 2012 **Follow-up:** 24 months
Type of analysis	**Intention-to - treat/per protocol**	N/A
Outcome	**Name**	Primary patency
	Unit	Freedom from >50% restenosis or digital subtraction angiography, and freedom from TLR
Effect size	**Value**	1 Year: **79.2 ± 2.6%** 2 Years: **53.7 ± 3.4%**
	95% CI	Not reported
Statistical test	**Type**	Kaplan-Meier
	p value	Not reported
Other outcome	**Name**	Clinically driven TLR
	Unit	Freedom from clinically driven TLR
Effect size	**Value**	1 Year: **85.4 ± 2.1%** 2 Years: **68.6 ± 3.0%**
	95% CI	Not reported
Statistical test	**Type**	Kaplan-Meier
	p value	Not reported
Other outcome	**Name**	Clinical improvement (Rutherford)
	Unit	Increase of at least 1 Rutherford category
Effect size	**Value**	1 Year: **73.3% of limbs** 2 Years: **66.4% of limbs**
	95% CI	Not reported
Statistical test	**Type**	Not applicable
	p value	Not applicable
Other outcome	**Name**	Clinical improvement (Rutherford)
	Unit	No change in Rutherford category
Effect size	**Value**	1 Year: **18.6% of limbs** 2 Years: **19.6% of limbs**
	95% CI	Not reported
Statistical test	**Type**	Not applicable
	p value	Not applicable
Other outcome	**Name**	Clinical improvement (Rutherford)
	Unit	Deterioration in Rutherford category
Effect size	**Value**	1 Year: **8.1% of limbs** 2 Years: **13.1% of limbs**
	95% CI	Not reported
Statistical test	**Type**	Not applicable
	p value	Not applicable

Other outcome	**Name**	Safety
	Unit	Cumulative major amputation rate
Effect size	**Value**	1 Year: **1.4% of limbs** 2 Years: **2.1% of limbs**
	95% CI	Not reported
Statistical test	**Type**	Not applicable
	p value	Not applicable
Other outcome	**Name**	Mortality
	Unit	Cumulative mortality rate
Effect size	**Value**	1 Year: **4.6% of patients** 2 Years: **10.4% of patients**
	95% CI	Not reported
Statistical test	**Type**	Kaplan Meier
	p value	Not reported
Comment		
Study name		**Prospective Registry** [Stabile et al 2012[13], Virga et al 2014[14]]
Size of study groups	**Treatment**	39 patients
	Control	Not provided
Study duration	**Time unit**	**Enrolment:** between December 2009 and December 2010 **Follow-up:** 24 months
Type of analysis	**Intention-to - treat/per protocol**	N/A
Outcome	**Name**	Primary patency
	Unit	PVR of <2.4 without TLR
Effect size	**Value**	1 year: **92.1%** 2 years: **70.3%**
	95% CI	Not reported
Statistical test	**Type**	Student t test
	p value	Not applicable
Other outcome	**Name**	TLR incidence
	Unit	Freedom from TLR
Effect size	**Value**	1 year: **92.1%** 2 years: **78.4%**
	95% CI	Not reported
Statistical test	**Type**	Kaplan-Meier
	p value	Not applicable
Other outcome	**Name**	Secondary patency
	Unit	Freedom from recurrent restenosis
Effect size	**Value**	1 year: **100%** 2 years: **87%**
	95% CI	Not applicable
Statistical test	**Type**	Not applicable
	p value	Not applicable
Other outcome	**Name**	Clinical success
	Unit	Change in Rutherford class
Effect size	**Value**	Baseline: **2.9 ± 0.7** 1 year: **0.8 ± 0.5**

		2 years: **06 ± 0.7**
	95% CI	See SD above
Statistical test	**Type**	Student t test
	p value	1 year: **<0.05** 2 years: **<0.05**
Other outcome	**Name**	Hemodynamic success
	Unit	Change in Ankle-Brachial Index
Effect size	**Value**	Baseline: **0.77 ± 0.09** 1 year: **0.98 ± 0.02** 2 years: **0.94 ±0.09**
	95% CI	See SD above
Statistical test	**Type**	Student t test
	p value	1 year: **<0.05** 2 years. **<0.05**
Other outcome	**Name**	Survival
	Unit	All-cause and cardiovascular mortality
Effect size	**Value**	1 year: **2.6%** 2 years: **5.1%**
	95% CI	Not reported
Statistical test	**Type**	Not applicable
	p value	Not applicable
Comment		
Study name		**DEBATE ISR Study** [Grotti et al 2016[15]]
Size of study groups	**Treatment**	PEB
	Control	BA
Study duration	**Time unit**	**Enrolment**: between January 2010 and December 2011 **Follow-up:** 36 months
Type of analysis	**Intention-to - treat/per protocol**	N/A
Outcome	**Name**	TLR incidence
	Unit	TLR incidence rate at 36 months
Effect size	**Value**	DEB: **40% ;** BA: **43%**
	95% CI	Not reported
Statistical test	**Type**	X^2 test or Fisher exact test
	p value	0.8
Other outcome	**Name**	TLR at 36 months (freedom)
	Unit	Freedom from TLR at 36 months
Effect size	**Value**	DEB: **60%;** BA: **57%**
	95% CI	See SD above
Statistical test	**Type**	Kaplan-Meier (log rank test)
	p value	0.59
Comment		.
Study name		**PACIFIER Trial** [Werk et al 2012[17]]
Size of study groups	**Treatment**	41 patients, 44 lesions
	Control	44 patients, 47 lesions

Study duration	**Time unit**	**Enrolment:** not reported **Follow-up:** 12 months
Type of analysis	**Intention-to - treat/per protocol**	Intention to treat
Outcome	**Name**	Primary endpoint
	Unit	Late lower loss at 6 months
Effect size	**Value**	DEB: **-0.01 mm;** Non-DEB**: 0.65 mm**
	95% CI	DEB: **[-0.29; 0.26];** Non-DEB: **[-0.37; 0.93]**
Statistical test	**Type**	Wilcoxon rank sum test
	p value	**0.001**
Other outcome	**Name**	Binary restenosis at 6 months
	Unit	Rate of binary restenosis at 6 months
Effect size	**Value**	DEB: **8.6%;** Non-DEB: **32.4%**
	95% CI	Not reported
Statistical test	**Type**	X^2 or Fisher exact test
	p value	**0.01**
Other outcome	**Name**	TLR at 6 months
	Unit	TLR incidence, n (%)
Effect size	**Value**	DEB: **3 (7.1%);** Non-DEB: **9 (21.4%)**
	95% CI	Not reported
Statistical test	**Type**	Proportional hazard Cox regression and log-rank tests
	p value	0.12 (referring to the number of cases with DEB)
Other outcome	**Name**	TLR at 12 months
	Unit	TLR incidence, n (%)
Effect size	**Value**	DEB: **3 (7.1%);** Non-DEB: **12 (27.9%)**
	95% CI	Not reported
Statistical test	**Type**	Proportional hazard Cox regression and log-rank tests
	p value	**0.02** (referring to the number of cases with DEB)
Other outcome	**Name**	Major adverse incidence (MAE) at 6 months
	Unit	Composite of death, amputation or TLR at 6 months, n (%)
Effect size	**Value**	DEB: **3 (7.1%);** Non-DEB: **11 (26.2%)**
	95% CI	Not reported
Statistical test	**Type**	Proportional hazard Cox regression and log-rank tests
	p value	**0.04**
Other outcome	**Name**	Major adverse incidence (MAE) at 12 months
	Unit	Composite of death, amputation or TLR at 12 months, n (%)
Effect size	**Value**	DEB: **3 (7.1%);** Non-DEB: **15 (34.9%)**
	95% CI	Not reported
Statistical test	**Type**	Proportional hazard Cox regression and log-rank tests
	p value	**0.003**
Other outcome	**Name**	Rutherford class at 6 months
	Unit	Change in Rutherford class at 6 months
Effect size	**Value**	Improvement: DEB: **80%;** Non-DEB: **68.4%** None: DEB: **20%**; Non-DEB: **31.6%** Worsening: DEB: **0%**; Non-DEB: **0%**
	95% CI	Not reported

Statistical test	**Type**	Multinomial regression model
	p value	0.36
Comment		
Study name		**Belgian diabetic IN.PACT Trial** [Debing et al 2016[18]]
Size of study groups	**Treatment**	DCB: 52 patients
	Control	POBA: 54 patients
Study duration	**Time unit**	**Enrolment:** Between September 2012 and December 2014 **Follow-up:** 6 months
Type of analysis	**Intention-to - treat/per protocol**	Intention to treat
Outcome	**Name**	Primary patency
	Unit	Primary patency at 6 months
Effect size	**Value**	DCB = **73%;** POBA = **51%**
	95% CI	Not reported
Statistical test	**Type**	X^2 or Fisher exact test
	p value	**0.03**
Outcome	**Name**	Mean diameter restenosis
	Unit	6-month mean diameter restenosis
Effect size	**Value**	DCB = **28.8 ± 36.2%;** POBA = **45.9 ± 34.9%**
	95% CI	See SD above
Statistical test	**Type**	X^2 or Fisher exact test
	p value	**0.032**
Outcome	**Name**	Binary restenosis
	Unit	Binary restenosis rate
Effect size	**Value**	DCB = **27%;** POBA = **49%**
	95% CI	Not reported
Statistical test	**Type**	X^2 or Fisher exact test
	p value	**0.03**
Other outcome	**Name**	clTLR incidence
	Unit	clTLR rate at 6 months
Effect size	**Value**	DCB = **19%;** POBA = **29%**
	95% CI	Not reported
Statistical test	**Type**	X^2 or Fisher exact test
	p value	0.12
Other outcome	**Name**	Rutherford stage
	Unit	Change in Rutherford stage after 6 months follow-up
Effect size	**Value**	*
	95% CI	Not reported
Statistical test	**Type**	X^2 or Fisher exact test
	p value	0.83
Other outcome	**Name**	Major adverse events
	Unit	Incidence of: • All-cause death; • Minor amputation; • Major amputation;

		• Myocardial infarction.
Effect size	**Value**	• All-cause death: (**DCB = 5.7%; POBA = 5.5%**); • Minor amputation (**DCB = 7.7%; POBA = 9.2%**); • Major amputation (**DCB = 1.9%; POBA = 0%**); • Myocardial infarction (**DCB = 0%; POBA = 1.8%**).
	95% CI	Not reported
Statistical test	**Type**	X^2 or Fisher exact test
	p value	0.74
Comment		*See diagram about distribution of Rutherford stage before angioplasty and at 6-month follow-up.
Study name		**DEBELLUM Trial** [Fanelli et al 2012[19]]
Size of study groups	**Treatment**	DEB: 25 patients, 57 lesions, 33 limbs.
	Control	AB: 25 patients, 65 lesions, 38 limbs.
Study duration	**Time unit**	**Enrollment:** between September 2010 and March 2011 **Follow-up:** 6 months
Type of analysis	**Intention-to - treat/per protocol**	Intention to treat
Outcome	**Name**	Primary endpoint – Lumen loss
	Unit	Mean late lumen loss at 6 months
Effect size	**Value**	DEB = **0.41 ± 0.5 mm;** AB = **1.55 ± 1.3 mm**
	95% CI	See SD above
Statistical test	**Type**	Student t test
	p value	**<0.05**
Other outcome	**Name**	Binary restenosis at 6 months*
	Unit	Binary restenosis rate at 6 months*
Effect size	**Value**	DEB = **9.1%;** AB = **28.9%**
	95% CI	Not reported
Statistical test	**Type**	Fisher exact test
	p value	**0.03**
Other outcome	**Name**	TLR at 6 months*
	Unit	TLR rate at 6 months*
Effect size	**Value**	DEB = **6.1%;** AB = **23.6%**
	95% CI	Not reported
Statistical test	**Type**	Fisher exact test
	p value	**0.02**
Other outcome	**Name**	Incidence of amputation at 6 months*
	Unit	Amputation rate at 6 months*
Effect size	**Value**	DEB = **3%;** AB = **7.9%**
	95% CI	Not reported
Statistical test	**Type**	Fisher exact test
	p value	0.36
Other outcome	**Name**	Improvement in ABI at 6 months*
	Unit	Change in ABI at 6 months compared to baseline*
Effect size	**Value**	Pre/post DEB: **0.55 ± 0.1/ 0.87 ± 0.2;** Pre/post AB: **0.57 ± 0.1/ 0.70 ± 0.1**
	95% CI	See SD above
Statistical test	**Type**	Student t test

	p value	**0.02** (DEB patients vs AB patients)
Other outcome	**Name**	Fontaine stage at 6 months
	Unit	Fontaine stage I at 6 months*
Effect size	**Value**	DEB = **88%**; AB = **64%**
	95% CI	Not reported
Statistical test	**Type**	Fisher exact test
	p value	0.04 DEB patients vs. AB patients)
Comment		*These data refer to DEB patients with either SFA and BTK lesions

Table B 10 Outcomes from unpublished studies

		IN.PACT Global Study – Full cohort and sub-cohort analyses. All data not highlighted was presented at the conferences specified and is therefore publicly available. Data highlighted in yellow is currently unpublished and therefore academic in confidence.					
Study name		**IN.PACT Global Full Clinical Cohort at 12 months (Jaff, VIVA 2015)**	**IN.PACT Global Long Lesion Imaging Cohort at 12 months (Scheinert, EuroPCR 2015)**	**IN.PACT Global ISR Imaging Cohort at 12 months (Brodmann, VIVA 2015)**	**IN.PACT Global CTO Imaging Cohort at 12 months (Tepe, Charing Cross 2014)**	**IN.PACT Global Severe Calcium Cohort (LL, CTO IMG) at 12 months (Fanelli, Charing Cross 2017)**	**IN.PACT Global Standard vs. Wider Use at 12 months (Ansel, Charing Cross 2017)**
Size of study groups	**Treatment**	1416 enrolled, 1406 ITT	157	131	126	72	Standard Use (SU) (n=281) Wider Use (WU) (n=1125)
	Control	N/A	N/A	N/A	N/A	N/A	N/A
Study duration	**Time unit**	12 months (out of 60-month follow-up)	12 months (out of 60-month follow-up)	12 months (out of 60-month follow-up)	12 months (out of 60-month follow-up)	12 months (out of 60-month follow-up)	12 months (out of 60-month follow-up)
Type of analysis	**Intention-to-treat/per protocol**	ITT	ITT	ITT	ITT	Ad-hoc Analysis	Ad-hoc Analysis
Outcome 1	**Name**	Clinically-driven TLR (CD-TLR)					
	Unit	CD-TLR adjudicated by an independent Clinical Event Committee, blinded to the assigned treatment based on any re-intervention at the target lesion due to symptoms or drop of ABI of ≥20% or >0.15 when compared to post procedure baseline ABI					
Effect size	**Value**	7.5% (98/1311)	6.0% (8/134)	7.3% (9/124)	11.3% (13/115)	8.5% (5/59)	SU: 3.4% (9/265) WU: 8.5%(89/1046)
	95% CI	N/A	N/A	N/A	N/A	N/A	N/A
Statistical test	**Type**	Descriptive	Descriptive	Descriptive	Descriptive	Descriptive	
	p value	N/A	N/A	N/A	N/A	N/A	0.004
Outcome 2	**Name**	Any TLR					

	Unit	Any TLR includes clinically-driven and incidental or duplex-driven TLR					
Effect size	**Value**	7.8% (102/1311)	6.0% (8/134)	8.1% (10/124)	12.2% (14/115)	8.5% (5/59)	SU: 3.8% (10/265) WU: 8.8% (92/1046)
	95% CI	N/A	N/A	N/A	N/A	N/A	N/A
Statistical test	**Type**	Descriptive	Descriptive	Descriptive	Descriptive	Descriptive	
	p value	N/A	N/A	N/A	N/A	N/A	0.005
Outcome 3	**Name**	Primary Sustained Clinical Improvement					
	Unit	Primary sustained clinical improvement defined as freedom from target limb amputation, freedom from target vessel revascularization and increase in Rutherford class at 12 months					
Effect size	**Value**	80.6% (953/1183)	79.5% (101/127)	77.3% (92/119)	80.8% (80/99)	74.1% (40/54)	SU: 88.0% (206/234) WU: 78.7% (747/949)
	95% CI	N/A	N/A	N/A	N/A	N/A	N/A
Statistical test	**Type**	Descriptive	Descriptive	Descriptive	Descriptive	Descriptive	
	p value	N/A	N/A	N/A	N/A	N/A	<0.001
Outcome 4	**Name**	Freedom from clinically-driven TLR (Kaplan Meier at 360 days)					
	Unit	Freedom from clinically-driven Target Lesion Revascularization through 1 year					
Effect size	**Value**	92.6%	94.2%	92.9%	89.1%	92.3%	SU: 96.6% - WU: 91.7%
	95% CI	N/A	N/A	N/A	N/A	N/A	N/A
Statistical test	**Type**	non-parametric/survival	non-parametric/survival	non-parametric/survival	non-parametric/survival	non-parametric/survival	non-parametric/survival
	p value	N/A	N/A	N/A	N/A	N/A	N/A
Outcome 5	**Name**	Primary Safety Composite					
	Unit	Safety composite endpoint consists of: Freedom from device- and procedure-related to 30 days, freedom from target limb major amputation within 12 months; and freedom from clinically-driven TVR within 12 months					
Effect size	**Value**	92.1% (1207/1311)	94.0% (126/134)	91.1% (113/124)	88.7% (102/115)	91.5% (54/59)	SU: 96.2% (255/265) WU: 91.0% (952/1046)
	95% CI	N/A	N/A	N/A	N/A	N/A	N/A
Statistical test	**Type**	Descriptive	Descriptive	Descriptive	Descriptive	Descriptive	
	p value	N/A	N/A	N/A	N/A	N/A	0.003

Outcome 6	**Name**	Major Adverse Events					
	Unit	Major Adverse Events (MAE) defined as all-cause death, clinically-driven TVR, major target limb amputation, thrombosis at the target lesion site at 360 days.					
Effect size	**Value**	12.0% (157/1311)	11.9% (16/134)	8.9% (11/124)	15.7% (18/115)	11.9% (7/59)	SU: 7.9% (21/265) WU: 13.0% (136/1046)
	95% CI	N/A	N/A	N/A	N/A	N/A	N/A
Statistical test	**Type**	Descriptive	Descriptive	Descriptive	Descriptive	Descriptive	
	p value	N/A	N/A	N/A	N/A	N/A	0.026
Outcome 7	**Name**	Primary Patency (Kaplan Meier at 360 days)					
	Unit	Freedom from core lab-assessed restenosis (duplex ultrasound ≤2.4) or clinically-driven target lesion revascularization through 12 months (adjudicated by a Clinical Events Committee)					
Effect size	**Value**	N/A	91.1%	88.7%	85.3%	88.8%	N/A
	95% CI	N/A	N/A	N/A	N/A	N/A	N/A
Statistical test	**Type**	N/A	non-parametric/survival	non-parametric/survival	non-parametric/survival	non-parametric/survival	N/A
	p value	N/A	N/A	N/A	N/A	N/A	N/A
Outcome 8	**Name**	Safety Outcome: Clinically-driven TVR					
	Unit						
Effect size	**Value**	8.1% (106/1311)	6.0% (8/134)	8.9% (11/124)	11.3% (13/115)	8.5% (5/59)	Standard Use: 4.2% (11/265) Wider Use: 9.1% (95/1046)
	95% CI	N/A	N/A	N/A	N/A	N/A	N/A
Statistical test	**Type**	Descriptive	Descriptive	Descriptive	Descriptive	Descriptive	
	p value	N/A	N/A	N/A	N/A	N/A	0.008
Outcome 9	**Name**	Safety Outcome: Device- or Procedure-related Death (@30 days)					
	Unit						
Effect size	**Value**	0.2% (3/1394)	0.0% (0/155)	0.0% (0/129)	0.0% (0/125)	0.0% (0/72)	SU: 0.4% (1/281) WU: 0.2% (2/1113)
	95% CI	N/A	N/A	N/A	N/A	N/A	N/A

Statistical test	**Type**	Descriptive	Descriptive	Descriptive	Descriptive	Descriptive	
	p value	N/A	N/A	N/A	N/A	N/A	0.491
Outcome 10	**Name**	Safety outcome - Target limb major amputation					
	Unit	% of patients with target limb major amputation					
Effect size	**Value**	0.2% (3/1311)	0.0% (0/134)	0.0% (0/124)	0.0% (0/115)	0.0% (0/59)	SU: 0.0% (0/265) WU: 0.3% (3/1046)
	95% CI	N/A	N/A	N/A	N/A	N/A	N/A
Statistical test	**Type**	Descriptive	Descriptive	Descriptive	Descriptive	Descriptive	
	p value	N/A	N/A	N/A	N/A	N/A	>0.999
Outcome 11	**Name**	Safety- All-Cause Death					
	Unit						
Effect size	**Value**	3.5% (46/1311)	4.5% (6/134)	0.0% (0/124)	4.3% (5/115)	5.1% (3/59)	SU: 3.8% (10/265) WU: 3.4% (36/1046)
	95% CI	N/A	N/A	N/A	N/A	N/A	N/A
Statistical test	**Type**	Descriptive	Descriptive	Descriptive	Descriptive	Descriptive	
	p value	N/A	N/A	N/A	N/A	N/A	0.852
Outcome 12	**Name**	Safety outcome- Thrombosis					
	Unit	% of patients with thrombosis					
Effect size	**Value**	2.9% (38/1311)	3.7% (5/134)	0.8% (1/124)	4.3% (5/115)	3.4% (2/59)	SU: 0.0% (0/265) WU: 3.3% (35/1046)
	95% CI	N/A	N/A	N/A	N/A	N/A	N/A
Statistical test	**Type**	Descriptive	Descriptive	Descriptive	Descriptive	Descriptive	
	p value	N/A	N/A	N/A	N/A	N/A	0.063
Outcome 13	**Name**	Any TVR					
	Unit						
Effect size	**Value**	8.4% (110/1311)	6.0% (8/134)	9.7% (12/124)	12.2% (14/115)	8.5% (5/59)	SU: 4.5% (12/265) WU: 9.4% (98/1046)
	95% CI	N/A	N/A	N/A	N/A	N/A	N/A

Statistical test	**Type**	Descriptive	Descriptive	Descriptive	Descriptive	Descriptive	
	p value	N/A	N/A	N/A	N/A	N/A	0.009
Comments		The prospective, multicentre, single arm, independently-adjudicated IN.PACT Global Study evaluated the one-year safety and effectiveness outcomes of the paclitaxel-coated IN.PACT Admiral DCB in a real-world patient cohort presenting with lifestyle limiting claudication and rest pain (Rutherford 2 to 4). The study enrolled 1535 subjects of whom 1406 with 1773 lesions were included in the predefined clinical cohort analysis. Mean lesion length was 12.09 ± 9.54 cm, total occlusion were treated in 35.5%, and severe calcification was present in 10.2%.	The IN.PACT Admiral DCB was safe and highly effective up to 12 months after treatment in an independently adjudicated analysis of subjects with long lesions (≥15 cm, mean length 26.40 ± 8.61 cm) in the full native SFA and/or full popliteal artery. A higher provisional stent rate was observed in patients with lesion length ≥25cm Subgroup analysis showed that patients who did not require provisional stenting demonstrated primary patency at 360 days of 92.5%, which confirms the effectiveness of the IN.PACT Admiral DCB as a stand-alone device in long, complex SFA lesions.				STANDARD USE: Defined as IDE-like patients and lesions typical of pivotal trials including: Simple de novo lesions, lesions ≤18cm Single lesion Total occlusions ≤10cm Calcium (none to mild) Excluding in-stent restenosis WIDER USE: Defined as complex patients and lesions, typically excluded from pivotal trials, including: Bilateral, multiple lesions]Calcium (moderate to severe)]All subjects that do not meet the “Standard Use” criteria

7.5.2 Justify the inclusion of outcomes in table B9 from any analyses other than intention-to-treat.

N/A. All RCTs mentioned above did follow an intention to treat principle.

7.6 Adverse events

In section 7.7 the sponsor is required to provide information on the adverse events experienced with the technology being evaluated in relation to the scope.

For example, post-marketing surveillance data may demonstrate that the technology shows a relative lack of adverse events commonly associated with the comparator.

7.6.1 Using the previous instructions in sections 7.1 to 7.6, provide details of the identification of studies on adverse events, study selection, study methodologies, critical appraisal and results.

Studies selected for sections 7.1 to 7.6 have been considered for the adverse events section. Study selection, methodology, critical appraisal and results are presented in the above-mentioned sections.

7.6.2 Provide details of all important adverse events reported for each study. A suggested format is shown in table B10.

Safety endpoints and composite endpoints already covered in section 7.6 have not been reported in the table below. For additional details regarding safety issues please refers to tables B8 and B9.

Table B 11 Adverse events across patient groups

IN.PACT SFA Trial [Tepe et al 2015[3], Laird et al 2015[4]]	***12 months***			***24 months***		
	***DCB* (n = *220*)**	***PTA* (n = *111*)**	**Relative risk (95% CI)**	***DCB* (n = *220*)**	***PTA* (n = *111*)**	**Relative risk (95% CI)**
Vessel thrombosis (%)	1.4	3.7	Not reported	1.5	3.8	Not reported
All-cause death (%)	1.9	0	Not reported	8.1	0.9	Not reported

DEBATE-SFA Trial [Liistro et al 2013[7]]	***12 months***		
	***PEB+BMS* (n = *53*)**	***PTA + BMS* (n = *51*)**	**Relative risk (95% CI)**
Stent fractured in 12 months	2	1	Not reported

PLAISIR Trial [Bague et al 2017[5]]	***12 months***	
	***PEB* (n = *53*)**	**Relative risk (95% CI)**
Vessel thrombosis	1	Not reported
Target extremity revascularization	10	Not reported
In-stent thrombosis	5	Not reported
In-stent restenosis	12	Not reported
Minor amputation	1	Not reported
Cardiovascular death	1	Not reported
Non-cardiovascular death	1	Not reported

FAIR Trial [Krankenberg et al 2015[6]]	***12 months***		
	***DCB* (n = *62*)**	***POBA* (n = *55*)**	**Relative risk (95% CI)**
Late stent thrombosis	1	0	Not reported
Subacute stent thrombosis after TLR	0	1	Not reported
Tibioperoneal trunk occlusion	0	1	Not reported
Transient ischemic attack not procedure-related	2	0	Not reported
Distant embolizations	2	0	Not reported

	12 months	***24 months***	

Multicentre Italian Registry [Micari et al 2012[8], 2013[9]]	***PEB* (n = *105*)**	**Relative risk (95% CI)**	***PEB* (n = *105*)**	**Relative risk (95% CI)**
Cardiovascular death	1	Not reported	0	Not reported
Non-cardiovascular death	1	Not reported	0	Not reported
Amputation	0	Not reported	1	Not reported
SFA-Long Study [Micari et al 2016[10], 2017[11]]	***12 months***		***24 months***	
	***PCB* (n = *105*)**	**Relative risk (95% CI)**	***PCB* (n = *105*)**	**Relative risk (95% CI)**
Vessel thrombosis	1	Not reported	1	Not reported
All-cause death	4	Not reported	1	Not reported
Real-World Registry [Schmidt et al 2016[12]]	***12 months***		***24 months***	
	DCB* (n = *260) 288 limbs	**Relative risk (95% CI)**	***DCB* (n = *260) 288 limbs***	**Relative risk (95% CI)**
All-cause death, %	4.6%	Not reported	5.8%	Not reported
Major amputation rate, %	1.4%	Not reported	2.1%	Not reported
Prospective Registry [Stabile et al 2012[13], Virga et al 2014[14]]	***12 months***		***24 months***	
	***DEB* (n = *39*)**	**Relative risk (95% CI)**	***DEB* (n = *39*)**	**Relative risk (95% CI)**
All-cause CV mortality	1	Not reported	1	Not reported
Class I restenosis	2	Not reported	0	--
Class II restenosis	1	Not reported	3	Not reported

Class III restenosis	0	--	5	Not reported	
DEBATE-ISR Study [Grotti et al 2016[15]]	***36 months***				
	***PEB* (n = *44*)**	***BA* (n = *42*)**	**Relative risk (95% CI)**		
All-cause death	9	9	Not reported		
Major amputation	1	1	Not reported		
Non-target lesion revascularization	10	8	Not reported		
PACIFIER Trial [Werk et al 2012[17]]	***6 months***			***12 months***	
	***DEB* (n = 41)**	***Non-DEB* (n = 44)**	**Relative risk (95% CI)**	***DEB* (n = 41)**	***Non-DEB* (n = 44)**	**Relative risk (95% CI)**
Cardiovascular Death	0	2	Not reported	0	0	Not reported
Major adverse event (Death, amputation or TLR)	3	11	Not reported	0	4	Not reported
Belgian diabetic IN.PACT Trial [Debing et al 2016[18]]	***6 months***				
	***DCB* (n = 52)**	***POBA* (n = 54)**	**Relative risk (95% CI)**		
All-cause death, %	5.7	5.5	Not reported		
Minor amputation, %	7.7	9.2	Not reported		
Major amputation, %	1.9	0	Not reported		
Myocardial infarction, %	0	1.8	Not reported		
DEBELLUM Randomized Trial [Fanelli et al 2012[19]]	***6 months***				
	***DEB* (n = 33 limbs)**	***AB* (n = 38 limbs)**	**Relative risk (95% CI)**		
Minor Amputation, %	0%	5.3%	Not reported		
Major Amputation, %	3%	2.6%	Not reported		
Thrombosis at 48 hours post-procedure	3	5.2	Not reported		
CI, confidence interval Adapted from European Public Assessment Reports published by the European Medicines Agency					

7.6.3 Describe all adverse events and outcomes associated with the technology in national regulatory databases such as those maintained by the MHRA and FDA (Maude).

The tables below outline the MDR and EU Vigilance data for both IN.PACT Admiral and IN.PACT Pacific. The information presented includes all MDR and Vigilance reportable complaints received by Medtronic for INPACT Admiral and INPACT Pacific from product launch through 18th September 2017. Adverse events and outcomes associated with IN.PACT DCB listed in national regulatory databases are consistent with those found in clinical trial publications. These include vessel or in-stent thrombosis, restenosis and minor amputations. The Complaint event rate for commercial files from launch to October 2016 was 0.0030 for IN.PACT Pacific and 0.0009 for IN.PACT Admiral. No IN.PACT Admiral or IN.PACT Pacific DCBs have been withdrawn from the market in any country for any reason:

IN.PACT Admiral MDR reporting since launch:

Failure Type	MDR YES
ALLERGIC REACTION	3
BALLOON BURST OVER RBP	1
BALLOON BURST UNDER/AT RBP	5
BALLOON CUT	2
BALLOON PINHOLE	5
CATHETER DETACHMENT OF COMPONENTS	5
DEATH	47
DEATH -CANCER RELATED	3
DEFLATING PROBLEM	2
DISSECTION	27
EMBOLI	9
EXPIRATION DATE EXCEEDED	8
FEVER	1
FRICTION WITH GUDING CATHETER INTRODUCER	2
GUIDE WIRE FRICTION	1
INFLATING PROBLEM	1
INFLATION DIFFICULTIES	1
KINK	1
NO KNOWN DEVICE PROBLEM	18
OCCLUSION	165
PERFORATION	1
PERIPHERAL VASCULAR DISEASE	3
PSEUDOANEURYSM	4
REACTION	17
REMOVAL/ RETRIEVAL PROBLEM	1
RESTENOSIS	305
SHAFT DAMAGED	10
THROMBUS	16
TVR	1
VASOCONSTRICTION	5
WELDING FAILURE	5
Grand Total	**675**

IN.PACT Admiral VIGILANCE reporting since launch:

Failure Type	VIG YES
BALLOON BURST OVER RBP	1
BALLOON BURST UNDER/AT RBP	5
BALLOON CUT	1
BALLOON PINHOLE	4
BALLOON, DETACHMENT OF	1
INFLATING PROBLEM	1
KINK	1
SHAFT DAMAGED	2
VASOCONSTRICTION	4
Grand Total	**20**

IN.PACT Pacific MDR reporting since launch:

Failure Type	MDR YES
BALLOON BURST UNDER/AT RBP	1
BALLOON BURST WITHOUT INDICATION RBP	2
BALLOON FOLDING PROBLEM	35
BALLOON RADIAL BURST	1
BALLOON, DETACHMENT OF	1
BONDS FAILURE	1
DEFLATING PROBLEM	2
INFLATING PROBLEM	72
NO KNOWN DEVICE PROBLEM	2
OCCLUSION	3
Grand Total	**120**

IN.PACT Pacific VIGILANCE reporting since launch:

Failure Type	VIG YES
BALLOON BURST UNDER/AT RBP	2
BALLOON BURST WITHOUT INDICATION RBP	2
BALLOON FOLDING PROBLEM	32
BALLOON RADIAL BURST	1
BALLOON, DETACHMENT OF	2
BONDS FAILURE	1
DEFLATING PROBLEM	3
INFLATING PROBLEM	69
NO KNOWN DEVICE PROBLEM	1
SHAFT LEAKAGE	1
VASOCONSTRICTION	1
Grand Total	**115**

7.6.4 Provide a brief overview of the safety of the technology in relation to the scope.

IN.PACT DCB is intended to treat obstructive diseases of peripheral arteries. Endovascular treatments include uncoated balloon angioplasty ("plain old" balloon angioplasty or POBA), atherectomy, and stents (including drug eluting stents). All types of treatment have shortcomings that can be addressed by DCBs, including but not limited to improved vessel patency and minimizing secondary interventions. Additionally, eliminating the use of stent further reduces risks associated with stent fracture, and in-stent restenosis. The clinical portfolio of evidence for both safety and effectiveness of IN.PACT DCB continues to grow. IN.PACT DCB has demonstrated clinical superiority to standard PTA and currently has evidence to support the best data of any treatment for the SFA as well as growing evidence in long, calcified lesions, and for in- stent restenosis offering additional benefits.

7.7 Evidence synthesis and meta-analysis

When more than one study is available and the methodology is comparable, a meta-analysis should be considered.

Section 7.8 should be read in conjunction with the 'Medical Technologies Evaluation Programme Methods Guide', available from www.nice.org.uk/mt

7.7.1 Describe the technique used for evidence synthesis and/or meta-analysis. Include a rationale for the studies selected, details of the methodology used and the results of the analysis.

For each study selected data were presented to establish the Freedom from TLR and the primary patency rate at 12 and 24 months in patients with peripheral arterial disease and treated with IN.PACT drug-coated balloon. Categorical variables were expressed as percentages and continuous variables as means ± standard deviation if normally distributed. The endpoints selected across different studies (RCTs, Prospective and Retrospective Cohort studies) were the Primary Patency percentage and Freedom from TLR at 12 and 24 months. Summary statistics of endpoints were expressed as percentage and were reported for each study selected (if available).
Pooled estimates were calculated with a DerSimonian and Laird (DL) random effects model to account for clinical and study design heterogeneity. The Higgins test (I2) statistic were calculated to test for evidence of statistical heterogeneity across studies.
The contribution of each study to the meta-analysis (weight), was calculated according to the amount of information it contains, in function of the number of patients and their variability. A sensitivity analysis was performed according to the type of lesions (de-novo or ISR).
Meta-regression analysis was conducted to investigate whether clinical heterogeneity of study was associated with the treatment effect by means the test of Moderators. Covariates included in the model for freedom from TLR at 12 and 24 months on the overall set were the lesion length, age, gender (male), smoking habit, hyperlipidaemia, hypertension and diabetes, for the other models the covariate included were only lesion length, age and gender to manage overfitting issue.
All analyses were performed by means of the statistical software R Project for Statistical Computing – version 3.4.1 (R Foundation for statistical computing).

7.7.2 If evidence synthesis is not considered appropriate, give a rationale and provide a qualitative review. The review should summarise the overall results of the individual studies with reference to their critical appraisal.

For the comparator arm it was not considered appropriate to carry out a meta-analysis using the studies identified via the IN.PACT DCB search criteria because this would exclude some key studies that should be used to calculate pooled estimates of the clinical endpoints for PTA (with or without bailout BMS).

The search criteria identified several recent analyses that have calculated pooled estimates for PTA (Katsanos et al., 2014[1]; Katsanos et al., 2016[27]; Herten et al, 2016[28]; Giacoppo et al., 2016[29]) and would be appropriate to use for the comparator. The economic submission (Section C) will use the 24-month pooled TLR estimates from the published UK economic analysis, "Economic analysis of endovascular drug-eluting treatments for femoropopliteal artery disease in the UK" (Katsanos et al, 2016) for the PTA arm (see figure 1 below) and will be updated to include any further studies that have been published since this publication.

Table 2 Total pooled 24-month TLR probabilities based on identified studies for therapies PTA, BMS, DCB and DES

Therapy	Study	12-Month reported TLR	Reported lesions (n)	Pooled 12-month TLR	24-Month reported TLR	Reported lesions (n)	Pooled 24-month TLR	Total pooled 24-month TLR estimate (%)
PTA	FAST[20]	18.3%	115	19.5%	Estimation of 24-month TLR based on constant hazard rate assumption			38.5
	ZILVER-PTX[21]	17.5%	223					
	PACIFIER[23]	27.9%	43					
	BIOLUX-PI[24]	41.7%	24					
	LEVANT 2[26]	16.8%	143					
	COMPLIANCE 360[27]	21.7%	23					
	THUNDER[17]				51.9%	54	44.7%	
	FEM-PAC[18]				50.0%	42		
	RESILIENT[8 19]				58.2%	72		
	LEVANT 1[25]				48.8%	41		
	IN.PACT SFA[11 7]				28.3%	106		
BMS	FAST[20]	14.9%	114	15.3%	Estimation of 24-month TLR based on constant hazard rate assumption			26.9
	DURABILITY I[4]	20.9%	134					
	Diehl *et al*[29]	17.4%	46					
	COBRA[30]	16.0%	43					
	ETAP[32]	14.7%	99					
	DURABILITY II[33]	14.0%	287					
	EPIC[34]	7.7%	88					
	Gabriella *et al*[35]	26.8%	68					
	SUPERB[36]	11.1%	235					
	MARIS[37]	17.2%	789					
	COMPLETE SE[9]	9.4%	191					
	SIROCCO[28]				13.3%	46	19.8%	
	RESILIENT[8 19]				22.2%	134		
	MISAGO-2 subc[31]				15.1%	41		
	Leipzig SUPERA 500[38]				21.0%	148		
DCB	PACIFIER[23]	7.1%	42	11.9%	Estimation of 24-month TLR based on constant hazard rate assumption			17.6
	BIOLUX-PI[24]	15.4%	25					
	LEVANT 2[26]	12.3%	285					
	THUNDER[17]				15.0%	47	14.0%	
	FEM-PAC[18]				13.0%	45		
	IT-Registry[40]				14.3%	98		
	LEVANT 1[25]				35.7%	42		
	ILLUMENATE FIH[41]				14.9%	47		
	IN.PACT SFA[11 7]				9.1%	198		
DES	STRIDES[43]	20.0%	103	20.0%	Estimation of 24-month TLR			19.4
	ZILVER-PTX[21]				14.4%	224	17.5%	
	ZILVER-PTX SAS[21]				19.5%	615		
	SIROCCO[28]				6.0%	47		

Continued

Figure 1: Total pooled 24-month TLR probabilities based on identified studies for therapies PTA, BMS, DCB and DES. (Taken from Katsanos K, Geisler BP, Garner AM, Zayed H, Cleveland T, Pietzsch JB. Economic analysis of endovascular drug-eluting treatments for femoropopliteal artery disease in the UK. BMJ Open. 2016;6(5):e011245[27]). Section C will use a combination of the pooled estimates shown here for PTA, BMS and DCB in addition to the section B Meta-analysis for IN.PACT DCB

Table B 12 Papers included in the meta-analysis at 12 months

First Author	Patients N	Lesion N	Lesion Length (mm)	AGE (years)	Male N (%)	Smoking N (%)	Hypertension N (%)	Hyperlipidemia N (%)	DM N (%)
Bague et al 2017[5]	53	55	86±32	69±12	42 (79)	17 (32)	43 (81)	41 (77)	16 (30)
Krankenberg et al 2015[6]	62	64	82±74	69±8	33 (53)	18 (29)	52 (84)	48 (77)	28 (45)
Grotti et al 2016[15]	44	44	132±86	74±11	32 (72)	--	--	--	44 (100)
Tepe et al 2015[3]	220	221	89±49	67±59	143 (65)	85 (39)	201 (91)	186 (84)	89 (40)
Liistro et al 2013[7]	53	55	94±60	74±9	40 (75)	25 (47)	47 (89)	33 (62)	41 (7)
Schmidt et al 2016[12]	260	288	24±10	68±11	164 (63)	157 (60)	250 (96)	188 (72)	120 (46)
Stabile et al 2012[13]	39	39	83±79	66±10	32 (82)	34 (87)	36 (93)	34 (87)	19 (49)
Werk et al 2012[17]	41	44	70±53	71±7	26 (59)	21 (49)	29 (66)	22 (54)	19 (43)
Fanelli et al 2012[19]	25	44	75±35	66±6	19 (76)	17(68)	19 (76)	12 (48)	13 (52)
Micari et al 2012[8]	105	114	76±38	68±9	85 (81)	66 (63)	90 (86)	78 (74)	51 (49)
Micari et al 2016[10]	105	105	251±79	68±9	86 (82)	72 (69)	93 (89)	82 (78)	60 (57)
OVERALL	***1007***	***1073***	***88***	***68***	***702 (70)***	***512 (53)***	***860 (85)***	***724 (75)***	***500 (50)***

Table B 13 Papers included in the meta-analysis at 24 months

First Author	Patients N	Lesion N	Lesion Length (mm)	AGE (years)	Male N (%)	Smoking N (%)	Hypertension N (%)	Hyperlipidemia N (%)	DM N (%)
Grotti et al 2016[15]	44	44	132±86	74±11	32 (72)	--	--	--	44 (100)
Laird et al 2015[4]	220	221	89±49	67±59	143 (65)	85 (39)	201 (91)	186 (84)	89 (40)
Schmidt et al 2016[12]	260	288	24±10	68±11	164 (63)	157 (60)	250 (96)	188 (72)	120 (46)
Virga et al 2014[14]	39	39	83±79	66±10	32 (82)	34 (87)	36 (93)	34 (87)	19 (49)
Micari et al 2013[9]	105	114	76±38	68±9	85 (81)	66 (63)	90 (86)	78 (74)	51 (49)
Micari et al 2017[11]	105	105	251±79	68±9	86 (82)	72 (69)	93 (89)	82 (78)	60 (57)
OVERALL	***773***	***811***	***109***	***69***	***542 (70)***	***414 (57)***	***670 (92)***	***568 (78)***	***383 (50)***

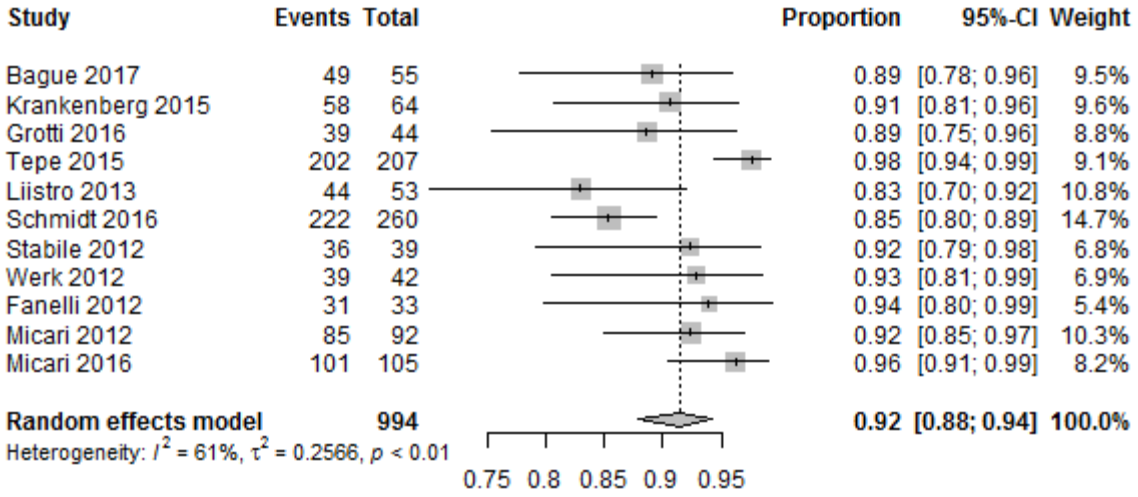
The article of Debing et al 2016[18] has been excluded from the meta-analysis since results were only available at 6 months.

Table B 14 Freedom from TLR at 12-months

Study	Design	Treatment	Type of lesions	Freedom from TLR at 12 months	Proportion (95% CI)
Bague et al 2017[5]	Prospective Cohort	DCB-ISR	ISR	90.2%	0.89 (0.78;0.96)
Krankenberg et al 2015[6]	Randomized controlled	SFA-ISR	ISR	90.8%	0.91 (0.81;0.96)
Grotti et al 2016[15]	Prospective Cohort	DCB-ISR	ISR	89.0%	0.89 (0.75;0.96)
Tepe et al 2015[3]	Randomized controlled	DCB	de-novo	97.5%	0.98 (0.94;0.99)
Liistro et al 2013[7]	Randomized controlled	DCB + BMS	de-novo	83.0%	0.83 (0.70;0.92)
Schmidt et al 2016[12]	Retrospective Cohort	DCB	de-novo/ISR	85.4%	0.85 (0.80;0.89)
Stabile et al 2012[13]	Prospective Cohort	SFA-ISR	ISR	92.1%	0.92 (0.79;0.98)
Werk et al 2012[17]	Randomized controlled	DCB	de-novo	92.9%	0.93 (0.81;0.99)
Fanelli et al 2012[19]	Randomized controlled	DCB	de-novo	93.9%	0.94 (0.80;0.99)
Micari et al 2012[8]	Prospective Cohort	DCB	de-novo	92.4%	0.92 (0.85;0.97)
Micari et al 2016[10]	Prospective Cohort	DCB	de-novo	96,0%	0.96 (0.91;0.99)
OVERALL					**0.92 (0.88;0.94)**

The table above shows the proportion of freedom from TLR at 12 months and the corresponding 95% confidence interval for each study and the overall proportion obtained with DerSimonian and Laird method 0.92 (0.88; 0.94) the heterogeneity test: I2=61%, p-value<0.01).
The figure below presents the forest plot showing the contribution of each study to the meta-analysis represented by the area of the box.

Figure 2 – Freedom from TLR at 12-months



As results of the meta-regression model the heterogeneity in the true effects is not related to some of the predictors/moderators included in the model.

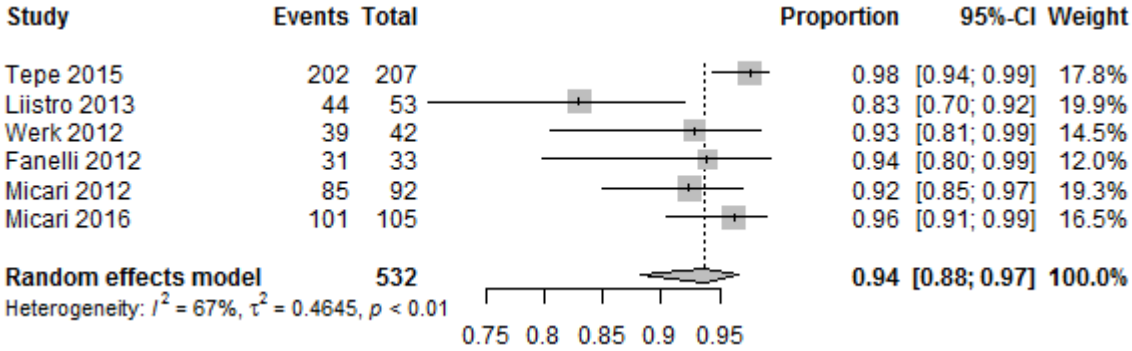
Table B 15 Freedom from TLR at 12-months (subset of de-novo lesions)

Study	Design	Treatment	Type of lesions	Freedom from TLR	Proportion (95% CI)

				at 12 months	
Tepe et al 2015[3]	Randomized controlled	DCB	de-novo	97.5%	0.98 (0.94;0.99)
Liistro et al 2013[7]	Randomized controlled	DCB + BMS	de-novo	83.0%	0.83 (0.70;0.92)
Werk et al 2012[17]	Randomized controlled	DCB	de-novo	92.9%	0.93 (0.81;0.99)
Fanelli et al 2012[19]	Randomized controlled	DCB	de-novo	93.9%	0.94 (0.80;0.99)
Micari et al 2012[8]	Prospective Cohort	DCB	de-novo	92.4%	0.92 (0.85;0.97)
Micari et al 2016[10]	Prospective Cohort	DCB	de-novo	96,0%	0.96 (0.91;0.99)
OVERALL					**0.94 (0.88;0.97)**

The table above shows, for the subset of patients with de-novo lesions, the proportion of freedom from TLR at 12 months and the corresponding 95% confidence interval for each study and the overall proportion obtained with DerSimonian and Laird method 0.94 (0.88; 0.97) the heterogeneity test: I^2=67%, p-value<0.01).
The figure below presents the forest plot showing the contribution of each study to the meta-analysis represented by the area of the box.

Figure 3 – Freedom from TLR at 12-months (subset of de-novo lesions)



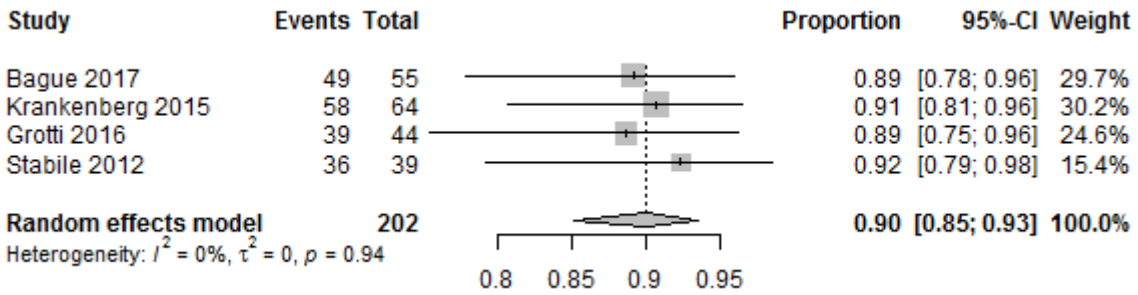
As results of the meta-regression model the heterogeneity in the true effects is related to hyperlipidaemia (p=0.02).

Table B 16 Freedom from TLR at 12-months (subset of ISR lesions)

Study	Design	Treatment	Type of lesions	Freedom from TLR at 12 months	Proportion (95% CI)
Bague et al 2017[5]	Prospective Cohort	DCB-ISR	ISR	90.2%	0.89 (0.78;0.96)
Krankenberg et al 2015[6]	Randomized controlled	SFA-ISR	ISR	90.8%	0.91 (0.81;0.96)
Grotti et al 2016[15]	Prospective Cohort	DCB-ISR	ISR	89.0%	0.89 (0.75;0.96)
Stabile et al 2012[13]	Prospective Cohort	SFA-ISR	ISR	92.1%	0.92 (0.79;0.98)
OVERALL					**0.90 (0.85;0.93)**

The table above shows, for the subset of patients with ISR lesions, the proportion of freedom from TLR at 12 months and, corresponding 95% confidence interval for each study and the overall proportion obtained with DerSimonian and Laird method 0.88 (0.81; 0.92) the heterogeneity test: I^2=0%, p-value=0.94).
The figure below presents the forest plot showing the contribution of each study to the meta-analysis represented by the area of the box.

Figure 4 – Freedom from TLR at 12-months (subset of ISR lesions)



As results of the meta-regression model the heterogeneity in the true effects is not related to some of the predictors/moderators included in the model.

Table B 17 Freedom from TLR at 12-months (subset of RCTs studies)

Study	Design	Treatment	Type of lesions	Freedom from TLR at 12 months	Proportion (95% CI)
Krankenberg et al 2015[6]	Randomized controlled	SFA-ISR	ISR	90.8%	0.91 (0.81;0.96)
Tepe et al 2015[3]	Randomized controlled	DCB	de-novo	97.5%	0.98 (0.94;0.99)
Liistro et al 2013[7]	Randomized controlled	DCB + BMS	de-novo	83.0%	0.83 (0.70;0.92)
Werk et al 2012[17]	Randomized controlled	DCB	de-novo	92.9%	0.93 (0.81;0.99)
Fanelli et al 2012[19]	Randomized controlled	DCB	de-novo	93.9%	0.94 (0.80;0.99)
OVERALL					**0.93 (0.85;0.97)**

The table above shows, for the subset of RCTs studies, the proportion of freedom from TLR at 12 months and the corresponding 95% confidence interval for each study and the overall proportion obtained with DerSimonian and Laird method 0.93 (0.85; 0.97) the heterogeneity test: I^2=70%, p-value<0.01).
The figure below presents the forest plot showing the contribution of each study to the meta-analysis represented by the area of the box.

Figure 5 – Freedom from TLR at 12-months (subset of RCTs studies)

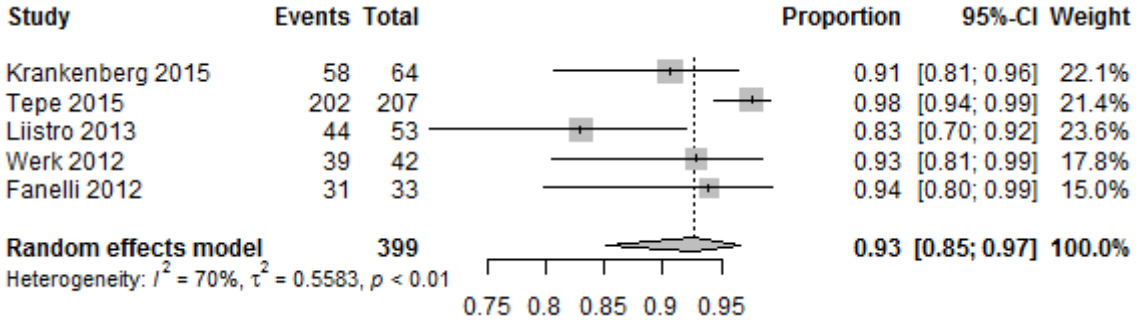


Table B 18 Freedom from TLR at 12-months (subset of observational studies)

Study	Design	Treatment	Type of lesions	Freedom from TLR at 12 months	Proportion (95% CI)
Bague et al 2017[5]	Prospective Cohort	DCB-ISR	ISR	90.2%	0.89 (0.78;0.96)
Grotti et al 2016[15]	Prospective Cohort	DCB-ISR	ISR	89.0%	0.89 (0.75;0.96)
Stabile et al 2012[13]	Prospective Cohort	SFA-ISR	ISR	92.1%	0.92 (0.79;0.98)
Micari et al 2012[8]	Prospective Cohort	DCB	de-novo	92.4%	0.92 (0.85;0.97)
Micari et al 2016[10]	Prospective Cohort	DCB	de-novo	96.0%	0.96 (0.91;0.99)
OVERALL					**0.92 (0.88;0.95)**

The table above shows, for the subset of prospective studies, the proportion of freedom from TLR at 12 months and the corresponding 95% confidence interval for each study and the overall proportion obtained with DerSimonian and Laird method 0.92 (0.88; 0.95) the heterogeneity test: I^2=0%, p-value=0.45).
The figure below presents the forest plot showing the contribution of each study to the meta-analysis represented by the area of the box.

Figure 6 – Freedom from TLR at 12-months (subset of observational studies)

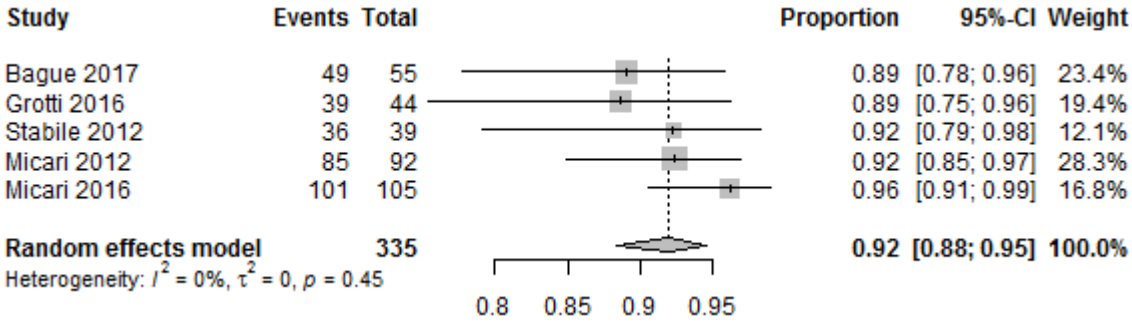
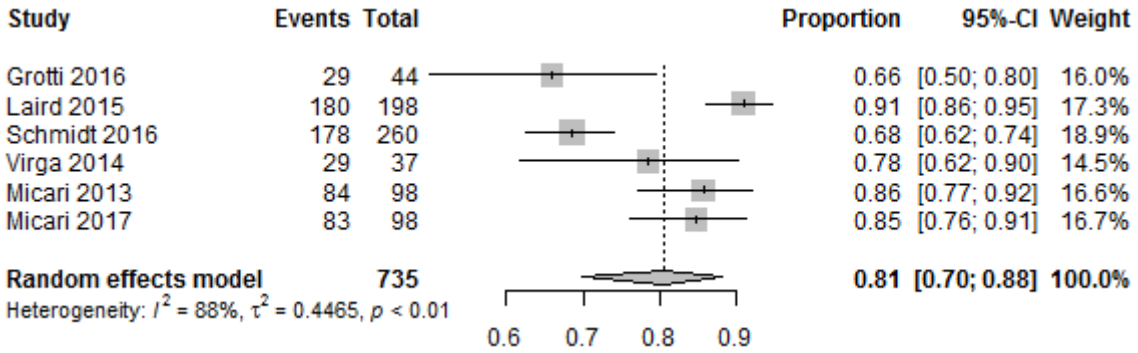


Table B 19 Freedom from TLR at 24-months

Study	Design	Treatment	Type of lesions	Freedom from TLR at 24 months	Proportion (95% CI)
Grotti et al 2016[15]	Prospective Cohort	DCB-ISR	ISR	67.0%	0.66 (0.50;0.80)
Laird et al 2015[4]	Randomized controlled	DCB	de-novo	91.0%	0.91 (0.86;0.95)
Schmidt et al 2016[12]	Retrospective Cohort	DCB	de-novo/ISR	68.6%	0.68 (0.62;0.74)
Virga et al 2014[14]	Prospective Cohort	SFA-ISR	ISR	78.4%	0.78 (0.62;0.90)
Micari et al 2013[9]	Prospective Cohort	DCB	de-novo	85.7%	0.86 (0.77;0.92)
Micari et al 2017[11]	Prospective Cohort	DCB	de-novo	84.7%	0.85 (0.76;0.91)
OVERALL					**0.81 (0.70;0.88)**

The table above shows the proportion of freedom from TLR at 24 months and the corresponding 95% confidence interval (Clopper-Pearson exact CI) for each study and the overall proportion obtained with DerSimonian and Laird method 0.81 (0.70; 0.88) the heterogeneity test: I2=88%, p-value<0.01).
The figure below presents the forest plot showing the contribution of each study to the meta-analysis represented by the area of the box.

Figure 7 – Freedom from TLR at 24-months



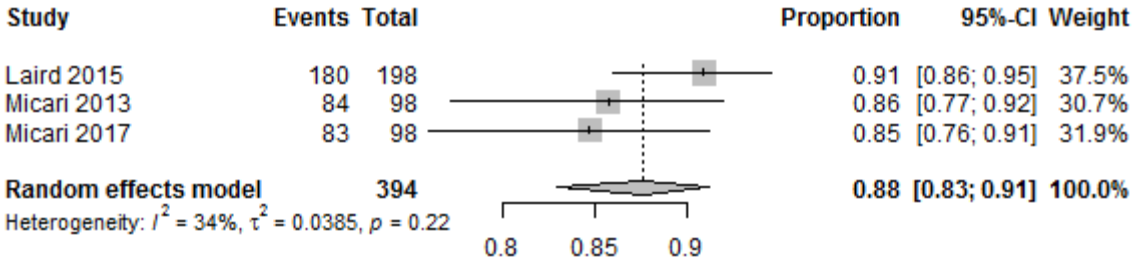
As results of the meta-regression model the heterogeneity in the true effects is related to the habit of smoking (p<0.001) and diabetes (p=0.04).

Table B 20 Freedom from TLR at 24-months (subset of de-novo lesions)

Study	Design	Treatment	Type of lesions	Freedom from TLR at 24 months	Proportion (95% CI)
Laird et al 2015[4]	Randomized controlled	DCB	de-novo	91.0%	0.91 (0.86;0.95)
Micari et al 2013[9]	Prospective Cohort	DCB	de-novo	85.7%	0.86 (0.77;0.92)
Micari et al 2017[11]	Prospective Cohort	DCB	de-novo	84.7%	0.85 (0.76;0.91)
OVERALL					**0.88 (0.83;0.91)**

The table above shows, for the subset of patients with de-novo lesions, the proportion of freedom from TLR at 24 months and the corresponding 95% confidence interval for each study and the overall proportion obtained with DerSimonian and Laird method 0.88 (0.83; 0.91) the heterogeneity test: I^2=92%, p-value=022).
The figure below presents the forest plot showing the contribution of each study to the meta-analysis represented by the area of the box.

Figure 8 – Freedom from TLR at 24-months (subset of de-novo lesions)



As results of the meta-regression model the heterogeneity in the true effects is related to the age (p<0.001), sex male (p<0.001), habit of smoking (p<0.001), hyperlipidaemia (p=0.05) and diabetes (p=0.05).

Table B 21 Freedom from TLR at 24-months (subset of ISR lesions)

Study	Design	Treatment	Type of lesions	Freedom from TLR at 24 months	Proportion (95% CI)
Grotti et al 2016[15]	Prospective Cohort	DCB-ISR	ISR	67.0%	0.66 (0.50;0.80)
Virga et al 2014[14]	Prospective Cohort	SFA-ISR	ISR	78.4%	0.78 (0.62;0.90)
OVERALL					**0.72 (0.58;0.82)**

The table above shows, for the subset of patients with ISR lesions, the proportion of freedom from TLR at 24 months and the corresponding 95% confidence interval for each study and the overall proportion obtained with DerSimonian and Laird method 0.72 (0.58; 0.82) the heterogeneity test: I^2=34%, p-value=0.22).
The figure below presents the forest plot showing the contribution of each study to the meta-analysis represented by the area of the box.

Figure 9 – Freedom from TLR at 24-months (subset of ISR lesions)

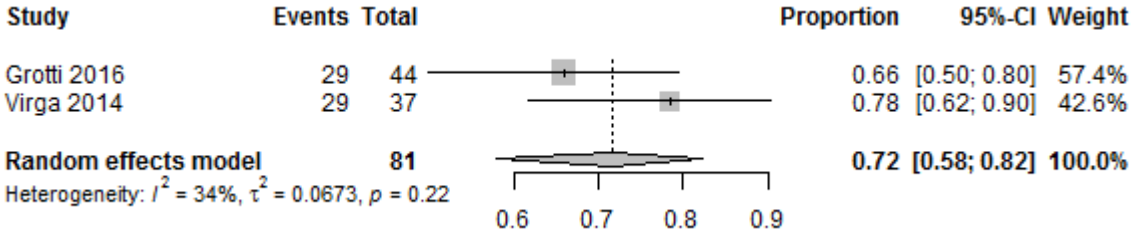
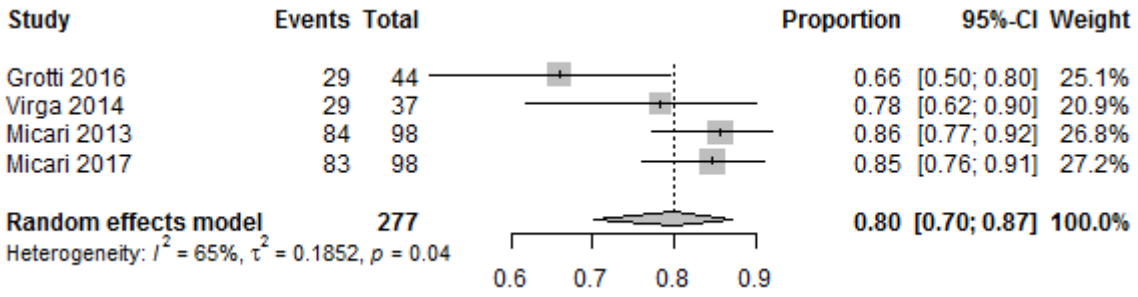


Table B 22 Freedom from TLR at 24-months (subset of observational studies)

Study	Design	Treatment	Type of lesions	Freedom from TLR at 24 months	Proportion (95% CI)
Grotti et al 2016[15]	Prospective Cohort	DCB-ISR	ISR	67.0%	0.66 (0.50;0.80)
Virga et al 2014[14]	Prospective Cohort	SFA-ISR	ISR	78.4%	0.78 (0.62;0.90)
Micari et al 2013[9]	Prospective Cohort	DCB	de-novo	85.7%	0.86 (0.77;0.92)
Micari et al 2017[11]	Prospective Cohort	DCB	de-novo	84.7%	0.85 (0.76;0.91)
OVERALL					**0.80 (0.70;0.87)**

The table above shows, for the subset of prospective cohort studies, the proportion of freedom from TLR at 24 months and the corresponding 95% confidence interval for each study and the overall proportion obtained with DerSimonian and Laird method 0.80 (0.70; 0.87) the heterogeneity test: I^2=65%, p-value=0.04).
The figure below presents the forest plot showing the contribution of each study to the meta-analysis represented by the area of the box.

Figure 10 – Freedom from TLR at 24-months (subset of observational studies)



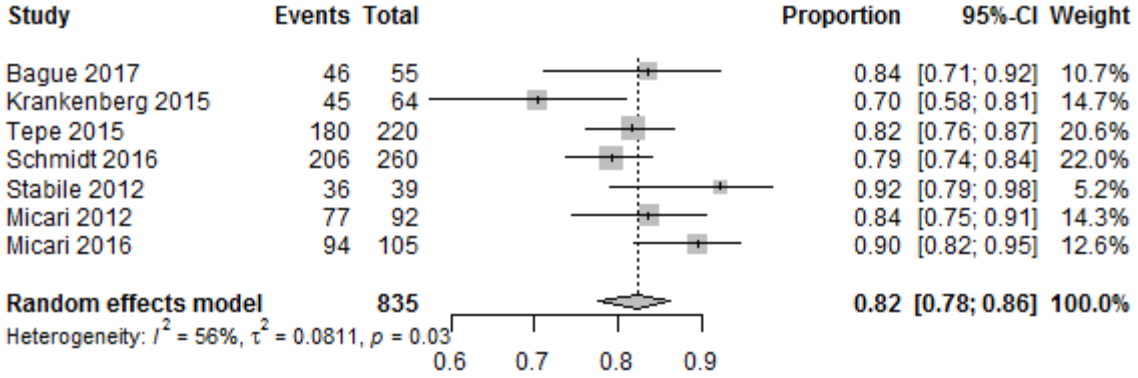
As results of the meta-regression model the heterogeneity in the true effects is related to the habit of smoking (p<0.001), hypertension (p=0.023) and hyperlipidaemia (p<0.001).

Table B 23 Primary Patency at 12-months

Study	Design	Treatment	Type of lesions	Primary Patency at 12 months	Proportion (95% CI)
Bague et al 2017[5]	Prospective Cohort	DCB-ISR	ISR	83.7%	0.84 (0.71;0.92)
Krankenberg et al 2015[6]	Randomised controlled	SFA-ISR	ISR	70.5%	0.70 (0.58;0.81)
Tepe et al 2015[3]	Randomised controlled	DCB	de-novo	82.2%	0.82 (0.76;0.87)
Schmidt et al 2016[12]	Retrospective Cohort	DCB	de-novo/ISR	79.2%	0.79 (0.74;0.84)
Stabile et al 2012[13]	Prospective Cohort	SFA-ISR	ISR	92.1%	0.92 (0.79;0.98)
Micari et al 2012[8]	Prospective Cohort	DCB	de-novo	83.7%	0.84 (0.75;0.91)
Micari et al 2016[10]	Prospective Cohort	DCB	de-novo	89.3%	0.90 (0.82;0.95)
OVERALL					**0.82 (0.78;0.86)**

The table above shows the proportion of primary patency at 12 months and the corresponding 95% confidence interval for each study and the overall proportion obtained with DerSimonian and Laird method 0.82 (0.78; 0.86) the heterogeneity test: I2=56%, p-value=0.03).
The figure below presents the forest plot showing the contribution of each study to the meta-analysis represented by the area of the box.

Figure 11 – Primary Patency at 12-months



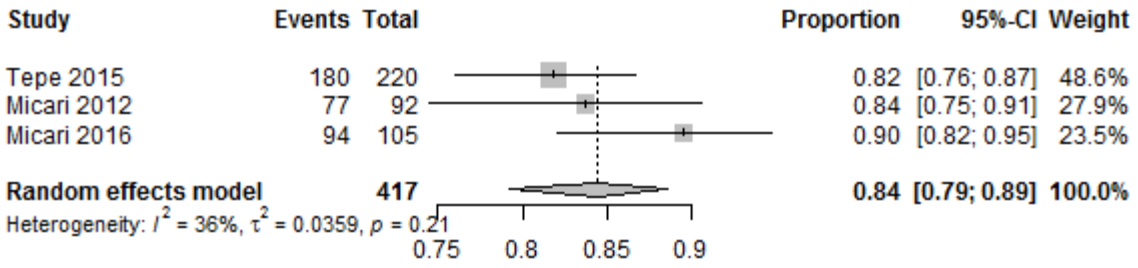
As results of the meta-regression model the heterogeneity in the true effects is not related to some of the predictors included in the model.

Table B 24 Primary Patency at 12-months (subset of de-novo lesions)

Study	Design	Treatment	Type of lesions	Primary Patency at 12 months	Proportion (95% CI)
Tepe et al 2015[3]	Randomized controlled	DCB	de-novo	82.2%	0.82 (0.76;0.87)
Micari et al 2012[8]	Prospective Cohort	DCB	de-novo	83.7%	0.84 (0.75;0.91)
Micari et al 2016[10]	Prospective Cohort	DCB	de-novo	89.3%	0.90 (0.82;0.95)
OVERALL					**0.84 (0.79;0.89)**

The table above shows, for the subset of patients with de-novo lesions, the proportion of primary patency at 12 months and the corresponding 95% confidence interval for each study and the overall proportion obtained with DerSimonian and Laird method 0.84 (0.79; 0.89) the heterogeneity test: I2=36%, p-value=0.21).
The figure below presents the forest plot showing the contribution of each study to the meta-analysis represented by the area of the box.

Figure 12 – Primary Patency at 12-months (subset of de-novo lesions)



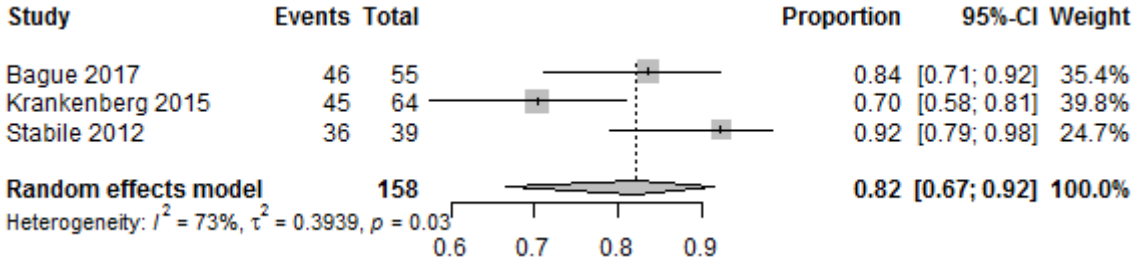
As results of the meta-regression model the heterogeneity in the true effects is related to the age (p<0.001).

Table B 25 Primary Patency at 12-months (subset of ISR lesions)

Study	Design	Treatment	Type of lesions	Primary Patency at 12 months	Proportion (95% CI)
Bague et al 2017[5]	Prospective Cohort	DCB-ISR	ISR	83.7%	0.84 (0.71;0.92)
Krankenberg et al 2015[6]	Randomized controlled	SFA-ISR	ISR	70.5%	0.70 (0.58;0.81)
Stabile et al 2012[13]	Prospective Cohort	SFA-ISR	ISR	92.1%	0.92 (0.79;0.98)
OVERALL					**0.82 (0.67;0.92)**

The table above shows, for the subset of patients with ISR lesions, the proportion of primary patency at 12 months and the corresponding 95% confidence interval for each study and the overall proportion obtained with DerSimonian and Laird method 0.82 (0.67; 0.92) the heterogeneity test: I2=73%, p-value=0.03).
The figure below presents the forest plot showing the contribution of each study to the meta-analysis represented by the area of the box.

Figure 13 – Primary Patency at 12-months (subset of ISR lesions)



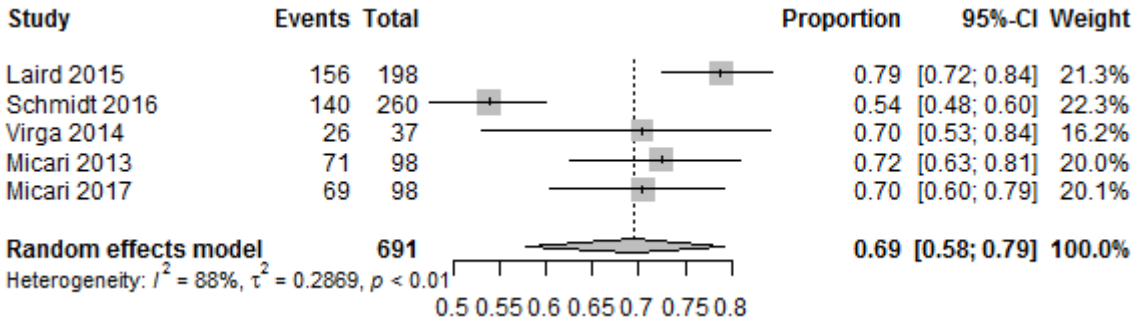
As results of the meta-regression model the heterogeneity in the true effects is related to the habit of smoking (p=0.05) and sex male (p=0.04).

Table B 26 Primary Patency rate at 24-months

Study	Design	Treatment	Type of lesions	Primary patency at 24 months	Proportion (95% CI)
Laird et al 2015[4]	Randomized controlled	DCB	de-novo	78.9%	0.79 (0.72;0.84)
Schmidt et al 2016[12]	Retrospective Cohort	DCB	de-novo/ISR	53.7%	0.54 (0.48;0.60)
Virga et al 2014[14]	Prospective Cohort	SFA-ISR	ISR	70.3%	0.70 (0.53;0.84)
Micari et al 2013[9]	Prospective Cohort	DCB	de-novo	72.4%	0.72 (0.63;0.81)
Micari et al 2017[11]	Prospective Cohort	DCB	de-novo	70.4%	0.70 (0.60;0.79)
OVERALL					**0.69 (0.58;0.79)**

The table above shows the proportion of primary patency at 24 months and the corresponding 95% confidence interval (Clopper-Pearson exact CI) for each study and the overall proportion obtained with DerSimonian and Laird method 0.69 (0.58; 0.79) the heterogeneity test: I2=88%, p-value<0.01).
The figure below presents the forest plot showing the contribution of each study to the meta-analysis represented by the area of the box.

Figure 14 – Primary Patency rate at 24-months



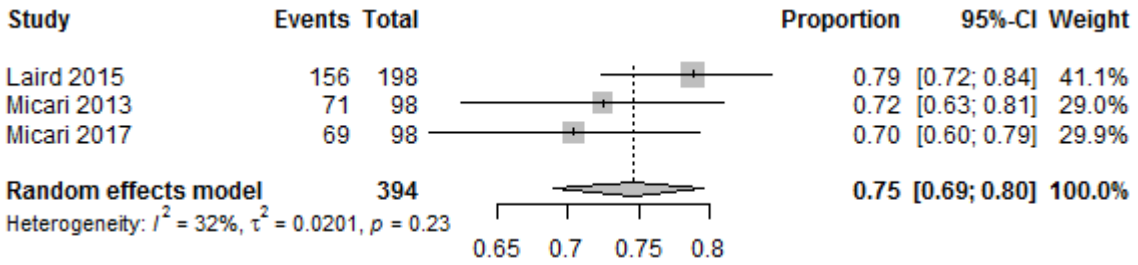
As results of the meta-regression model the heterogeneity in the true effects is related to the habit of smoking (p=0.022).

Table B 27 Primary Patency at 24-months (subset of de-novo lesions)

Study	Design	Treatment	Type of lesions	Primary patency at 24 months	Proportion (95% CI)
Laird et al 2015[4]	Randomized controlled	DCB	de-novo	78.9%	0.79 (0.72;0.84)
Micari et al 2013[9]	Prospective Cohort	DCB	de-novo	72.4%	0.72 (0.63;0.81)
Micari et al 2017[11]	Prospective Cohort	DCB	de-novo	70.4%	0.70 (0.60;0.79)
OVERALL					**0.75 (0.69;0.80)**

The table above shows, for the subset of patients with de-novo lesions, the proportion of primary patency at 24 months and the corresponding 95% confidence interval (Clopper-Pearson exact CI) for each study and the overall proportion obtained with DerSimonian and Laird method 0.75 (0.69; 0.80) the heterogeneity test: I2=32%, p-value=0.23).
The figure below presents the forest plot showing the contribution of each study to the meta-analysis represented by the area of the box.

Figure 15 – Primary Patency at 24-months (subset of de-novo lesions)



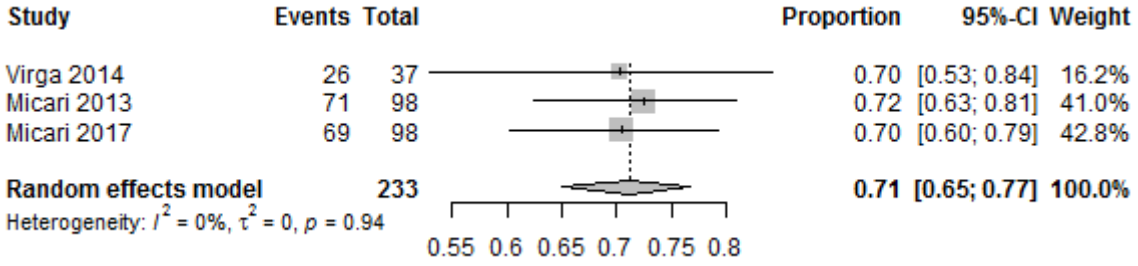
As results of the meta-regression model the heterogeneity in the true effects is not related to some of the predictors/moderators included in the model.

Table B 28 Primary Patency at 24-months (subset of observational studies)

Study	Design	Treatment	Type of lesions	Primary patency at 24 months	Proportion (95% CI)
Virga et al 2014[14]	Prospective Cohort	SFA-ISR	ISR	70.3%	0.70 (0.53;0.84)
Micari et al 2013[9]	Prospective Cohort	DCB	de-novo	72.4%	0.72 (0.63;0.81)
Micari et al 2017[11]	Prospective Cohort	DCB	de-novo	70.4%	0.70 (0.60;0.79)
OVERALL					**0.71 (0.65;0.77)**

The table above shows, for the subset of prospective cohort studies, the proportion of primary patency at 24 months and the corresponding 95% confidence interval (Clopper-Pearson exact CI) for each study and the overall proportion obtained with DerSimonian and Laird method 0.71 (0.65; 0.77) the heterogeneity test: I2=0%, p-value=0.94).
The figure below presents the forest plot showing the contribution of each study to the meta-analysis represented by the area of the box.

Figure 16 – Primary Patency at 12-months (subset of observational studies)



7.8 Interpretation of clinical evidence

7.8.1 Provide a statement of principal findings from the clinical evidence highlighting the clinical benefit and any risks relating to adverse events from the technology.

In both pivotal randomized clinical trial and real-world registry data, IN.PACT DCB demonstrates strong effectiveness and safety outcomes, and significantly improves key clinical outcomes for patients with femoropopliteal artery disease compared to PTA, including decreased rates of disease recurrence, subsequent interventions and future hospitalizations, and improvements in pain and symptoms. The main end-points selected across different studies (RCTs, Prospective and Retrospective Cohort studies) were the Primary Patency percentage and freedom from TLR at 12 months. Every study analysed reported superiority in these two clinical end-points across the DCB population.
Potential adverse events which may be associated with peripheral balloon catheterization may include, but are not limited to: abrupt vessel closure, access site pain, allergic reaction to contrast medium, antiplatelet therapy, or catheter system components (materials, drugs, and excipients), amputation/loss of limb, arrhythmias, arterial aneurysm, arterial thrombosis, arteriovenous (AV) fistula, death, dissection, embolization, fever, hematoma, haemorrhage, hypotension/hypertension, inflammation, ischemia or infarction of tissue/organ, local infection at access site, local or distal embolic events, perforation or rupture of the artery, pseudoaneurysm, renal insufficiency or failure, restenosis of

the dilated artery, sepsis or systemic infection, shock, stroke, systemic embolization, vessel spasms or recoil, and vessel trauma which requires surgical repair.
Potential complications of peripheral balloon catheterization include, but are not limited to: balloon rupture, detachment of a component of the balloon and/or catheter system, failure of the balloon to perform as intended, and failure to cross the lesion.
The complete list of all the adverse events and complications occurred in the analysed trials have been reported in Table B11.

7.8.2 Provide a summary of the strengths and limitations of the clinical-evidence base of the technology.

DCB have demonstrated promising results in the femoropopliteal artery in several RCTs. DCB was associated with a significantly reduced angiographic LLL, a significant reduction in binary restenosis, and a significant TLR reduction, supporting the significantly higher effectiveness of DCBs over plain balloon angioplasty, bare nitinol stents, and covered stent-grafts in the femoropopliteal segment. Efficacy was maintained whether DCBs were applied in combination with systematic stenting as the primary treatment mode or for the treatment of late ISR.

Unfortunately, certain study protocols did not include a blinded angiographic core laboratory analysis or independent event adjudication, and nearly all trials had a single-blind or open-label study design resulting in potential performance bias. In addition, the clinical indications and actual settings that dictated TLR were variable or absent in the individual studies, which may introduce some uncertainty in the interpretation of that endpoint. Finally, the dosages of antiplatelet and statin therapies were variable or scarcely reported across the studies.

7.8.3 Provide a brief statement on the relevance of the evidence base to the scope. This should focus on the claimed patient- and system-benefits described in the scope.

Significantly improved primary patency (restored blood flow)

The primary effectiveness endpoint in the IN.PACT SFA Trial was primary patency (defined as freedom from clinically-driven target lesion revascularization (CD-TLR) and freedom from restenosis at 12 months). Results showed that the IN.PACT Admiral DCB demonstrated significantly better primary patency compared to plain balloon angioplasty through 3 years (Krishnan, 2016)

The multi-centre, randomized, single-blinded PACIFIER trial comparing IN.PACT Pacific with standard PTA for treating SFA lesions showed a statistically significant decrease in late lumen loss (LLL) in the DEB group compared to the control group ($p<0.001$) (Werk et al 2012[17]).

In the DEB-SFA Italian Registry which assessed outcomes in 105 patients treated with the IN.PACT Admiral DCB, authors reported that the 6 and 12 months primary patency rates were 87.8% and 83.7%, respectively (Micari et al 2012[8], Micari et al 2013[9]).

The DEBELLUM study compared PTA to IN.PACT PCB for the treatment of stenosis or occlusions of the femoropopliteal or below-the-knee (BTK) arteries. Results showed that late lumen loss was significantly lower in DCB group vs. the PTA group (Fanelli et al 2012[19]).

A controlled, prospective, multicentre study assessed the efficacy of DCB to inhibit restenosis of the infra- inguinal arteries, vs PTA, in an exclusively diabetic population from 11 sites in Belgium found that the 6-month mean diameter restenosis was significantly lower in the DCB arm than in the POBA group ($p=0.032$); binary restenosis rate was significantly lower in DCB patients compared with the POBA's ($p=0.03$) and primary patency was significantly better in the paclitaxel coated balloon group ($p=0.03$). The authors concluded that treatment of diabetic PAD of the infra-inguinal arteries with the DCB provides a better primary patency rate compared with the plain old balloon angioplasty (Debing et al 2016[18]).

A randomized study compared predilatation with DCB vs conventional PTA prior to BMS implantation, for treatment of complex femoropopliteal artery lesions showed that there was a significantly lower rate of binary restenosis at 12 months, in the DCB arm vs the PTA arm ($p = 0.008$). The authors concluded that pre-dilation with PEB angioplasty prior to BMS implantation, as compared to PTA + BMS in complex FPA lesions, reduces restenosis (Liistro et al 2013[7], Grotti et al 2016[15]).

Substantial and significant decrease in rates of repeat interventions (subsequent therapeutic interventions)
In the IN.PACT SFA trial, patients in the DCB group achieved substantially and significantly lower clinically-driven target lesion revascularization (CR-TLR) and clinically-driven target vessel revascularization (CD-TVR) rates in comparison to

plain balloon angioplasty through 36 months (Tepe et al 2015[3], Laird et al 2015[4], Krishnan 2016). Both 12- and 24-month CD-TLR rates are the lowest reported in published medical data for a femoropopliteal endovascular therapy, as of the writing of this summary (Laird et al 2015[4]).
Substantially lower TLR rates in the DEB group were reported in the PACIFIER study at 12 months. The results led the authors to conclude that DCB provides durable safety and effectiveness in patients with femoropopliteal arterial disease (Werk et al 2012[17]).

The DEB-SFA Italian Registry found a low TLR rate and provides further confirmatory evidence of DCB for treating femoro-popliteal artery disease (Micari et al 2012[8], Micari et al 2013[9]).
The DEBELLUM study compared PTA to IN.PACT DCB and showed a significantly reduced TLR rate in the DCB group vs. the PTA group (p=0.02) (Fanelli et al 2012[19]).
Moreover, patients in the IN.PACT Global study experienced a low CD-TVR at 1 year, further demonstrating the safety of IN.PACT Admiral DCB in the treatment of femoropopliteal PAD in real-world patients with complex lesions (Jaff, 2016).

Significantly higher primary sustained clinical improvement
The improvements in primary patency and TLR rates in patients treated with IN.PACT DCB were associated with a significantly higher primary sustained clinical improvement compared with the PTA arm. Between 1 and 3 years, patients in the DCB arm showed a significantly higher primary sustained clinical improvement (defined as freedom from target limb amputation, target vessel revascularization, and worsening Rutherford class), compared with the PTA arm. The following outcomes regarding sustained clinical improvement were reported at the 1, 2 and 3-year time-points: 85.2% (167/196) of patients in the DCB arm vs. 68.9% (73/106 in the PTA arm achieved sustained clinical improvement at 12 months (p<0.001) (Tepe et al 2015[3]). At 24 months, results were 76.9% (133/173) vs. 59.2% (61/103) (p=0.003) (Laird et al 2015[4]), and at 36 months 68.7% (114/166) vs. 52.6% (51/97) (p=0.012) in the DCB vs. PTA arms, respectively (Krishnan, 2016). These results demonstrate much lower symptom severity and better clinical improvement in patients treated with DCB compared to those in the PTA arm.

Similar to the results of the IN.PACT SFA RCT, patients enrolled in the real-world IN.PACT Global study reported a clinical improvement of 80.6% (953/1,183) at 12 months. (Jaff, 2016)
In the PACIFIER trial, the DEB group experienced a greater improvement in Rutherford class at 6 months vs. the PTA group (Werk et al 2012[17]).
Similarly, DEB patients in the DEB-SFA Italian Registry reported a statistically significant improvement in Rutherford classes from baseline to post procedure through 12 months (Micari et al 2012[8]). This significant, sustained improvement was maintained after 24 months (Micari et al 2013[9]).

Improvement in quality of life and function
The pivotal IN.PACT SFA Trial showed that patients experienced significant improvement in quality-of-life and functional outcomes from baseline through 24 months (Tepe et al 2015[3], Laird et al 2015[4]). While patients in both arms - PTA and DCB - showed similar functional outcomes at 12 months, PTA subjects required repeat revascularization to achieve the same level of functional outcomes as the subjects treated with IN.PACT DCB (Tepe et al 2015[3]). Moreover, the substantially lower re-intervention rate with IN.PACT DCB can be considered to reflect lower morbidity and discomfort associated with the re-intervention procedure, compared to patients in the PTA arm who had to undergo a higher rate of repeat interventions. The quality of life at 24 months was similarly improved from baseline for both treatment groups; however, the DCB arm achieved this level of improvement with 58% fewer reinterventions (Laird et al 2015[4]).
Patients with IN.PACT Admiral DCB in the DEB-SFA Italian Registry reported a statistically significant improvement in quality of life (assessed using the Euro QoL-5D) at 3, 6, and 12 month intervals following the procedure. These patients experienced fewer problems with mobility, usual activities, pain, and anxiety/depression. The quality of life at 3 months was 81.3±12.7 and 77.6±12.4 through 12 months (p<0.001 for both) (Micari et al 2012[8]). This statistically significant improvement in the quality of life was also maintained after 2 years (Micari et al 2013[9]).
The IN.PACT SFA Trial also evaluated functional capacity measures such as walking impairment and walking distance between treatment groups. Walking impairment was measured using a walking impairment questionnaire to assess the degree of impairment performing daily activities such as walking distance, speed, and ability to climb stairs. Additionally, a 6-minute walk test was used to assess functional exercise capacity. At 3 years, DCB patients achieved the same level of function with 48% fewer re-interventions (Krishnan, 2016).

Claimed system benefit
Repeat revascularization is an important endpoint because it exposes patients to additional procedure risks and morbidity and reflects a further use of medical resources. Target lesion revascularization (TLR) is defined as a repeat percutaneous or surgical (bypass) revascularization to the target lesion or due to a failure of the initial therapy.
Patients treated with DCB in the IN.PACT SFA Trial experienced a highly significant reduction in clinically-driven target lesion revascularization versus PTA-treated patients at 12 months (p<0.001) (Tepe et al 2015[3]), and 24 months

(p<0.001) (Laird et al 2015[4]). This clinical benefit extends through 36 months: patients treated with IN.PACT DCB had a TLR rate of 15.2% (30/197) in comparison to 31.1% (32/103) in the PTA arm (p=0.002) (Krishnan, 2016).

7.8.4 Identify any factors that may influence the external validity of study results to patients in routine clinical practice.

This is a comprehensive systematic review and meta-analysis pooling the outcomes of several different DCB designs (RCTs, Prospective and Retrospective Cohort studies) while exploring potential confounders (patients number, age, lesion length, gender, smoking, hypertension, hyperlipidaemia) of the clinical outcome.

Tables B12 and B13 summarize the evidence for the outcome. The point estimate was stable across the various sensitivity analyses (random vs fixed effects meta-analyses and subgroup analyses). There were no significant differences when examining each individual study separately. Although statistical heterogeneity was moderate within the studies, summary estimates from a random effect model were reported to account also for design differences between the included studies. The overall estimate in terms of freedom from TLR is 0.91 (0.87; 0.94) and 0.81 (0.70-0.91) at 12 and 24 months respectively. Results were also stable across nearly all baseline confounders and no covariate resulted to influence the pooled results (Test of moderators p-value=0.57) at 12 months while at 24 months the heterogeneity in the true effects is related to the habit of smoking (p<0.001) and diabetes (p=0.04).

Meta-regression demonstrated that lesion length (p=0.005), age (p<0.001) and gender male (p=0.004) significantly affected treatment outcomes in the de-novo lesions subgroups (Table B15- Figure 3) at 12 months while habits of smoking significantly affected treatment outcomes at 24 months (p<0.001).
In the ISR subgroup, lesion length (p<0.001) and age (p<0.001) significantly affected treatment outcomes in the (Table B16 - Figure 4) at 12 months.

7.8.5 Based on external validity factors identified in 7.9.4 describe any criteria that would be used in clinical practice to select patients for whom the technology would be suitable.

As previously mentioned in paragraph 3.2 and 3.3, NICE guideline CG147 accurately describes the recommended clinical pathway of care for PAD patients. This submission recommends the primary use of IN.PACT DCB in place of PTA with bailout BMS, which is currently recommended within the treatment section of the clinical guideline.

Section C – Economic evidence

Section C requires sponsors to present economic evidence for their technology.

All statements should be evidence-based and directly relevant to the decision problem.

The approach to the de novo cost analysis expected to be appropriate for most technologies is cost-consequence analysis. Sponsors should read section 7 of the Medical Technologies Evaluation Programme Methods guide on cost-consequences analysis, available from www.nice.org.uk/mt

Sponsors are requested to submit section C with the full submission. For details on timelines, see the NICE document 'Guide to the Medical Technologies Evaluation Programme process', available from www.nice.org.uk/mt

8 Existing economic evaluations

8.1 Identification of studies

The review of the economic evidence should be systematic and transparent and a suitable instrument for reporting such as the PRISMA statement (www.prisma-statement.org/statement.htm).

A PDF copy of all included studies should be provided by the sponsor.

8.1.1 Describe the strategies used to retrieve relevant health economics studies from the published literature and to identify all unpublished data. The search strategy used should be provided as in section 10, appendix 3.

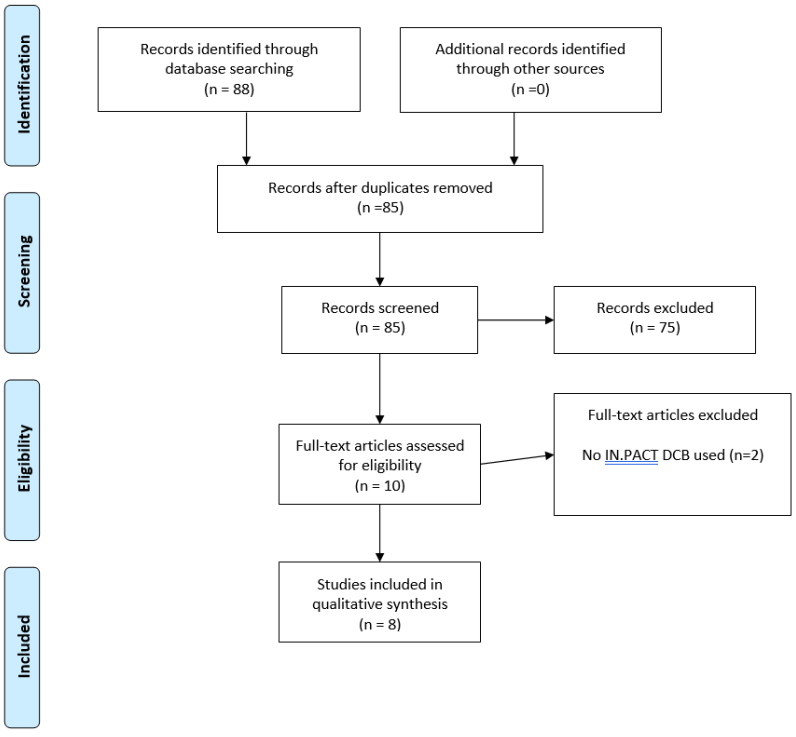
A manual and electronic search (section 10, appendix 3) was performed to systematically review all economic evidence related to drug-coated balloons, rather than a search specific to IN.PACT DCB. This was in order that a full review of the economic evidence available could be performed and submitted. We have then indicated whether the evidence is "IN.PACT DCB economic evidence" or "General DCB economic evidence" in table C2. The literature search has been limited to published studies, available in full- text and only publications in English has been considered. Where both IC and CLI patient populations were considered, we have reported IC results only as per the scope issued by NICE for this review of IN.PACT DCB.

8.1.2 Describe the inclusion and exclusion criteria used to select studies from the published and unpublished literature. Suggested headings are listed in the table below. Other headings should be used if necessary.

Table C1 Selection criteria used for health economic studies

Inclusion criteria	
Population	Patients with peripheral arterial disease as an indication for invasive treatment.
Interventions	Percutaneous Transluminal Angioplasty (PTA) compared to Drug Coated Balloon (DCB).
Outcomes	Any Health Economic outcome
Study design	All types of economic evaluation and cost studies, including cost analyses and cost-effectiveness and budget-impact analyses
Language restrictions	English only
Search dates	2004 to present
Exclusion criteria	
Population	• Patients without Peripheral Artery Disease • Patients with below-the-knee lesion (BTK) only
Interventions	• Patients NOT treated with DCB
Outcomes	Where no Health Economic outcomes are explored
Study design	Studies in which economic evaluation or cost studies are not included.
Language restrictions	Non-English
Search dates	Pre 2004

8.1.3 Report the numbers of published studies included and excluded at each stage in an appropriate format.



8.2 Description of identified studies

8.2.1 Provide a brief review of each study, stating the methods, results and relevance to the scope. A suggested format is provided in table C2.

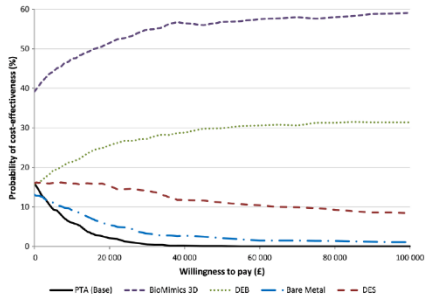
Outcome measures should be included if applicable. Patient outcomes could include gains in life expectancy, improved quality of life, longer time to recurrence, and comparative costs.

Table C2 Summary list of all evaluations involving costs

Study name (year)	**Location of study**	**Summary of model and comparators**	**Patient population *(key characteristics, average age)***	**Costs *(intervention and comparator)***	***Patient outcomes (clinical outcomes, utilities, life expectancy, time to recurrence for intervention and comparator)***	***Results (annual cost savings, annual savings per patient, incremental cost per QALY)***
Cost-effectiveness analysis of paclitaxel-coated balloons for endovascular therapy of femoropopliteal arterial obstructions. (Diehm and Schnieder 2013) General DCB economic evidence	Switzerland	A decision analytic model based on TLR rates and follow-up costs associated with in-hospital patient treatment during 1 year of follow up. Balloon angioplasty vs DEB.	Patient with critical limb ischemia and infrapopliteal arterial obstructions.	**Cost Inputs per patient (sFr):** BA: 6432 DEB: 7976 **Resulting total in hospital charges for 100 patients (sFr) at 12 months:** BA: 951,877 DEB: 861,916	Clinical outcomes came from THUNDER study (RCT). The reduction of restenosis led to lower rate of redo interventions (TLRs) 6 months: (p,0.001) DEB: 4% (2/48) BA: 37% (20/54) 12 months: (p,0.001) DCB: 10% (5/48) BA: 48% (26/54)	At 1 year, use of DEB was associated with substantially lower total inpatient treatment costs when compared with BA despite the need for a greater investment at baseline related to higher prices for DEBs. In absence of dedicated reimbursement incentives, use of DEB was shown to be financially less favourable treatment from physician provider perspective.

Cost-Effectiveness of Endovascular Femoropopliteal Intervention Using Drug-Coated Balloons Versus Standard Percutaneous Transluminal Angioplasty: Results From the IN.PACT SFA II Trial. (Salisbury *et al.* 2016) IN.PACT DCB Economic Evidence	United States of America	A prospective economic study (Markov Model) alongside RCT. Data collected over 2 year follow up. Patients with femoropopliteal disease randomized to IN.PACT DCB vs standard PTA with or without bailout BMS.	Patients undergoing revascularisation for symptomatic severe femoropopliteal PAD.	**Cost Inputs:** Total procedure costs ($): DCB: 5953 ± 2,426 PTA: 4604 ± 2331 Total hospitalisation cost: DCB: 8293± 3230 PTA: 7164 ± 3325 **Resulting Costs:** 2-year follow up costs: TLR hospitalisations ($): DCB: 2171 ± 12,208 PTA: 3,158 ± 7143 **Overall 2-year Costs:** **DCB: 2984 ± 13247** **PTA: 4196 ± 8251**	2-year follow up events: Target limb/ vessel revascularisation and amputation procedures less frequent in patients treated with DCB angioplasty vs PTA. **TLR:** DCB: 20.7 ± 99.9, PTA: 41.7 ± 78.7 **TVR:** DCB: 19.8 ± 99.7, PTA: 38.3 ± 78.3 **Amputation:** DCB: 1.7 ± 12.8, PTA: 5.0 ± 38.7 QALY over 2-year follow up: *Health utilities assessed using EQ5D. **DCB: 1.53± 0.44** **Standard PTA: 1.47 ± 0.42** Reduction in QALYs associated with repeat revascularisation vs patients who did not require repeat revascularisation: **1.47 vs 1.52**	Cost effectiveness: Under base case assumptions, index DCB angioplasty treatment economically dominant strategy with lower 2-year costs and a small gain in QALYs of 0.01.

Are drug-coated balloons cost effective for femoropopliteal occlusive disease? A comparison of bare metal stents and uncoated balloons. (Poder and Fisette 2016) General DCB Economic Evidence	Canada	Cost-effectiveness analysis based on 2-year perspective. Drug coated balloons compared to bare metal stents and uncoated balloons.	Femoropopliteal occlusive disease	**Cost input of de novo revascularisation for the femoropopliteal artery**: DCB: $7868.98 BMS: $7589.49 Uncoated Balloon: $6375.60 **Cost Input of reintervention for the femoropopliteal artery**: DCB: $6807.61 BMS: $9434.42 Uncoated Balloon: $7330.28	Clinical outcomes were extracted from a published meta-analysis (as outlined below): **Target Lesion Revascularisation** (1 year follow up) BMS: DCB: 8% Uncoated Balloon: 22% BMS: 16% **Vascular restenosis rate**: DCB: 19% Uncoated Balloon: 45% BMS: 35%	The cost effectiveness analysis indicated that DCB were generally more efficient than bare metal stents, particularly for patients with higher risk of reintervention. The higher the patients risk of reintervention, the higher the savings associated with the use of DCBs, although DCB are still first choice endovascular intervention for patients at lower risks. “The median scenario shows that DEBs are more cost-effective than BMS when the analysis includes all categories. However, greater savings are observed [when using DEBs] in patients with greater risks (TASC II C or TASC II D) particularly due to the high difference in reintervention costs.” “The median scenario is cost effective for the DEBs compared with uncoated balloons only if the target-lesion revascularization rate for uncoated balloons is very high (i.e., 50%).” The higher the risk for reintervention the greater the cost-effectiveness of DEBs.

Cost-effectiveness of superficial femoral artery endovascular interventions in the UK and Germany: A modelling study. (Kearns and Thomas 2017) General DCB Economic Evidence	United Kingdom	An existing decision analytical model with updated effectiveness data. Percutaneous transluminal angioplasty with bail-out bare metal stenting (SoC) compared with alternatives: primary bare metal stents, drug-eluting stents, drug-eluting balloons (DEBs) and biomimetic stents.	Patients with intermittent claudication of the femoropopliteal arteries eligible for endovascular treatment.	**Procedural Cost Inputs:** PTA with BMS: £3248 Bare Metal stents: £3848 Drug-eluting stents: £4208 Drug- eluting balloons: £4604 Biomimetic stent: £3968 **Costing Results:** **Costs of re-operations (£)** *UK perspective*: All reinterventions with PTA: Biomimetic stents: 2893 PTA with BMS: 3454 DEB: 2920 DES: 3047 BMS: 3273 All reinterventions DEB: Biomimetic stents: 3261 PTA with BMS: 3787 DEB: 3287 DES: 3399 BMS: 3612	**Relative risk of return of symptoms (defined as the need for clinically driven TLR):** PTA with bail out bare metal stents: 1 Bare Metal stents: 0.7261 Drug-eluting stents: 0.5216 Drug- eluting balloons: 0.2739 Biomimetic stent: 0.2711 **QALY's**: Derived by applying utility weight to life years experienced. Utility data for PAD were taken from previous economic evaluation. The underlined results are the relevant results according to the scope of this review by NICE. *UK perspective*: **All reinterventions with PTA**: Biomimetic stents: 6.302 PTA with BMS: 6.213	Use of a biomimetic stent, BioMimics 3D, was always estimated to dominate the other interventions, having lower lifetime costs and greater effectiveness, as measured by QALYs. Of the remaining interventions, DEBs were always the most effective, and PTA the least effective. There was uncertainty in the cost-effectiveness results, with key drivers being the costs and effectiveness of the biomimetic stent along with the costs of DEBs. **Probability each intervention is cost-effective for different willingness to pay thresholds:**  **Figure 2** The probability that each of the interventions is cost-effective, for different willingness to pay values. DEB, drug-eluting balloon; DES, drug-eluting stent; QALYs, quality-adjusted life years.

				Costs of PAD management (£): *UK perspective*: All reinterventions with PTA: Biomimetic stents: 524 PTA with BMS: 1153 DEB: 540 DES: 713 BMS: 950 All reinterventions DEB: Biomimetic stents: 312 PTA with BMS: 544 DEB: 320 DES: 368 BMS: 457 *German similar results to UK so not reported.*	DEB: 6.275 DES: 6.3 BMS: 6.242 **All reinterventions with DEB**: Biomimetic stents: 6.33 PTA with BMS: 6.286 DEB: 6.302 DES: 6.318 BMS: 6.329 *German Perspective*: (All reinterventions with DEB) Biomimetic stents: 6.330 PTA with BMS: 6.286 DEB: 6.329 DES: 6.318 BMS: 6.302	

Economic analysis of endovascular interventions for femoropopliteal arterial disease: A systematic review and budget impact model for the United States and Germany. (Pietzsch 2014) General DCB economic evidence	United States and Germany	A decision analytical Markov model was used to assess the budget impact from payers and providers perspectives. Four index procedure strategies (BMS, DES, DCB and PTA).	Patients with PAD requiring revascularisation.	**Cost Inputs:** Device Cost: USA: PTA: $180 BMS: $1244 DES: $1944 DCB: $1350 Germany: PTA: €180 BMS: €532 DES: €710 DCB: €817	24-month probability of TLR for each treatment weighted by sample size: DCB:14.4% DES 19.2% BMS 28.0% PTA 40.3%	The drug eluting strategies had a lower projected budget impact over 24 months compared to BMS and PTA for US Medicare DCB: $10,214, DES: $12,904, Uncoated balloons $13,114, BMS: $13,802) German public healthcare system: DCB: €3619, DES €3632, BMS €4026, PTA €4290 DCB and DES compared to BMS and PTA are associated with lower probabilities of target lesion revascularisation and cost savings for US and Germany.

Economic analysis of endovascular drug-eluting treatments for femoropopliteal artery disease in the UK. (Katsanos *et al.* 2016) General DCB economic evidence AND In.Pact DCB (3.5 µg/mm2 urea excipient-based DCBs) Economic Evidence	United Kingdom	Model- based (decision analytical) per patient cost impact and quasi cost-effectiveness projection over 24 months based on pooled TLRs and current reimbursement. Intervention: PTA. Comparators: bare metal stent (BMS), drug coated balloon (DCB) and drug eluting stent (DES)	Patients presenting with symptomatic femoropopliteal disease eligible for endovascular treatment.	**Device input cost (£) (added to respective procedure cost):** BMS: 384 DES: 474 DCB (Other): 512 DB (In.Pact): 636 **Resulting 24-month costs (£)**: PTA: £2863 BMS: £2975 DCB: £2906 DES: £2907 DCB (In.Pact): £2896 DCB (Other): £2998	Mean 24-month proportion of TLRs: PTA: 38.5% BMS: 26.9% DES: 19.4% DCB: 17.6% DCB (In.Pact): 11.2% DCB (Other): 21.9% TLRS avoided: BMS: 0.093, DCB: 0.187 DES: 0.168 NNT to avoid 1 TLR BMS: 10.8 DCB: 5.4 DCB (In.Pact): 4.0 DCB (Other): 7.0 DES: 6.0 Estimated QALY gain computed by multiplying difference in TLR rate by QALY decrement (0.06) under assumption of no mortality difference. QALY gains: BMS: 0.005	ICERS: DCB: £3983 (DCB), DCB (In.Pact): £2259 DCB (Other): £16290 DES: £4534 BMS: £20 719 Cost per TLR avoided: BMS: £1,204 DCB: £231 DCB (In.Pact): £31 DCB (Other): £947 DES: £264 Overall reduction of 10% in DCB and DES prices made drug- eluting treatments dominant. Results: N=28 studies were identified, reporting on 5167 femoropopliteal lesions. Over 24 months, DCB, DES and BMS reduced TLRs of de novo lesions from 36.2% to 17.6%, 19.4% and 26.9%, respectively, at an increased cost of £43, £44 and £112. NNTs to avoid 1 TLR in 24 months were 5.4, 6.0 and 10.8, resulting in cost per TLR avoided of £231, £264 and £1204. DCB was estimated to add 0.011 QALYs, DES 0.010 QALYs

					DCB: 0.011 DES: 0.010	and BMS 0.005 QALYs, resulting in estimated ICERs of £3983, £4534 and £20 719 per QALY gained. A subset analysis revealed more favourable clinical and economic outcomes for a 3.5 µg/mm2 DCB with urea excipient, compared with the rest of DCBs. A modest reduction of 10% in DCB and DES prices made drug eluting treatments dominant. Conclusions: Widespread adoption of drug-eluting endovascular therapies for femoropopliteal disease would add meaningful clinical benefit at reasonable additional costs to the NHS. Based on currently available data, DCBs offer the highest clinical and economic value.

Enhancements to angioplasty for peripheral arterial occlusive disease: Systematic review, cost-effectiveness assessment and expected value of information. (Simpson 2014) General DCB Economic Evidence	United Kingdom	A discrete event simulation model was developed to assess cost effectiveness. Patient populations with intermittent claudication (IC) and critical limb ischaemia (CLI) were modelled separately. IC is the in-scope population for this search, thus these results only are outlined. Conventional PTA was the main comparator. Interventions: PTA no bail out stenting, PTA with bail out paclitaxel	Symptomatic PAD undergoing endovascular treatment for disease distal to the inguinal ligament.	**Cost Inputs (£):** Base Case (PTA with bail out BMS): 3837 PTA no bail out stenting: 3661 PTA with bail out paclitaxel eluting stents: 3949 Paclitaxel coated balloon: 4071 BMS: 4316 Paclitaxel eluting stent: 4525 EVBT: 6171 Stent graft: 6561 Cryoplasty: 7367 **Resulting costs for IC Population (£):** Paclitaxel coated balloon: 12,668 PTA with bail out DES: 13,032 PTA with bail out BMS: 14,637 PTA no bail out stenting: 14, 787 BMS: 15,030 Paclitaxel eluting stent: 15,692 EVBT: 15, 891	Relative risk/ transition probabilities of: **Late failure:** Base Case (PTA with bail out BMS): 1 PTA, no bail out stenting: 1 PTA with bail out paclitaxel eluting stents: 0.82 Paclitaxel coated balloon: 0.4 BMS: 0.58 Paclitaxel eluting stent: 0.53 EVBT: 0.63 Stent graft: 0.58 Cryoplasty: 2.2 **QALYs for IC population (evaluations used EQ-5D):** Paclitaxel coated balloon: 6.120 PTA with bail out DES: 6.081 PTA with bail out BMS: 5.956 PTA no bail out stenting: 5.931	The use of DCBs dominated both the assumed standard practice of PTA with bail-out BMSs and all other interventions because it lowered lifetime costs and improved QoL. This was seen for both patient populations IC and CLI.

		eluting stents, DEB, BMS, Paclitaxel eluting stent, EVBT, Stent graft, Cryoplasty.		Stent-graft: 16,171 Cryoplasty: 17, 578	BMS: 5.989 Paclitaxel eluting stent: 5.993 EVBT: 5.984 Stent-graft: 5.989 Cryoplasty: 5.934	

8.2.2 Provide a complete quality assessment for each health economic study identified. A suggested format is shown in table C3.

Table C3 Quality assessment of health economic studies

Study name Cost effectiveness of superficial femoral artery endovascular interventions in the UK and Germany: a modelling study (Kearns and Thomas 2017)		
Study design Cost effectiveness analysis.		
Study question	**Response (yes/no/not clear/N/A)**	**Comments**
1. Was the research question stated?	Yes	To assess the lifetime costs and cost-effectiveness of 5 endovascular interventions to treat superficial femoral arterial disease.
2. Was the economic importance of the research question stated?	Yes	Alternatives to PTA such as BMS, DES and DEBs have been demonstrated to have favourable outcomes.
3. Was/were the viewpoint(s) of the analysis clearly stated and justified?	Yes	To update the previous economic evaluation to incorporate the latest evidence to both the clinical effectiveness of treatments and the impact cost-effectiveness using different pricing schemes and reintervention methods.
4. Was a rationale reported for the choice of the alternative programmes or interventions compared?	Yes	Alternative interventions for PAD
5. Were the alternatives being compared clearly described?	Yes	Bare metal stents, drug eluting stents and drug eluting balloons compared to percutaneous angioplasty.
6. Was the form of economic evaluation stated?	Yes	A cost-effectiveness model. An existing decision analytical model was used with updated effectiveness data taken from the literature and updated costs based on purchasing.
7. Was the choice of form of economic evaluation justified in relation to the questions addressed?	Yes	From a decision-making viewpoint, cost-effectiveness is important because not all effective interventions can be funded.
8. Was/were the source(s) of effectiveness estimates used stated?	Yes	Taken from systematic review and meta-analysis of Jens *et al.* Evidence for biomimetic stents were taken from the Mimics study.
9. Were details of the design and results of the effectiveness study given (if based on a single study)?	Yes	The Mimics study was a multicentre RCT of patients receiving femoropopliteal intervention. 50 patients received Biomimics 3D stent and 26 patients received bare metal (nitinol) stent. Follow-up 2 years. 2 main drivers cost savings observed for biomimetic stents: a reduction in number of repeat operations required and reduction in average time spent with PAD. DEB use for reinterventions instead of PTA lowered lifetime costs of PAD management but increased the costs of reoperations.
10. Were details of the methods of synthesis or meta-analysis of estimates given (if based on an overview of a number of effectiveness studies)?	Yes	Details on the derivations of RRs from the Jen *et al.* meta-analysis are provided in the online supplementary material.
11. Were the primary outcome measure(s) for the economic evaluation clearly stated?	Yes	The change in re-intervention rates, based on clinically driven target lesion revascularisation (TLR).
12. Were the methods used to value health states and other benefits stated?	Yes	Estimated costs to healthcare system and patient benefits measured by QALYs, considered over a lifetime horizon. Derived by applying a utility (weight) to life years experienced with a utility of one (perfect health) and 0 (death).
13. Were the details of the subjects from whom valuations were obtained given?	No	Patient baseline characteristics not outlined

14. Were productivity changes (if included) reported separately?	N/A	
15. Was the relevance of productivity changes to the study question discussed?	N/A	
16. Were quantities of resources reported separately from their unit cost?	No	
17. Were the methods for the estimation of quantities and unit costs described?	No	They state costs were based on a mixture of company prices, hospital prices and expert opinion.
18. Were currency and price data recorded?	Yes	£
19. Were details of price adjustments for inflation or currency conversion given?	Yes	For the analysis from a German perspective cost of PTA with bail out bare metal stents obtained by converting the £ to Euros, assuming conversion rate of 1.2.
20. Were details of any model used given?	Yes	Decision Analytical Model to synthesise data on clinical effectiveness, healthcare costs and patients QoL. Patients entered the DAM on receiving PTA or another alternative intervention and had probability of perioperative mortality or acute failure. Patients who remained alive, outcome modelled.
21. Was there a justification for the choice of model used and the key parameters on which it was based?	Yes	An existing DAM used with updated effectiveness data and costs.
22. Was the time horizon of cost and benefits stated?	Yes	Considered over a lifetime horizon.
23. Was the discount rate stated?	Yes	3.5%
24. Was the choice of rate justified?	Yes	As recommended by NICE
25. Was an explanation given if cost or benefits were not discounted?	N/A	
26. Were the details of statistical test(s) and confidence intervals given for stochastic data?	N/A	
27. Was the approach to sensitivity analysis described?	Yes	Conducted in which the cost of a reintervention was triple that of the initial procedure.
28. Was the choice of variables for sensitivity analysis justified?	Yes	
29. Were the ranges over which the parameters were varied stated?	Yes	
30. Were relevant alternatives compared? (That is, were appropriate comparisons made when conducting the incremental analysis?)	No	No direct comparison between effectiveness of biomimetic stents and DEBs.
31. Was an incremental analysis reported?	Yes	Figure 1, displays incremental costs and effects estimated from each PSA for each intervention compared to PTA with bail out BMS (under UK perspective, with PTA for re-interventions). Primary outcome measure was incremental cost-effectiveness ratio between 2 treatments.
32. Were major outcomes presented in a disaggregated as well as aggregated form?	Yes	

33. Was the answer to the study question given?	Yes	Use of biomimetic stent, BioMimics 3D always estimated to dominate the other interventions having lower lifetime costs and greater effectiveness. Of the remaining interventions DEB was always the most effective and PTA the least effective. However, evidence for biomimetic stents were taken solely from a small Mimics study with only 76 patients. Thus, this is not an accurate representation/ less reliable. Secondly, no direct comparison between effectiveness of biomimetic stents and DEBs.
34. Did conclusions follow from the data reported?	Yes	
35. Were conclusions accompanied by the appropriate caveats?	Yes	There are no head to head comparisons between biomimetic stents and DEBs, the relatively small sample size for biomimetic stents and heterogeneity in purchasing strategies led to variation in the estimated costs of the interventions.
36. Were generalisability issues addressed?	No	Potential one or more assumptions may be incorrect or may not be applicable in different HCS, limiting generalisability.
Study name Cost-Effectiveness of Endovascular Femoropopliteal Intervention Using Drug-Coated Balloons Versus Standard Percutaneous Transluminal Angioplasty. (Salisbury *et al.* 2016)		
Study design Cost-effectiveness Study		
Study question	**Response (yes/no/not clear/N/A)**	**Comments**
1. Was the research question stated?	Yes	To evaluate the cost-effectiveness of drug-coated balloon (DCB) angioplasty vs standard percutaneous transluminal angioplasty (PTA).
2. Was the economic importance of the research question stated?	Yes	Recent trials have reported lower rates of target lesion revascularisation with DCB angioplasty vs PTA, however, the cost effectiveness of DCB angioplasty is unknown.
3. Was/were the viewpoint(s) of the analysis clearly stated and justified?	Yes	Prospective health economic assessment alongside the IN.PACT SFA II trial (IN.PACT Admiral Drug Coated Balloon vs Standard Balloon Angioplasty for the Treatment of Superficial Femoral Artery (SFA) and Proximal Popliteal Artery (PPA).
4. Was a rationale reported for the choice of the alternative programmes or interventions compared?	Yes	Recently paclitaxel coated balloons have shown to reduce rates of restenosis and repeat revascularization for patients undergoing femoropopliteal intervention without the need for stent implantation leading FDA approval of 2 devices. DCB are significantly more expensive than standard PTA balloons and given large patient number it is important assess cost-effectiveness.
5. Were the alternatives being compared clearly described?	Yes	IN.PACT Admiral Drug Coated Balloon vs Standard Balloon Angioplasty for the Treatment of Superficial Femoral Artery (SFA) and Proximal Popliteal Artery (PPA)
6. Was the form of economic evaluation stated?	Yes	State transition Markov model to project 2 year costs and QALYs for the IN.PACT SFA II population.
7. Was the choice of form of economic evaluation justified in relation to the questions addressed?	Yes	Differential mortality would have led to lower than expected costs and QALYs in the DCB angioplasty group thus patient level cost effectiveness analysis could not be undergone.

8. Was/were the source(s) of effectiveness estimates used stated?	Yes	IN.PACT SFA II trial (NCT01566461)
9. Were details of the design and results of the effectiveness study given (if based on a single study)?	Yes	Multicentre RCT, of IN.PACT Admiral DCB vs standard PTA in patients undergoing revascularisation for symptomatic femoropopliteal PAD. Target limb revascularisation procedures less frequent in patients treated with DCB angioplasty vs PTA
10. Were details of the methods of synthesis or meta-analysis of estimates given (if based on an overview of a number of effectiveness studies)?	N/A	
11. Were the primary outcome measure(s) for the economic evaluation clearly stated?	Yes	Number of repeat revascularization procedures.
12. Were the methods used to value health states and other benefits stated?	Yes	Quality of life was assessed using the EQ5D which was administered to patients at baseline and at 1,6,12,24 month follow up.
13. Were the details of the subjects from whom valuations were obtained given?	Yes	Baseline Patient Characteristics outlined (age, gender, diabetes, smoking, Rutherford Class, target lesion length, occlusion and stenosis percentage)
14. Were productivity changes (if included) reported separately?	N/A	
15. Was the relevance of productivity changes to the study question discussed?	N/A	
16. Were quantities of resources reported separately from their unit cost?	Yes	Broken down into procedure resource use and costs.
17. Were the methods for the estimation of quantities and unit costs described?	Yes	Procedural costs estimated on basis of the mean hospital acquisition cost in 2014 and other hospital costs determined using “top down” accounting methods.
18. Were currency and price data recorded?	Yes	$
19. Were details of price adjustments for inflation or currency conversion given?	No	Inflation not mentioned. Currency conversion N/A
20. Were details of any model used given?	Yes	State transition Markov model to project 2 year costs and QALYS for the IN.PACT SFA II population.
21. Was there a justification for the choice of model used and the key parameters on which it was based?	Yes	Patient level cost-effectiveness analysis not performed as imbalance in 2-year mortality. Differential mortality will lead to lower than expected costs and QALYs thus Markov model developed to project 2-year costs and QALYs.
22. Was the time horizon of cost and benefits stated?	Yes	2 years
23. Was the discount rate stated?	No	
24. Was the choice of rate justified?	No	
25. Was an explanation given if cost or benefits were not discounted?	No	
26. Were the details of statistical test(s) and confidence intervals given for stochastic data?	Yes	Categorical data reported as frequencies and were compared using the Fisher exact test. Continuous data reported as mean SD and were compared using the Student t tests or the Wilcoxon rank sum test. Cost data not normally distributed so they were compared using nonparametric bootstrapping. P value (<0.05 considered statistical significance)

27. Was the approach to sensitivity analysis described?	Yes	One-way sensitivity analysis each model parameters identify which factors had greatest impact on ICERs. Probabilistic sensitivity analysis in which all model parameters sampled from respective distributions. Results reported in cost-effectiveness acceptability curve.
28. Was the choice of variables for sensitivity analysis justified?	Yes	
29. Were the ranges over which the parameters were varied stated?	Yes	
30. Were relevant alternatives compared? (That is, were appropriate comparisons made when conducting the incremental analysis?)	Yes	Yes DCB vs standard balloon PTA.
31. Was an incremental analysis reported?	Yes	ICER for drug coated balloon vs standard balloon PTA.
32. Were major outcomes presented in a disaggregated as well as aggregated form?	Yes	
33. Was the answer to the study question given?	Yes	For patients with femoropopliteal disease, DCB angioplasty is associated with better 2-year outcomes and similar target limb-related costs compared with standard PTA. Cost-effectiveness analysis suggests use of DCB angioplasty is economically attractive.
34. Did conclusions follow from the data reported?	Yes	Target limb revascularisation procedures less frequent in patients treated with In.Pact DCB vs PTA.
35. Were conclusions accompanied by the appropriate caveats?	Yes	Relatively small number of patients were included in the analysis and it is possible that outliers more strongly influenced costs and clinical outcomes. Providers evaluating patients at follow-up were not blinded to treatment assignment in IN.PACT SFA.
36. Were generalisability issues addressed?	No	Only patients from United States included, thus results may not be generalisable to patients in other healthcare systems.
Study name Are drug-coated balloons cost effective for femoropopliteal occlusive disease? A comparison of bare metal stents and uncoated balloons. (Poder and Fisette 2016)		
Study design Cost effectiveness analysis		
Study question	**Response (yes/no/not clear/N/A)**	**Comments**
1. Was the research question stated?	Yes	To perform a cost-effectiveness analysis to help hospital decision makers with the use of drug-coated balloons compared with bare metal stents and uncoated balloons for femoropopliteal occlusive disease.
2. Was the economic importance of the research question stated?	Yes	To evaluate which technology option is the most efficient for the first intervention (*de novo*)
3. Was/were the viewpoint(s) of the analysis clearly stated and justified?	Yes	2-year perspective. Clinical outcomes extracted from the results of published meta-analyses and cost units are those used in Quebec healthcare network.
4. Was a rationale reported for the choice of the alternative programmes or interventions compared?	Yes	As solely assessing first intervention (*de novo*) drug eluting stents are excluded from the analysis as they remain restricted to reintervention of the lesion.
5. Were the alternatives being compared clearly described?	Yes	Drug coated balloon (paclitaxel), uncoated balloon, bare metal stent

6. Was the form of economic evaluation stated?	Yes	Cost-effectiveness analysis
7. Was the choice of form of economic evaluation justified in relation to the questions addressed?	Yes	With respect to high quality patient care and better use of available resources necessary to evaluate the cost-effectiveness of these technologies.
8. Was/were the source(s) of effectiveness estimates used stated?	Yes	Used literature review to source published meta-analyses and used results to perform a cost-effectiveness analysis.
9. Were details of the design and results of the effectiveness study given (if based on a single study)?	N/A	
10. Were details of the methods of synthesis or meta-analysis of estimates given (if based on an overview of a number of effectiveness studies)?	N/A	
11. Were the primary outcome measure(s) for the economic evaluation clearly stated?	Yes	Effectiveness of DCB compared with bare metal stents and uncoated balloons given by the hazard ratio of the target lesion revascularisation rate.
12. Were the methods used to value health states and other benefits stated?	No	
13. Were the details of the subjects from whom valuations were obtained given?	No	
14. Were productivity changes (if included) reported separately?	N/A	
15. Was the relevance of productivity changes to the study question discussed?	N/A	
16. Were quantities of resources reported separately from their unit cost?	Yes	
17. Were the methods for the estimation of quantities and unit costs described?	Yes	Costs were calculated from the suppliers. The initial extra cost associated with use of DCB compared with bare metal stent or uncoated balloon calculated from purchase price of devices and utilisation rates in their angiography department.
18. Were currency and price data recorded?	Yes	$
19. Were details of price adjustments for inflation or currency conversion given?	No	
20. Were details of any model used given?	Yes	
21. Was there a justification for the choice of model used and the key parameters on which it was based?	Yes	
22. Was the time horizon of cost and benefits stated?	Yes	2-year perspective.
23. Was the discount rate stated?	No	
24. Was the choice of rate justified?	N/A	
25. Was an explanation given if cost or benefits were not discounted?	Yes	Considering the evaluation period was short, we decided not to use a discount rate.
26. Were the details of statistical test(s) and confidence intervals given for stochastic data?	N/A	
27. Was the approach to sensitivity analysis described?	Yes	

28. Was the choice of variables for sensitivity analysis justified?	Yes	A sensitivity analysis was performed considering an interval of several values regarding relative efficacy of drug coated balloons compared with bare metal stents or uncoated balloons. Several simulations were performed by considering several groups of patients eligible for drug-coated balloons.
29. Were the ranges over which the parameters were varied stated?	Yes	
30. Were relevant alternatives compared? (That is, were appropriate comparisons made when conducting the incremental analysis?)	Yes	Drug coated balloons compared with bare metal stents or uncoated balloons.
31. Was an incremental analysis reported?	Yes	
32. Were major outcomes presented in a disaggregated as well as aggregated form?	Yes	
33. Was the answer to the study question given?	Yes	Drug-coated balloons were more efficient than bare metal stents, particularly for patients with higher risk of reintervention. Compared with uncoated balloons, results indicated DCB were more efficient if the reintervention rate associated with uncoated balloons is very high and for patients with higher risk of reintervention.
34. Did conclusions follow from the data reported?	Yes	Target Lesion Revascularisation: compared with DCB the repetition rate of procedure is higher when uncoated balloon used. Significantly lower reintervention rate for DCB vs. BMS, The higher a patient's risk of reintervention, the higher the savings associated with the use of DCB will be. For patients at lower risk, the uncoated balloon strategy is still recommended as a first choice for endovascular intervention.
35. Were conclusions accompanied by the appropriate caveats?	Yes	
36. Were generalisability issues addressed?	No	
Study name Economic analysis of endovascular drug-eluting treatments for femoropopliteal artery disease in the UK. (Katsanos *et al.* 2016).		
Study design Decision analytic budget impact model		
Study question	**Response (yes/no/not clear/N/A)**	**Comments**
1. Was the research question stated?	Yes	To estimate the clinical and economic impact of drug-eluting endovascular treatment strategies for femoropopliteal artery disease compared with current standard of care.
2. Was the economic importance of the research question stated?	Yes	Peripheral artery disease causes significant morbidity and reduced quality of life for patients with vascular restenosis and vessel failure leading to frequent revascularisation or amputations representing a significant economic burden on the UK NHS.

3. Was/were the viewpoint(s) of the analysis clearly stated and justified?	Yes	DCB has shown promising results in femoropopliteal segment by reducing vascular restenosis and the need for target lesion revascularisation. DCB in particular is a relatively novel and effective treatment approach that does not require long term device implant, not yet considered in the current NICE guidance.
4. Was a rationale reported for the choice of the alternative programmes or interventions compared?	Yes	Current NICE guidance recommends percutaneous transluminal balloon angioplasty (PTA). If stenting is needed or offered NICE recommends bare metal stents although drug eluted stents and DCB have shown promising results in the femoropopliteal segment by reducing vascular restenosis and the need for target lesion revascularisation.
5. Were the alternatives being compared clearly described?	Yes	
6. Was the form of economic evaluation stated?	Yes	Decision-analytic budget impact model, considering index procedure and up to one reintervention, over a 24-month analysis horizon.
7. Was the choice of form of economic evaluation justified in relation to the questions addressed?	Yes	
8. Was/were the source(s) of effectiveness estimates used stated?	Yes	
9. Were details of the design and results of the effectiveness study given (if based on a single study)?	N/A	Systematic literature search. Mean 24-month proportion of TLRs: PTA: 38.5% BMS: 26.9% DES: 19.4% DCB: 17.6% DCB (In.Pact): 11.2% DCB (Other): 21.9% NNT to avoid 1 TLR BMS: 10.8 DCB: 5.4 DCB (In.Pact): 4.0 DCB (Other): 7.0 DES: 6.0
10. Were details of the methods of synthesis or meta-analysis of estimates given (if based on an overview of a number of effectiveness studies)?	Yes	Estimates of 24-month TLR probabilities of each of the four interventions were computed using a weighted pooling approach based on sample size. For studies only reporting shorter follow-up of 12 months, the 12-month TLR rates were pooled and then extrapolated leading to the corresponding 24 month TLR probability assuming constant hazard rate.
11. Were the primary outcome measure(s) for the economic evaluation clearly stated?	Yes	24-month per patient cost impact to NHS. Pooled 24-month TLR rates Numbers needed to treat
12. Were the methods used to value health states and other benefits stated?	Yes	Estimated QALY gain was computed by multiplying the difference in TLR rate by the QALY decrement (0.06), under the assumption of no mortality difference.
13. Were the details of the subjects from whom valuations were obtained given?	No	Study characteristics of included patient population(s) described in manuscript and supplement.

14. Were productivity changes (if included) reported separately?	N/A	
15. Was the relevance of productivity changes to the study question discussed?	N/A	
16. Were quantities of resources reported separately from their unit cost?	Yes	
17. Were the methods for the estimation of quantities and unit costs described?	Yes	Costs were assumed based on the current 2015/2016 NHS England Tariff, Hospital Episodes Statistics and market research data on BMS, DCB and DES. 24-month costs included reimbursement for the index procedure and applicable reintervention.
18. Were currency and price data recorded?	Yes	£
19. Were details of price adjustments for inflation or currency conversion given?	N/A	
20. Were details of any model used given?	Yes	Decision-analytic Budget Impact Model developed to estimate, by index procedure strategy, the primary and secondary end points of this analysis.
21. Was there a justification for the choice of model used and the key parameters on which it was based?	Yes	24-month TLR computed. Mortality was not considered given the limited time horizon of the analysis, and included clinical studies do not suggest mortality difference related to study devices.
22. Was the time horizon of cost and benefits stated?	Yes	24- month as it reflects the follow-up horizon available for most of the included studies.
23. Was the discount rate stated?	N/A	No discounting performed because of short model timeframe of only 24 months
24. Was the choice of rate justified?	N/A	
25. Was an explanation given if cost or benefits were not discounted?	Yes	Opted not to discount costs or effects because of the short follow up horizon of the analysis of only 24 months and the fact that most costs are incurred at time zero.
26. Were the details of statistical test(s) and confidence intervals given for stochastic data?	N/A	No statistical significance testing was performed for the purposes of this study, as it was not part of the study objective.
27. Was the approach to sensitivity analysis described?	Yes	Several were performed to study the effect of parameter uncertainty on the base case and subset analysis results.
28. Was the choice of variables for sensitivity analysis justified?	Yes	Among others: Assumed device of 1.5 instead of 1 to account for longer lesions Decrease in assumed device costs by 20% Increase in device cost by 10%.
29. Were the ranges over which the parameters were varied stated?	Yes	Best- and worst-performing study for each treatment modality was used to define boundaries for sensitivity analysis.
30. Were relevant alternatives compared? (That is, were appropriate comparisons made when conducting the incremental analysis?)	Yes	
31. Was an incremental analysis reported?	Yes	Cost per TLR avoided and estimated incremental cost-effectiveness ratio (ICER) in £ per QALY.
32. Were major outcomes presented in a disaggregated as well as aggregated form?	Yes	
33. Was the answer to the study question given?	Yes	

34. Did conclusions follow from the data reported?	Yes	Widespread adoption of drug-eluting endovascular therapies for femoropopliteal disease would add meaningful clinical benefit at reasonable additional costs to the NHS. Based on currently available data, DCBs offer the highest clinical and economic value.
35. Were conclusions accompanied by the appropriate caveats?	Yes	Used decision analytical budget impact model Analysis limited to 2 year time horizon and the ICER projections based on simplified computer simulations index certain health utility assumptions.
36. Were generalisability issues addressed?	Yes	Authors discuss that the synthesised evidence mostly applied for intermittent claudication and the population of CLI was underrepresented, resembling only 15–20% of enrolled participants in the included studies.
Study name. Economic Analysis of Endovascular Interventions for Femoropopliteal Arterial Disease (Pietzsch *et al.* 2014)		
Study design: Budget Impact Model for the United States and Germany.		
Study question	**Response (yes/no/not clear/N/A)**	**Comments**
1. Was the research question stated?	Yes	To study the economic impact on payers and providers of the four main endovascular strategies for the treatment of infrainguinal peripheral artery disease.
2. Was the economic importance of the research question stated?	Yes	Bare metal stents, drug eluting stents and drug coated balloons are associated with lower target lesion revascularisation probabilities than percutaneous transluminal angioplasty (PTA) but the economic impact is unknown.
3. Was/were the viewpoint(s) of the analysis clearly stated and justified?	Yes	A decision analytic Markov model was used to assess the budget impact from payers and facility providers perspectives of the four index strategies (BMS, DES, DCB, PTA). Base case: US Medicare and the Germany statutory sickness fund perspectives.
4. Was a rationale reported for the choice of the alternative programmes or interventions compared?	Yes	PTA original treatment alternative to surgical revascularisation. BMS and DES have demonstrated lower incidence rates of target lesion revascularisation. More recently, drug coated balloons have emerged and hold promise of reducing TLRs further and to avoid stent-related risks such as in-stent restenosis and stent fracture, while maintaining all therapeutic options for subsequent reinterventions.
5. Were the alternatives being compared clearly described?	Yes	PTA, bare metal stents, drug eluting stents, and drug coated balloons
6. Was the form of economic evaluation stated?	Yes	State transition or Markov model developed estimate 24-month budget impact of index procedures and reinterventions in the US and German Health care systems.
7. Was the choice of form of economic evaluation justified in relation to the questions addressed?	Yes	Transition probabilities varied with index procedure (PTA, BMS, DES, DCB)
8. Was/were the source(s) of effectiveness estimates used stated?	Yes	Systematic literature search
9. Were details of the design and results of the effectiveness study given (if based on a single study)?	N/A	No effectiveness study was performed. Rather, effectiveness data were identified through systematic search.

10. Were details of the methods of synthesis or meta-analysis of estimates given (if based on an overview of a number of effectiveness studies)?	Yes	Use a described weighted pooling approach which assumed constant hazard rate to extrapolate shorter follow ups for TLR estimates.
11. Were the primary outcome measure(s) for the economic evaluation clearly stated?	Yes	24-month probability of TLR for each treatment weighted by sample size: The pooled 24-month probabilities DCB (14.3%), DES (19.3%), BMS (28.1%), PTA (40.3%).
12. Were the methods used to value health states and other benefits stated?	Yes	Cost associated with reintervention state were described.
13. Were the details of the subjects from whom valuations were obtained given?	Yes	Cohort characteristics summarized in manuscript and further detailed in supplement.
14. Were productivity changes (if included) reported separately?	N/A	
15. Was the relevance of productivity changes to the study question discussed?	N/A	
16. Were quantities of resources reported separately from their unit cost?	Yes	
17. Were the methods for the estimation of quantities and unit costs described?	Yes	The Medicare reimbursement rate for revascularisation with DCB assumed similar to that with a bare PTA balloon and reimbursement for revascularisation with DES was assumed similar to that with BMS. US payer perspective used current Medicare fiscal year 2013 national reimbursement rates for peripheral vascular interventions. For inpatient reimbursement rates, a case mix-adjusted average of payment rates across 3 Medicare severity diagnosis related groups was used.
18. Were currency and price data recorded?	Yes	Data for US and German analyses presented in respective currencies ($ and €). Price data detailed.
19. Were details of price adjustments for inflation or currency conversion given?	Yes	All cost data were current year data, so no adjustment needed.
20. Were details of any model used given?	Yes	A state transition/ Markov model. Cycle length of the model one week and in each week a constant proportion of remaining patients at risk could be subject to revascularisation following index procedure.
21. Was there a justification for the choice of model used and the key parameters on which it was based?	Yes	Choice of therapy used in reinterventions was based on the opinion of two co-authors and was assumed to be dependent on the type of index procedure therapy.
22. Was the time horizon of cost and benefits stated?	Yes	24 months
23. Was the discount rate stated?	No	No discounting performed because of short analysis horizon of 24 months.
24. Was the choice of rate justified?	No	No discounting performed because of short analysis horizon of 24 months.
25. Was an explanation given if cost or benefits were not discounted?	Yes	Short time horizon no discounting was applied.
26. Were the details of statistical test(s) and confidence intervals given for stochastic data?	N/A	No statistical significance testing and confidence interval computation was pursued for the purposes of this analysis.
27. Was the approach to sensitivity analysis described?	Yes	Supporting Information Appendix for detailed description of the analysis performed.

28. Was the choice of variables for sensitivity analysis justified?	Yes	Varying the TLR rates, cost inputs, and number of devices used per procedure
29. Were the ranges over which the parameters were varied stated?	Yes	The lowest and highest reported TLR rates were used to assess impact on budget for each therapy. Ranges for cost and number of devices were provided.
30. Were relevant alternatives compared? (That is, were appropriate comparisons made when conducting the incremental analysis?)	Yes	See above.
31. Was an incremental analysis reported?	Yes	Absolute cost difference and incremental cost to payers per TLR avoided.
32. Were major outcomes presented in a disaggregated as well as aggregated form?	Yes	
33. Was the answer to the study question given?	Yes	The drug eluting strategies had a lower projected budget impact over 24 months compared to BMS and PTA in both the US Medicare and German public health systems.
34. Did conclusions follow from the data reported?	Yes	DCB and DES compared to BMS and PTA are associated with lower probabilities of target lesion revascularisation and cost savings for U.S. and German payers.
35. Were conclusions accompanied by the appropriate caveats?	Yes	As analysis was a health-economic research question, we did not conduct formal hypothesis testing to establish non-inferiority among therapies. The pooled DES group differed in terms of critical limb ischemia rate and lesion length from other populations may have impacted the DES analysis. Extrapolated data from 12 to 24 months.
36. Were generalisability issues addressed?	Yes	“The base case results can therefore not be generalized to cases where more than one device is used. However, we performed sensitivity analyses to test the effect of the use of more than one device.”

Study name HTA: Enhancements to angioplasty for peripheral arterial occlusive disease: a systematic review, cost-effectiveness assessment and expected value of information analysis. (Simpson *et al.* 2014)		
Study design Cost-effectiveness		
Study question	**Response (yes/no/not clear/N/A)**	**Comments**
1. Was the research question stated?	Yes	To assess current clinical effectiveness and cost effectiveness evidence of additional techniques to standard PTA for PAD and develop a health economic model to assess cost-effectiveness.
2. Was the economic importance of the research question stated?	Yes	There have been rapid technological developments aimed at improving short and long-term results of percutaneous transluminal balloon angioplasty in peripheral arterial occlusive disease (PAD).
3. Was/were the viewpoint(s) of the analysis clearly stated and justified?	Yes	Assess cost-effectiveness of the interventions from a health service perspective.
4. Was a rationale reported for the choice of the alternative programmes or interventions compared?	Yes	The techniques considered were those that are used either as a replacement for or in conjunction with conventional balloon angioplasty.
5. Were the alternatives being compared clearly described?	Yes	PTA with secondary BMS (base case) Primary BMS, PTA using DC, Primary DES, PTA with secondary DES, Stent-graft, Cryoplasty, EVBT
6. Was the form of economic evaluation stated?	Yes	A discrete event simulation model. A lifetime horizon was used to ensure all differences in costs and benefits were captured.
7. Was the choice of form of economic evaluation justified in relation to the questions addressed?	Yes	A discrete event simulation model developed to determine cost-effectiveness of each enhancement compared with angioplasty alone.
8. Was/were the source(s) of effectiveness estimates used stated?	Yes	QALYs were used as the measure of effectiveness.
9. Were details of the design and results of the effectiveness study given (if based on a single study)?	N/A	
10. Were details of the methods of synthesis or meta-analysis of estimates given (if based on an overview of a number of effectiveness studies)?	Yes	Data to populated the model were based on systematic review.
11. Were the primary outcome measure(s) for the economic evaluation clearly stated?	Yes	Outcomes included measures of clinical effectiveness, restenosis and reintervention and costs sourced from literature-review. Evidence significant reduction restenosis rates for DCB compared with PTA. Significantly lower rates for reintervention reported for DCB compared with PTA. The main model outcome is the incremental cost per QALY gained. A secondary outcome of incremental cost per life year gained also presented.
12. Were the methods used to value health states and other benefits stated?	Yes	QoL as measured by EQ5D
13. Were the details of the subjects from whom valuations were obtained given?	Yes	Starting age, general mortality, excess risk outlined. Population of patients with intermittent claudication (IC) and critical leg ischaemia (CLI) modelled separately.
14. Were productivity changes (if included) reported separately?	N/A	

15. Was the relevance of productivity changes to the study question discussed?	N/A	
16. Were quantities of resources reported separately from their unit cost?	Yes	
17. Were the methods for the estimation of quantities and unit costs described?	Yes	The NICE CEA costs using the same perspective and time frame (2009/10 NHS reference costs), thus costs taken from this.
18. Were currency and price data recorded?	Yes	£
19. Were details of price adjustments for inflation or currency conversion given?	No	
20. Were details of any model used given?	Yes	A discrete event simulation model.
21. Was there a justification for the choice of model used and the key parameters on which it was based?	Yes	A DESM was used in preference to a state transition model primarily because of the larger number of patient characteristics that require tracking over time. DESM also more appropriately models time to event based on stochastic distributions.
22. Was the time horizon of cost and benefits stated?	Yes	100 years to ensure all differences in costs and benefits are captured in the model.
23. Was the discount rate stated?	Yes	3.5%
24. Was the choice of rate justified?	Yes	Standard- recommended by NICE
25. Was an explanation given if cost or benefits were not discounted?	N/A	
26. Were the details of statistical test(s) and confidence intervals given for stochastic data?	No	
27. Was the approach to sensitivity analysis described?	Yes	To estimate costs and QALYs, PSA was performed with 1000 runs used to calculate the probability that any given intervention is cost-effective in comparison with all other interventions. Cost effectiveness acceptability curve and cost-effectiveness plane are included to give a measure of uncertainty in the model. To explore models sensitivity to parameter values and assumptions, a range of univariate sensitivity analysis were performed.
28. Was the choice of variables for sensitivity analysis justified?	Yes	
29. Were the ranges over which the parameters were varied stated?	Yes	
30. Were relevant alternatives compared? (That is, were appropriate comparisons made when conducting the incremental analysis?)	Yes	Cost-effectiveness of each enhancement compared with angioplasty alone.
31. Was an incremental analysis reported?	Yes	Paclitaxel DCB is both less expensive and more clinically effective than all of the other options and therefore dominates them. Cost-effectiveness plane shown.
32. Were major outcomes presented in a disaggregated as well as aggregated form?	Yes	

33. Was the answer to the study question given?	Yes	The use of DCB dominated both the assumed standard practice of PTA with bailout BMS and all other interventions because it lowered lifetime costs and improved quality of life. Sensitivity analysis showed results were robust to different assumptions about the clinical benefits attributable to the interventions suggesting the use of DCB is cost saving.
34. Did conclusions follow from the data reported?	Yes	Evidence significant reduction restenosis rates for DCB compared with PTA. Significantly lower rates for reintervention reported for DCB compared with PTA.
35. Were conclusions accompanied by the appropriate caveats?	Yes	Differing definitions of restenosis made direct comparison across trials difficult. There is little data on QoL.
36. Were generalisability issues addressed?	No	Clinical evidence based on demographic, clinical and anatomical features of patients recruited to the clinical trials.
Study name Cost- Effectiveness Analysis of Paclitaxel Coated Balloons for Endovascular Therapy of Femoropopliteal Arterial Obstructions (Diehm and Schneider 2013)		
Study design: Cost-effectiveness		
Study question	**Response (yes/no/not clear/N/A)**	**Comments**
1. Was the research question stated?	Yes	To explore the cost-effectiveness of using drug-eluting balloon (DEB) angioplasty for the treatment of femoropopliteal arterial lesions.
2. Was the economic importance of the research question stated?	Yes	DEB have shown to significantly lower the rates of target lesion revascularisation (TLR) compared with standard balloon angioplasty.
3. Was/were the viewpoint(s) of the analysis clearly stated and justified?	Yes	Budgets were analysed in the context of current Swiss DRG reimbursement figures and calculated from two different perspectives: a general budget on total treatment costs and budget focusing on the physician/ facility provider perspective.
4. Was a rationale reported for the choice of the alternative programmes or interventions compared?	Yes	DEBs are a new approach to treatment of PAD with proven superiority over BA.
5. Were the alternatives being compared clearly described?	Yes	
6. Was the form of economic evaluation stated?	Yes	Simplified decision analytic model based on TLR rates.
7. Was the choice of form of economic evaluation justified in relation to the questions addressed?	Yes	Economic model is deliberately simple. Since the focus of the analysis was initial investments and follow-up costs associated with each method, seemed justified to reduce the scope of the economic comparison to the financial perspective.
8. Was/were the source(s) of effectiveness estimates used stated?	Yes	TLR rates as reported in the THUNDER study, RCT comparing DEB vs BA strategy for endovascular revascularisation of the femoropopliteal arteries.

9. Were details of the design and results of the effectiveness study given (if based on a single study)?	Yes	154 PAD patients randomised to DEB, BA with standard balloon and BA with a standard balloon together. Clinical outcomes came from THUNDER study (RCT). The need for TLR considered primary outcome measure for assessment cost-effectiveness important surrogate marker for durability of intervention. Use of DEBs significantly reduced the extent of restenosis compared to BA. The reduction of restenosis led to lower rate of redo interventions (TLRs) in the DEB vs BA groups. 4% (2/48) vs. 37% (20/54) - at 6 months (p,0.001) and 10% (5/48) vs. 48% (26/54) at 12 months (p,0.001), respectively.
10. Were details of the methods of synthesis or meta-analysis of estimates given (if based on an overview of a number of effectiveness studies)?	N/A	
11. Were the primary outcome measure(s) for the economic evaluation clearly stated?	Yes	TLR considered primary outcome measure for assessment of cost-effectiveness since it is an important surrogate marker for durability of the intervention and the costs subsequent to the initial revascularisation procedure.
12. Were the methods used to value health states and other benefits stated?	No	Kept the model simple, decided against expanding it to QoL.
13. Were the details of the subjects from whom valuations were obtained given?	No	No patient baseline characteristics
14. Were productivity changes (if included) reported separately?	N/A	
15. Was the relevance of productivity changes to the study question discussed?	N/A	
16. Were quantities of resources reported separately from their unit cost?	Yes	
17. Were the methods for the estimation of quantities and unit costs described?	Yes	Costs were calculated per 100 patients treated. Cost structures of a Swiss university hospital for the present study.
18. Were currency and price data recorded?	Yes	Costs were expressed in Swiss Francs (sFr).
19. Were details of price adjustments for inflation or currency conversion given?	No	
20. Were details of any model used given?	Yes	A simplified decision analytic model based on TLR rates reported in the literature applied to baseline and follow up costs associated with in-hospital patient treatment during 1 year follow up
21. Was there a justification for the choice of model used and the key parameters on which it was based?	Yes	Yes reduced the scope so solely from a financial perspective.
22. Was the time horizon of cost and benefits stated?	Yes	1 year
23. Was the discount rate stated?	No	
24. Was the choice of rate justified?	No	
25. Was an explanation given if cost or benefits were not discounted?	No	

26. Were the details of statistical test(s) and confidence intervals given for stochastic data?	No	
27. Was the approach to sensitivity analysis described?	No	
28. Was the choice of variables for sensitivity analysis justified?	No	
29. Were the ranges over which the parameters were varied stated?	No	
30. Were relevant alternatives compared? (That is, were appropriate comparisons made when conducting the incremental analysis?)	Yes	
31. Was an incremental analysis reported?	No	
32. Were major outcomes presented in a disaggregated as well as aggregated form?	Yes	
33. Was the answer to the study question given?	Yes	Use of DEBs maybe cost-effective through prevention of TLR at 1 year of follow-up. The introduction of dedicated financial incentives aimed at improving DEB reimbursements may help lower total healthcare costs.
34. Did conclusions follow from the data reported?	Yes	Use of DEBs significantly reduced the extent of restenosis compared to BA.
35. Were conclusions accompanied by the appropriate caveats?	Yes	Only direct costs associated with disease and treatments were considered, indirect and intangible costs were not covered. True value of DEB from society perspective have been underestimated. Assumed costs were stable throughout period of observation.
36. Were generalisability issues addressed?	No	The present model is based on a variety of assumptions which may preclude the generalizability of results to all patients encountered in clinical practice and various international healthcare scenarios. Study based clinical outcome on lesions of only moderate complexity and therefore findings may not hold true for all patients.
Adapted from Drummond MF, Jefferson TO (1996) Guidelines for authors and peer reviewers of economic submissions to the BMJ. The BMJ Economic Evaluation Working Party. British Medical Journal 313 (7052): 275–83. Cited in Centre for Reviews and Dissemination (2008) Systematic reviews. CRD's guidance for undertaking reviews in health care. York: Centre for Reviews and Dissemination		

9 De novo cost analysis

Section 9 requires the sponsor to provide information on the de novo cost analysis.

The de novo cost analysis developed should be relevant to the scope.

All costs resulting from or associated with the use of the technology should be estimated using processes relevant to the NHS and personal social services.

Note that NICE cites the price of the product used in the model in the Medical Technology guidance.

9.1 Description of the de novo cost analysis

9.1.1 Provide the rationale for undertaking further cost analysis in relation to the scope.

The previous economic evaluations for IN.PACT DCB were either not conducted with current U.K. costs or tariffs, or they did not include the latest evidence (Katsanos et al. 2016). In addition, the majority of economic analyses outlined in section 8 were not specific to IN.PACT DCB and instead looked at other DCBs or DCB as a class effect.

Patients

9.1.2 What patient group(s) is (are) included in the cost analysis?

Patients with femoro-popliteal peripheral arterial disease undergoing revascularization for intermittent claudication either due to a *de novo* lesion (primary analysis) or an in-stent restenosis (subanalysis) of a previously treated lesion.

Technology and comparator

9.1.3 Provide a justification if the comparator used in the cost analysis is different from the scope.

The comparator was percutaneous transluminal angioplasty (PTA) with a non-drug coated balloon (with or without bailout stenting using bare metal stents) – in line with the scope. This comparator is referred to as Plain Old Balloon Angioplasty (POBA) for the remainder of the submission.

Model structure

9.1.4 Provide a diagram of the model structure you have chosen.

See next page for a schematic depiction.

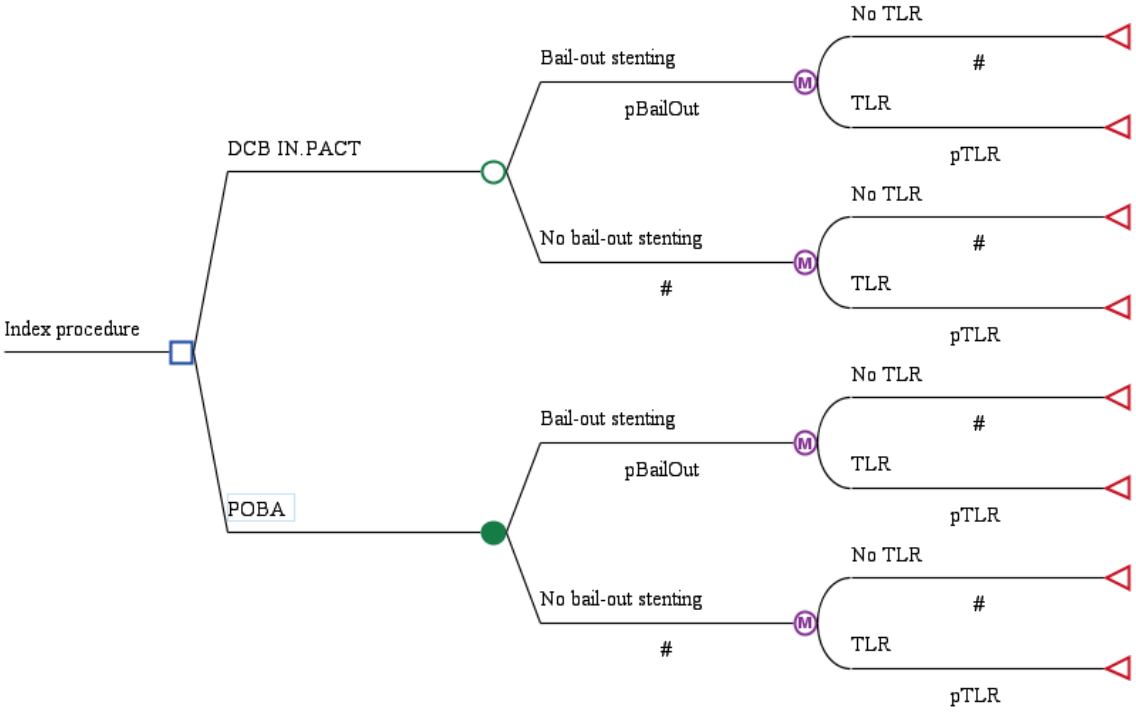


Figure 17: Schematic representation of the model

9.1.4.1 Justify the chosen structure in line with the clinical pathway of care identified in response to question 3.3.

As per NICE guideline CG147, we assume that patients are eligible for percutaneous transluminal angioplasty, referred to as POBA. Patients will have had imaging (e.g., duplex ultrasound) that confirmed a lesion suitable for percutaneous transluminal angioplasty. They should already have participated in supervised exercise programmes, with unrelenting intermittent claudication, and be managed concomitantly in regards to smoking cessation, dyslipidaemia, and on one or more antiplatelet agents.

In line with the scope, the model compares percutaneous transluminal angioplasty with a 3.5 µg/mm^2 paclitaxel-coated balloon with urea as an excipient (IN.PACT – Pacific or Admiral versions) to the existing standard of care, percutaneous transluminal angioplasty with a non-drug coated balloon (POBA, with or without bailout stenting). In line with the scope, our primary analysis did not compare with other DCB products; however, an analysis was performed outside of the primary analysis to show results for other DCB, in comparison to the results obtained for IN.PACT DCB; these results are presented in the miscellaneous results section (9.5.11)

As nothing else is changed in the clinical pathway, our model structure focuses solely on capturing cost and outcome differences resulting from use of IN.PACT DCB (referred to as DCB for the remainder of the *de novo* cost analysis, with or without bailout stenting) in the index procedure, and changes in clinically driven target lesion revascularization (TLR).

9.1.5 Provide a list of all assumptions in the cost model and a justification for each assumption.

- Only patients who are eligible for PTA treatment as per NICE Guidance are considered:
    - Imaging has confirmed a lesion suitable for percutaneous transluminal intervention
    - Patients have already participated in a supervised exercise programme and still have intermittent claudication
    - Smoking cessation programmes, management of dyslipidaemia, and at least one anti-platelet agent are used simultaneously

      [Justification: analyse only patients eligible for PTA treatment as per CG147]

- Patient characteristics (age, gender) of the modelled cohorts are comparable to populations studied in underlying clinical trials

  [Justification: use appropriate patient profile]

- A certain proportion of ballooned lesions show either an inadequate post-treatment flow or a significant dissection is present – either case leads to a certain proportion of lesions being treated with a bare metal stent (“bail-out stenting”)

  [Justification: To properly reflect clinical practice]

- Regardless of whether stenting will be performed (either as primary treatment strategy or secondary to poor post-ballooning flow or dissection), dilation or pre-dilation will always be performed with a balloon first (no direct stenting as in coronary lesions)

  [Justification: To properly reflect clinical practice]

- DCB and BMS (in case of bailout BMS) device utilization averages more than one device each, as some lesions might be longer or require more than one device for treatment.

  [Justification: underlying clinical trial data suggest the use of 1.4 DCB and 1.5 BMS devices (Tepe et al. 2015 and Krankenberg et al. 2015), on average; note that, in the future, devices of longer length may be available, which might reduce utilization to one device per procedure, a scenario that we explore in sensitivity analysis]

- Bailout stenting rates differ between POBA and DCB during the index procedure

[Justification: The IN.PACT SFA study found 7.3% of DCB-treated lesions and 12.6% of POBA-treated lesions required bailout stenting (Salisbury et al. 2016)]

- In patients treated with BMS bailout stenting, TLR rates are assumed to be the same as the rate of the underlying index procedure treatment

  [Justification: Clinical study-reported TLR rates are reported for the combined bailout/no bailout cohort, without differentiation.]

- Target lesions are only revascularised if clinical symptoms are present ("clinically-driven target lesion revascularisation").

  [Justification: To properly reflect clinical practice]

- TLR rates differ between DCB and POBA

  [Justification: As per the clinical evidence synthesized in other parts of this submission]

- Only up to one TLR per subject is considered in the model

  [Justification: While some in-stent restenosis data are available, it was perceived that evidence was too limited to support incorporation of a second TLR treatment in the cost model. Not considering a repeat TLR, however, is a more conservative approach. Health-related quality of life does not differ between the two modelled cohorts, other than an assumed quality of life decrement associated with necessary retreatment

  [Justification: In the IN.PACT SFA study, no statistically significant difference was observed between EQ-5D utility values of POBA and DCB patients at all follow-up time points (Salisbury et al. 2016). Our analysis uses a utility estimate of 0.82 for both arms of the model, based on the average EQ-5D utilities observed at follow-up points through two years in the IN.PACT SFA study.]

- Any reintervention (TLR) is associated with a QALY decrement of 0.059.

  [Justification: In the IN.PACT SFA study, a QALY decrement of 0.059 QALYs was found to be associated with a TLR (Salisbury et al. 2016)]

- No mortality difference is assumed between the intervention and comparator cohorts

  [Justification: The IN.PACT SFA and PACIFIER studies did not show a statistically significant difference in all-cause mortality (Tepe et al. 2015 and Werk et al. 2015)]

- Subjects in the model have an elevated mortality (HR 3.1) compared to the general population

  [Justification: PAD was found to be associated with increased mortality risk in several studies. We use the hazard ratio of 3.1 identified by Criqui et al. 1992]

- To reduce the risk of thrombus formation, subjects receive a dual antiplatelet (DAPT) regimen for four weeks in POBA and DCB index procedures, and for three months if bailout stenting is performed.

  [Justification: While no formal guideline currently exists for DAPT use in endovascular treatment of peripheral lesions, 4 weeks and 3 months of DAPT treatment post-intervention are common practice. In the IN.PACT SFA trial, 100% of DCB patients and 98% of POBA patients were on DAPT at the time of discharge. The IN.PACT Admiral instructions for use prescribe 30 days of DAPT use in case of non-stented lesions, and 3 months if a bailout stent is used.]

9.1.6 Define what the model's health states are intended to capture.

Target lesion revascularization captures both the utility decrement from the recurrent symptoms as well as the cost of the revascularization procedure.

9.1.7 Describe any key features of the cost model not previously reported. A suggested format is presented below.

Table C4 Key features of model not previously reported

Factor	Chosen values	Justification	Reference
Time horizon of model	36 months	Reflects the maximum follow-up horizon available among the included studies.	Salisbury et al, 2016; Dake et al., 2016
Discount rate for costs	3.5%	Per NICE Guidance	
Discount rate for outcomes	3.5%	Per NICE Guidance	
Perspective (NHS/PSS)	NHS	N/A	
Cycle length	0.25 years	TLR proportion of 7 to 21% per year necessitates cycle length shorter than one year	Sonnenberg and Beck 1993
NHS, National Health Service; PSS, Personal Social Services			

9.2 Clinical parameters and variables

9.2.1 Describe how the data from the clinical evidence were used in the cost analysis.

Except for the exclusions noted below, all data regarding the proportion of patients with clinically-driven target lesion revascularization (TLR) from the clinical evidence was utilised.

Of note, Liistro et al. 2013 was excluded because this study reported on combined therapy of DCB and BMS; similarly, Fanelli et al. 2012 was excluded for the purposes of the cost analysis, as this study included around 25% below-the-knee lesions. Micari et al. 2016 was excluded given the long lesion size (>15 cm) in that study, as the search strategy for comparator studies had previously been deliberately limited to require mean lesion length of less than 125 mm for overall comparability in the analysis.

Random effects models were used to pool TLR rates by follow-up time horizon (12, 24, and 36 months) similar to the model displayed in the clinical event section. The approach used proportions from raw cell counts with Freeman-Tukey double arcsine transformation and exact confidence intervals for the individual studies (STATA METAPROP routine). Each study was included only once, at the longest follow-up reported up to 36 months.

Subsequently, proportions obtained from the random effects modelling at the follow-up horizons of 12 and 24 months were converted to rates, and a multiplier applied to convert these rates to 36 months. The resulting proportions were then weighted by sample size to obtain an aggregate 36-month TLR proportion (de facto, a fixed effects approach for this last step, given no second random effects model should have been applied). The following page displays the results by treatment strategy.

Studies examining de novo lesions

DCB IN.PACT	Year	36m prob	24m prob	12m prob	36m rate	24m rate	12m rate	36 prob	sample size
IN.PACT SFA	2016	15.5%			0.168419			15.5%	153
Micari	2013		14.3%		0.231476	0.154317		20.7%	98
PACIFIER				7.1%	0.220940		0.073647	19.8%	42
Fixed effects estimate								17.8%	

POBA	36m prob	24m prob	12m prob	36m rate	24m rate	12m rate	36 prob	sample size
RE model 36mo (RESILIENT, ZILVER PTX, IN.PACT SFA)	39.2%			0.49758			39.2%	278
RE model 24mo (THUNDER, FEM-PAC, LEVANT I)		50.4%		1.051769	0.701179		65.1%	137
RE model 12mo (6 studies)			21.1%	0.710967		0.236989	50.9%	446
Fixed effects estimate							49.4%	

9.2.2 Are costs and clinical outcomes extrapolated beyond the study follow-up period(s)? If so, what are the assumptions that underpin this extrapolation and how are they justified?

Given that the longest follow-up time point in the clinical studies was 36 months, the time horizon was decided to be 36 months. We assumed that longer time horizons would lower the incremental costs of DCB compared to POBA and might make the model less conservative – both in terms of costs and effectiveness. In addition, evidence beyond 36 months is limited or not available at all.

9.2.3 Were intermediate outcome measures linked to final outcomes (for example, was a change in a surrogate outcome linked to a final clinical outcome)? If so, how was this relationship estimated, what sources of evidence were used and what other evidence is there to support it?

Clinically driven target lesion revascularization was used as an intermediate outcome measure given that it both impacts costs and quality of life.

9.2.4 Were adverse events such as those described in section 7.7 included in the cost analysis? If appropriate, provide a rationale for the calculation of the risk of each adverse event.

The main adverse event that was indirectly considered was dissection. We assumed that a significant (i.e., flow-limiting) dissection would be subject to "bail out stenting" and thus be treated initially. However, in practice, if significant dissections would not be detected during the intra-procedural imaging, this would increase the target lesion revascularisation rate. We therefore assumed, that undetected and untreated dissections leading to TLRs would be included in the overall TLR figures. Any other adverse events were considered to be short-term adverse events. If cost or resource utilization would be required for treating them, they are captured in the index procedure cost assumptions.

9.2.5 Provide details of the process used when the sponsor's clinical advisers assessed the applicability of available or estimated clinical model parameter and inputs used in the analysis.

The main assumptions for the model were compiled by the authors of the Katsanos et al. 2016 economic study. This author group included 3 clinical advisors as follows:

- **Dr. Konstantinos Katsanos (KK)**
  Current Professional Title: Assistant Professor, Department of Radiology, Health Sciences Division, School of Medicine, University of Patras
  Previous Professional Title: Consultant Interventional Radiologist, Guy's and St.Thomas' Hospitals, NHS Foundation Trust (Jan 2012 – August 2016)
- **Dr. Trevor Cleveland (TC)**
  Consultant Vascular Radiologist Sheffield Teaching Hospitals
  Honorary Senior Lecturer University of Sheffield
- **Mr. Hany Zayed (HZ)**
  Consultant Vascular and Endovascular Surgeon, Guy's and St.Thomas' Hospitals, NHS Foundation Trust

When selecting the clinical experts, Medtronic's aim was to meet the following criteria:

- 3 clinical experts including at least 1 vascular surgeon and 1 interventional radiologist, all with experience of IN.PACT DCB.
- At least one advisor to have prior experience in health economic analysis or appraisal
- All three physicians should be reputable within their speciality
- Expert advisors should not have any conflicts of interest to avoid any potential bias in the economic analysis.

Dr. Cleveland, Dr. Katsanos and Mr. Zayed were the only expert advisors approached by Medtronic and all agreed to participate in providing advice on the model inputs and subsequent publication (Katsanos, 2016). Expert advisors were provided with full visibility of the economic model and all parameters were discussed to ensure consensus was met on all cost and clinical inputs and assumptions. Any potential variance in assumption was explored via sensitivity analysis. All discussions were via teleconference with all 3 clinical experts present, and by email among the author group.

In addition to a full review of each model input, the following assumptions were not available in the literature and therefore expert consensus was required:

- Appropriateness of cost estimates for BMS and DCBs provided by Medtronic
- Outpatient work-up, including vascular surgery visit and ultrasound imaging
- Scenarios for retreatment in case of TLR

The declaration of potential conflicts of interest were included within the publication as follows: *"For the purposes of this project, KK, HZ and TC served as unpaid scientific advisors to Medtronic, a manufacturer of angioplasty balloons and stents. Wing Tech Inc. (JBP, BPG, AMG) provides health economic consulting services to Medtronic"* (Katsanos, 2016).

Both Dr. Trevor Cleveland and Dr. Konstantinos Katsanos agreed to be listed as expert advisors within the initial MTEP notification for IN.PACT DCB and so their contact details are available to NICE for any further clarifications.

This submission included some updates to the previously published economic analysis (Katsanos et al.). However, all of these updates did not require expert clinical advisor input. They related to the following:

- Updating of study evidence and of study horizon (now 36 months, as 3-year data are available)
- Incorporation of mortality into the model
- Incorporation of discounting on costs and effects
- Incorporation of actual study-reported QALY decrement associated with TLR (as opposed to author-derived estimate from prior stent studies)
- Incorporation of dual-antiplatelet medication regimen based on instructions for use (IFU)
- Use of NHS reference costs instead of tariff costs for base case
- Inclusion of bailout stenting percentages from the studied technology (as opposed to assumptions for all types of DCB studied in the previous model)
- Inclusion of average number of devices based on published studies, as opposed to relying on base case assumption of 1.0 devices for DCB and BMS.

Note that all of these assumptions added additional detail to further improve the quality of the model-based cost calculations.

9.2.6 Summarise all the variables included in the cost analysis. Provide cross-references to other parts of the submission. A suggested format is provided in table C5 below.

Table C5 Summary of variables applied in the cost model

Variable	Value	Range	Source
Age	68 years	65 to 71	Laird et al. 2015
Overall survival	British lifetables multiplied with PAD-specific hazard ratio 3.10	1.9 to 4.9	The Office for National Statistics (ONS) 2017; Criqui et al. 1992
Target lesion revascularization	See above	POBA: 30.0% to 66.6% DCB: 15.5% to 19.8 %	See above
Cost of IN.PACT DCB device	£603	£550 to £650	The average selling price of £603 was calculated from rolling 12month sales data for all IN.PACT DCB sales in the UK. Medtronic are happy for this to be quoted in the published guideline
Cost of BMS device	£384	£269 to £499	Katsanos et al. 2016
Cost of POBA procedure	£2,214	£1,550 to £2,878	2015/16 Elective Inpatient National Reference Costs
Cost of POBA procedure with BMS bailout	£2,214 plus device	£1,550 to £2,878	2015/16 Elective Inpatient National Reference Costs
Cost of DCB procedure	£2,214 plus device	£1,550 to £2,878	2015/16 Elective Inpatient National Reference Costs
Cost of DCB procedure with BMS bailout	£2,214 plus devices	£1,550 to £2,878	2015/16 Elective Inpatient National Reference Costs
Cost of pre-operative workup for any procedure	£367	£257 to £477	2015/16 Elective Outpatient Reference Costs
Cost of DAPT (in case of no bailout)	£32	N/A	Aspirin (75/300mg), Clopidogrel 75mg daily for 4 weeks, BNF 73, 2017
Cost of DAPT (in case of bailout)	£103	N/A	Aspirin (75/300mg), Clopidogrel 75mg daily for 3 months, BNF 73, 2017
Proportion of POBA index procedures that receive bailout stenting	12.6%	0% to 40%	Laird et al. 2015
Proportion of DCB index procedures that receive bailout stenting	7.3%	0% to 25%	Laird et al. 2015
Proportion of TLR procedures that receive bailout stenting	20%	0 to 40%	Katsanos et al, 2016 (assumption based on Schillinger et al, 2006, and Laird et al, 2015)
Baseline utility for PAD post-procedure	0.82		Salisbury et al, 2016; average of PTA and DCB utilities, 1m - 24mo
Utility decrement for TLRs	0.059		Salisbury, 2016 (IN.PACT SFA)

9.3 Resource identification, measurement and valuation

NHS costs

9.3.1 Describe how the clinical management of the condition is currently costed in the NHS in terms of reference costs and the payment by results (PbR) tariff.

The current reimbursement for the outpatient workup is described by HRG RD47Z and treatment function code 107. However, in the present analysis, we used the 2015-16 reference costs to most closely reflect actual cost.

2015/15 National Reference Costs (Elective):

The below table outlines the list of reference costs that are relevant to the index and comparator procedures i.e. POBA and DCB, both with/without bailout BMS. A PTA procedure (with or without DCB) on a single blood vessel will map to YR11. A PTA procedure on a single blood vessel (with or without DCB) **with bailout BMS** will map to either YR14 or YR15 depending on the number of stents used. A weighted average of the CC scores within YR11 was used in the base case of the model plus the cost of IN.PACT DCB and BMS where relevant. This decision was made because this assumption provided the most conservative result of overall cost difference between IN.PACT DCB (with/without bailout BMS) and POBA (with/without bailout BMS). The alternative would have been to use YR14 and YR15 for the stent bailout procedure costs:

Currency Code	Currency Description	Number of FCEs (Used to find weighted average)	National Average Unit Cost
YR10A	Percutaneous Transluminal Angioplasty of Multiple Blood Vessels with CC Score 6+	174	£4,646
YR10B	Percutaneous Transluminal Angioplasty of Multiple Blood Vessels with CC Score 3-5	364	£2,507
YR10C	Percutaneous Transluminal Angioplasty of Multiple Blood Vessels with CC Score 0-2	303	£2,306
YR11A	**Percutaneous Transluminal Angioplasty of Single Blood Vessel with CC Score 9+**	**209**	**£4,466**
YR11B	**Percutaneous Transluminal Angioplasty of Single Blood Vessel with CC Score 6-8**	**610**	**£2,602**
YR11C	**Percutaneous Transluminal Angioplasty of Single Blood Vessel with CC Score 3-5**	**1857**	**£2,141**
YR11D	**Percutaneous Transluminal Angioplasty of Single Blood Vessel with CC Score 0-2**	**1689**	**£1,875**
YR12Z	Percutaneous Transluminal Angioplasty with Insertion of Stent Graft into Peripheral Blood Vessel	223	£5,829
YR13Z	Percutaneous Transluminal Angioplasty with Insertion of, Drug-Eluting, Coated or Embolic Protection Stent, into Peripheral Blood Vessel	296	£3,866
YR14A	Percutaneous Transluminal Angioplasty with Insertion of Multiple Metal Stents into Peripheral Blood Vessels, with CC Score 3+	337	£5,789
YR14B	Percutaneous Transluminal Angioplasty with Insertion of Multiple Metal Stents into Peripheral Blood Vessels, with CC Score 0-2	244	£4,419
YR15A	Percutaneous Transluminal Angioplasty with Insertion of Single Metal Stent into Peripheral Blood Vessel, with CC Score 6+	279	£5,632
YR15B	Percutaneous Transluminal Angioplasty with Insertion of Single Metal Stent into Peripheral Blood Vessel, with CC Score 3-5	727	£3,450
YR15C	Percutaneous Transluminal Angioplasty with Insertion of Single Metal Stent into Peripheral Blood Vessel, with CC Score 0-2	739	£3,123

		Total		
Service code	Service description	Activity	Unit Cost	Total Cost

107	Vascular Surgery	461,546	£153.01	£70,620,840

Outpatient	RD47Z	Vascular Ultrasound Scan	£58

2017/18 National Tariffs excluding Market Forces Factor (also excluding cost of stents and DCB as these are on the NHS High Cost Devices list and are therefore excluded from tariff):

HRG code	HRG name	Combined day case / ordinary elective spell tariff (£)
YR10A	Percutaneous Transluminal Angioplasty of Multiple Blood Vessels with CC Score 6+	2,483
YR10B	Percutaneous Transluminal Angioplasty of Multiple Blood Vessels with CC Score 3-5	1,475
YR10C	Percutaneous Transluminal Angioplasty of Multiple Blood Vessels with CC Score 0-2	1,212
YR11A	Percutaneous Transluminal Angioplasty of Single Blood Vessel with CC Score 9+	4,664
YR11B	Percutaneous Transluminal Angioplasty of Single Blood Vessel with CC Score 6-8	1,701
YR11C	Percutaneous Transluminal Angioplasty of Single Blood Vessel with CC Score 3-5	1,329
YR11D	Percutaneous Transluminal Angioplasty of Single Blood Vessel with CC Score 0-2	1,139
YR12Z	Percutaneous Transluminal Angioplasty with Insertion of Stent Graft into Peripheral Blood Vessel	1,454
YR13Z	Percutaneous Transluminal Angioplasty with Insertion of, Drug-Eluting, Coated or Embolic Protection Stent, into Peripheral Blood Vessel	1,454
YR14A	Percutaneous Transluminal Angioplasty with Insertion of Multiple Metal Stents into Peripheral Blood Vessels, with CC Score 3+	1,696
YR14B	Percutaneous Transluminal Angioplasty with Insertion of Multiple Metal Stents into Peripheral Blood Vessels, with CC Score 0-2	1,394
YR15A	Percutaneous Transluminal Angioplasty with Insertion of Single Metal Stent into Peripheral Blood Vessel, with CC Score 6+	1,956
YR15B	Percutaneous Transluminal Angioplasty with Insertion of Single Metal Stent into Peripheral Blood Vessel, with CC Score 3-5	1,528
YR15C	Percutaneous Transluminal Angioplasty with Insertion of Single Metal Stent into Peripheral Blood Vessel, with CC Score 0-2	1,309

9.3.2 State the Office of Population, Censuses and Surveys Classification of Surgical Operations and Procedures (OPCS) codes for the operations, procedures and interventions relevant to the use of the technology for the clinical management of the condition.

The relevant OPCS codes are as follows. L771 would require a site code to specify the artery. There is no specific OPCS code to specify to use of a DCB:

L631	Percutaneous transluminal angioplasty of femoral artery
L711	Percutaneous transluminal angioplasty of artery
L761	Endovascular placement of one metallic stent
L763	Endovascular placement of two metallic stents
L765	Endovascular placement of three or more metallic stents

Resource identification, measurement and valuation studies

9.3.3 Provide a systematic search of relevant resource data for the NHS in England. Include a search strategy and inclusion criteria, and consider published and unpublished studies.

No systematic literature or web search was conducted to identify relevant resource data. The justification for this is that PTA is an existing procedure with known costs and established reimbursement codes; the only difference of the new procedure is the price of a newly introduced consumable, the DCB device. Hence, we used the applicable 2015/16 Elective Inpatient and Outpatient Reference Costs for the analysis. As an additional scenario analysis, we used the 2017-18 NHS tariffs, adjusted by market forces factor.

9.3.4 Provide details of the process used when clinical advisers assessed the applicability of the resources used in the model[2].

Does not apply, per response in 9.3.3. See also 9.2.5 for explanation of clinical adviser input.

Technology and comparators' costs

9.3.5 Provide the list price for the technology.

The UK list price for all Medtronic DCB (Pacific and Admiral) is £910.

9.3.6 If the list price is not used in the de novo cost model, provide the alternative price and a justification.

The average selling price of £603 has been used in the model as a more accurate representation of the price paid by the NHS. This price was calculated from rolling 12-month sales data for all IN.PACT DCB sales in the UK. Medtronic are happy for this to be quoted in the published guideline.

9.3.7 Summarise the annual costs associated with the technology and the comparator technology (if applicable) applied in the cost model. A suggested format is provided in tables C6 and C7. Table C7 should only be completed when the most relevant UK comparator for the cost analysis refers to another technology.

We did not include annual costs for peripheral artery disease such as for GP visits, visits to vascular specialists, supervised exercise programmes, and costs for smoking cessation, anti-platelet agents (low-dose aspirin, e.g. 81-100mg +/- second anti-platelet agent), and high potency statin (e.g., atorvastatin 80 mg).

The first reason why we did not include these costs is that they would be incurred regardless of the use of angioplasty with POBA or DCB. Secondly, there is no reason to assume any difference between the technology and the comparator arm, meaning they would not drive any cost difference between the strategies, given the mortality is not different. In case of TLR, an additional GP visit might occur prior to referral to a vascular surgeon. However, we opted to take a conservative assumption and not include such potential cost, which would be in favour of DCB if included.

As stated earlier, we consider DAPT for 4 weeks/3 months after endovascular procedures, the cost of which are assumed to be incurred at the time of treatment. All other costs are associated with any applicable clinically-driven TLR.

[2] Adapted from Pharmaceutical Benefits Advisory Committee (2008) Guidelines for preparing submissions to the Pharmaceutical Benefits Advisory Committee (Version 4.3). Canberra: Pharmaceutical Benefits Advisory Committee.

Table C6 Costs per treatment/patient associated with the technology in the cost model

Items	Value	Source
Price of the technology per treatment/patient	£2,214 (procedure cost, excluding high cost devices which are listed below)	2015/16 Elective Inpatient National Reference Costs
Consumables (if applicable)	£603 per DCB device (1.4 devices on average) + 7.3% BMS bailout at £384 per device (1.5 devices on average)	Sponsor; Laird et al. 2015; estimate for UK NHS
Maintenance cost	n.a.	
Training cost	n.a.	
Other costs	DAPT regimen (£32.16 (4 weeks), £103.37 (3 months))	BNF 73, 2017
Total cost per treatment/patient	£3,504 (out of which £2,618 for procedure, outpatient cost, and DAPT, and the remainder for DCB and BMS devices)	

Table C7 Costs per treatment/patient associated with the comparator technology in the cost model

Items	Value	Source
Cost of the comparator per treatment/patient	£2,214 (procedure cost, excluding high cost devices which are listed below)	2015/16 Elective Inpatient National Reference Costs
Consumables (if applicable)	POBA included; additionally, 12.6% bailout * £384	Laird et al. 2015; estimate for UK NHS
Maintenance cost	n.a.	
Training cost	n.a.	
Other costs	DAPT regimen (£32.16 (4 weeks), £103.37 (3 months))	BNF 73, 2017
Total cost per treatment/patient	£2,694 (out of which £2,622 for procedure, outpatient cost, and DAPT, and the remainder for BMS devices)	

Health-state costs

9.3.8 If the cost model presents health states, the costs related to each health state should be presented in table C8. The health states should refer to the states in section 9.1.7. Provide a rationale for the choice of values used in the cost model.

Table C8 List of health states and associated costs in the economic model

Health states	Items	Value	Reference
TLR	**Outpatient costs**	£367	2015/16 National Reference Costs: 2 x Vascular Outpatient Attendances (£153) 1 Outpatient vascular ultrasound scan (RD47Z) (£61)
	Repeat procedure	£2,214	2015/16 Elective Inpatient National Reference Costs, weighted average of YR11
	BMS bailout (£384 per BMS device, 1.5 devices, in 20% of subjects)	£115	Estimate for UK NHS; Katsanos et al, 2016 (assumption based on Schillinger et al, 2006, and Laird et al, 2015)
	DAPT regimen	£46	BNF 73
	Total	£2,742	

No TLR		£0	

Adverse-event costs

9.3.9 Complete table C9 with details of the costs associated with each adverse event referred to in 9.2.4 included in the cost model. Include all adverse events and complication costs, both during and after longer-term use of the technology.

Table C9 List of adverse events and summary of costs included in the cost model

Adverse event	Items	Value	Reference
TLR	**Outpatient costs**	£367	2015/16 National Reference Costs: 2 x Vascular Outpatient Attendances (£153) **1 Outpatient vascular ultrasound scan (RD47Z) (£61)**
	Repeat procedure	£2,214	2015/16 Elective Inpatient National Reference Costs, weighted average of YR11 **2015/16 Elective Inpatient National Reference Costs**
	BMS bailout (£384 per BMS device, 1.5 devices, in 20% of subjects)	£115	Estimate for UK NHS; Katsanos et al, 2016 (assumption based on Schillinger et al, 2006, and Laird et al, 2015)
	DAPT regimen	£46	BNF 73
	Total	£2,742	

Miscellaneous costs

9.3.10 Describe any additional costs and cost savings that have not been covered anywhere else (for example, PSS costs, and patient and carer costs). If none, please state.

Beyond outpatient work-up for the procedures and the DAPT regimen, no additional miscellaneous costs were included.

9.3.11 Are there any other opportunities for resource savings or redirection of resources that it has not been possible to quantify?

No opportunities for resource savings or redirection of resources other than the reduction of 1) bail-out stenting and subsequently decrease DAPT usage; and 2) the reduction of target-lesion revascularisations (which was quantified as per above) was considered. As stated earlier, our model considers only up to one reintervention. Any additional TLRs avoided would lead to additional resource savings.

9.4 Approach to sensitivity analysis

Section 9.4 requires the sponsor to carry out sensitivity analyses to explore uncertainty around the structural assumptions and parameters used in the analysis. All inputs used in the analysis will be estimated with a degree of imprecision. For technologies whose final price/acquisition cost has not been confirmed, sensitivity analysis should be conducted over a plausible range of prices.

Analysis of a representative range of plausible scenarios should be presented and each alternative analysis should present separate results.

9.4.1 Has the uncertainty around structural assumptions been investigated? State the types of sensitivity analysis that have been carried out in the cost analysis.

A subgroup analysis for in-stent restenosis patients was conducted. Deterministic sensitivity analysis for all parameters was performed. We also tested the impact of varying the time horizon on the endpoints.

Furthermore, we pooled evidence of other DCB devices to resemble a “non-Medtronic DCB” analysis for comparison purposes, in line with analyses conducted in the prior Katsanos et al, 2016 study.

9.4.2 Was a deterministic and/or probabilistic sensitivity analysis undertaken? If not, why not? How were variables varied and what was the rationale for this? If relevant, the distributions and their sources should be clearly stated.

For the purposes of this cost analysis, sensitivity analyses were limited to exhaustive one- and multi-way deterministic analyses and the subgroup analyses.

9.4.3 Complete table C10.1, C10.2 and/or C10.3 as appropriate to summarise the variables used in the sensitivity analysis.

Table C10.1 Variables used in one-way scenario-based deterministic sensitivity analysis

Variable	Base-case value	Range of values
Age	68 years	65 to 71
Overall survival	British lifetables multiplied with PAD-specific hazard ratio 3.10	1.9 to 4.9
36-month Proportion of TLR for POBA	49.4%	30.0% to 66.6%
36-month Proportion of TLR for DCB	17.8%	15.5% to 19.8 %
Cost of IN.PACT DCB device	£603	£550 to £650
Cost of BMS device	£384	£269 to £499
Number of DCB devices used	1.4	1.0 to 2.0
Number of BMS devices used (if bailout)	1.5	1.0 to 2.0
Cost of POBA procedure (also used as basis for DCB procedure costing)	£2,214 plus BMS device price (of bailout	£1,550 to £2,878 plus BMS device price (of bailout
Cost of POBA procedure with BMS bailout	£2,214 plus BMS device price (of bailout	£1,550 to £2,878 plus BMS device price (of bailout
Number of BMS used in bailout	1.5	1.0 to 2.0
Number of DCB used	1.4	1.0 to 2.0
Cost of pre-operative workup for any procedure	£367	£257 to £477
Proportion of POBA index procedures that receive bailout stenting	12.6%	0% to 40%
Proportion of DCB index procedures that receive bailout stenting	7.3%	0% to 25%
Proportion of TLR procedures that receive bailout stenting	20%	0 to 40%
Time Horizon	36 months	48 months
Discount Rate	3.5%	0% to 5%
Cost basis	Reference costs	2017-18 Tariffs

Table C10.2 Variables used in multi-way scenario-based sensitivity analysis

Note: Ranges for proportion of TLR for POBA and DCB were determined based on best- and worst-performing underlying clinical study. For POBA, this resulted in estimated 36-month proportion of 20.0% and 66.6%, for DCB of 15.5% and 19.8%.

Variables	*36-month Proportion of TLR for POBA*	*36-month Proportion of TLR for DCB*
Base case	49.4%	17.8%
Scenario 1	20.0%	15.5%
Scenario 2	20.0%	19.8%
Scenario 3	66.6%	15.5%
Scenario 4	66.6%	19.8%
Variables	*Number of DCB used*	*Number of BMS used in bailout*
Base case	1.4	1.5
Scenario 1	1.0	1.0
Scenario 2	1.0	2.0
Scenario 3	2.0	1.0
Scenario 3	2.0	2.0
Variable	*Number of DCB used*	*DCB device price*
Scenario 1	1.0	£550
Scenario 2	1.0	£650
Scenario 3	2.0	£550
Scenario 3	2.0	£650

Table C10.3 Variable values used in probabilistic sensitivity analysis

Variable	**Base-case value**	**Distribution**
A probabilistic sensitivity analysis was not performed		

9.4.4 If any parameters or variables listed in section 9.2.6 were omitted from the sensitivity analysis, provide the rationale.

All parameters were subject to sensitivity analyses.

9.5 Results of de novo cost analysis

Section 9.5 requires the sponsor to report the de novo cost analysis results. These should include the following:

- costs
- disaggregated results such as costs associated with treatment, costs associated with adverse events, and costs associated with follow-up/subsequent treatment
- a tabulation of the mean cost results
- results of the sensitivity analysis.

Base-case analysis

9.5.1 Report the total costs associated with use of the technology and the comparator(s) in the base-case analysis. A suggested format is presented in table C11.

Table C11 Base-case results

	Total per patient cost (£)
DCB IN.PACT	£3,947
POBA	£3,936

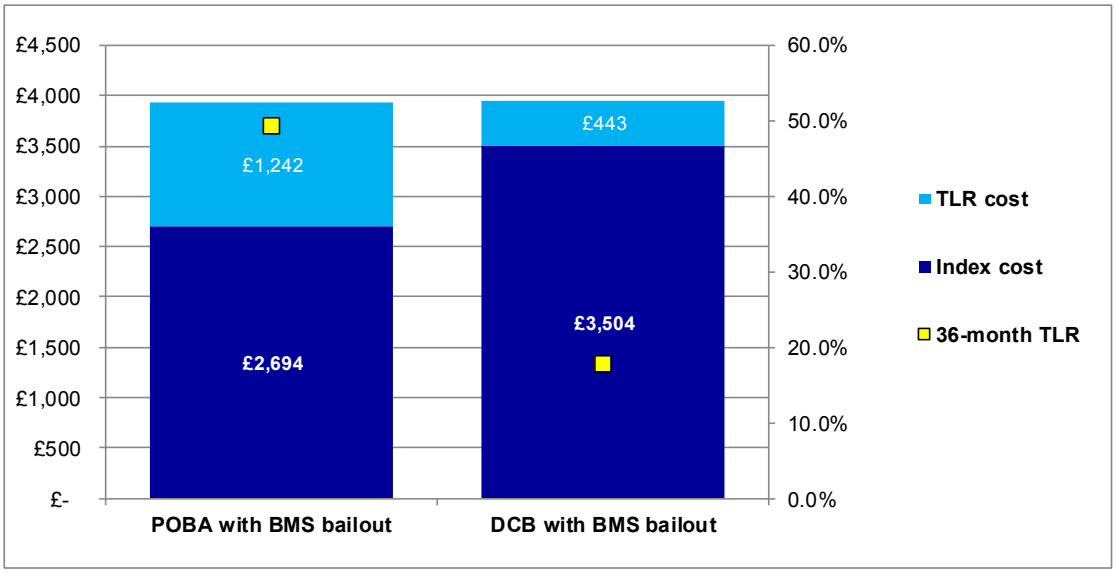


Figure 18: Index procedure and reintervention costs, and estimated 36-month TLR proportions for Comparator and DCB.

9.5.2 Report the total difference in costs between the technology and comparator(s).

The total difference in costs between IN.PACT DCB and PTA is £11 at 36 months model horizon. At 48-month analysis horizon, savings of £95 are realized.

In addition to total cost difference between the strategies, we also made an effort to estimate the potential number of TLRs avoided if current index procedures would be converted to DCB. The HES data for NHS FY15/16 report a total of 12,356 femoropopliteal PTA/BMS procedures were carried out in 2015/16 in NHS England. Under assumption 80% of these were de novo procedures, this is equal to 9,884 annual procedures. Per the National Vascular Registry 2016 Annual Report, 41.5% of endovascular revascularisations were for intermittent claudication, resulting in a total estimate of 4,102 index procedures. Based on our model calculations, for every 1,000 index procedures treated with DCB instead of POBA, 316 TLRs might be avoided over 36 months. This results in an estimated 1,296 repeat procedures avoided with DCB.

Further, the incremental cost-effectiveness was estimated at £665 per QALY gained at 36 months. At an analysis horizon of 48-months, DCB was found to be the dominant strategy, providing improved outcomes at lower total cost.

9.5.3 Provide details of the costs for the technology and its comparator by category of cost. A suggested format is presented in table C12.

Table C12 Summary of costs by category of cost per patient

Item	Cost *intervention (X)*	Cost *comparator (Y)*	Increment
Technology cost	*£844 (1.4 devices at £603*	*£0*	*£844*
Dual anti-platelet treatment	*DAPT regimen £37*	*DAPT regimen £41*	*-£5*
Mean total treatment cost	*£2,214*	*£2,214*	*£0*
Bailout Stenting (index procedure)	*£409*	*£439*	*-£30*
TLR Costs	*£443*	*£1,242*	*-£799*
Total	*£3,947*	*£3,936*	*£11*

9.5.4 If appropriate, provide details of the costs for the technology and its comparator by health state. A suggested format is presented in table C13.

It is not appropriate in this analysis to break down the costs for the technology and its comparator by health state.

9.5.5 If appropriate, provide details of the costs for the technology and its comparator by adverse event. A suggested format is provided in table C14.

Table C14 Summary of costs by adverse events per patient

It is not appropriate in this analysis to break down the costs of the technology and its comparator by adverse event per patient.

Sensitivity analysis results

9.5.6 Present results of deterministic one-way sensitivity analysis of the variables described in table C10.1.

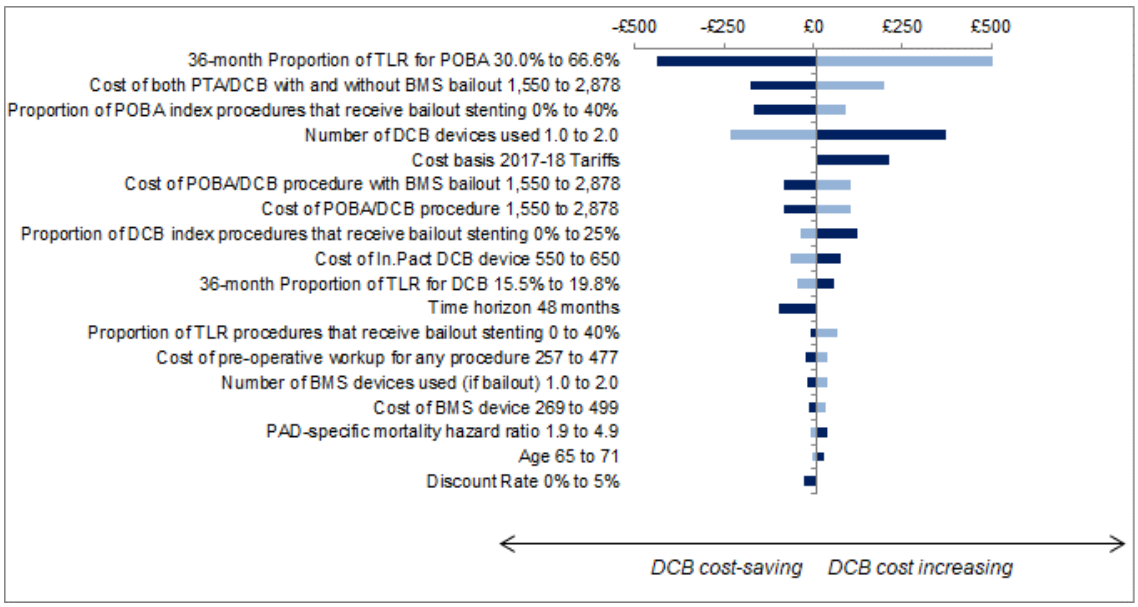


Figure 19: Tornado Diagram for Costs. Low parameter input results shown in light blue, high parameter input results in dark blue.

Table: Outcome of Deterministic One-way Sensitivity Analysis for Endpoint Costs

Parameter	Range	Incremental costs low value	Incremental costs high value
Age	65 to 71	£0	£29
PAD-specific mortality hazard ratio	1.9 to 4.9	-£8	£39
36-month Proportion of TLR for POBA	30.0% to 66.6%	£504	-£435
36-month Proportion of TLR for DCB	15.5% to 19.8 %	-£46	£61
Cost of IN.PACT DCB device	£550 to £650	-£63	£77
Cost of BMS device	£269 to £499	£36	-£13
Number of DCB devices used	1.0 to 2.0	-£230	£373
Number of BMS devices used (if bailout)	1.0 to 2.0	£38	-£16
Cost of POBA/DCB procedure	£1,550 to £2,878	£104	-£82
Cost of POBA/DCB procedure with BMS bailout	£1,550 to £2,878	£106	-£83
Cost of both PTA/DCB with and without BMS bailout	£1,550 to £2,878	£199	-£177
Cost of pre-operative workup for any procedure	£257 to £477	£42	-£20
Proportion of POBA index procedures that receive bailout stenting	0% to 40%	£93	-£166
Proportion of DCB index procedures that receive bailout stenting	0% to 25%	-£36	£126
Proportion of TLR procedures that receive bailout stenting	0 to 40%	£69	-£5
Time horizon	48 months		-£95
Discount Rate	0% to 5%	-£27	-£26
Cost basis	2017-18 Tariffs	£200	

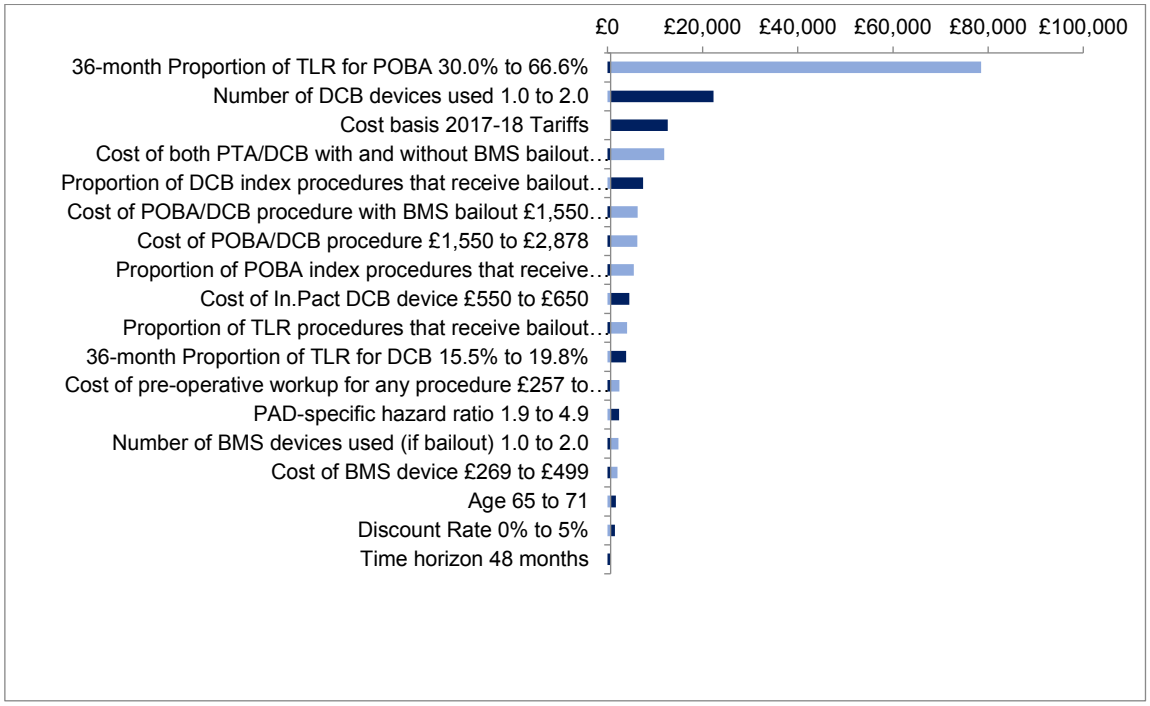


Figure 20: Tornado Diagram for Cost-effectiveness

Table: Outcome of Deterministic One-way Sensitivity Analysis for Endpoint Cost-effectiveness

Parameter	Range	ICER low value	ICER high value
Base case	N/A	£665/QALY	
Age	65 to 71	DCB dominant	£1,776/QALY
PAD-specific mortality hazard ratio	1.9 to 4.9	DCB dominant	£2,423/QALY
36-month Proportion of TLR for POBA	30.0% to 66.6%	£78,545/QALY	DCB dominant
36-month Proportion of TLR for DCB	15.5% to 19.8 %	DCB dominant	£3,901/QALY
Cost of IN.PACT DCB device	£550 to £650	DCB dominant	£4,598/QALY
Cost of BMS device	£269 to £499	£2,133/QALY	DCB dominant
Number of DCB devices used	1.0 to 2.0	DCB dominant	£22,290/QALY
Number of BMS devices used (if bailout)	1.0 to 2.0	£2,299/QALY	DCB dominant
Cost of PTA/DCB procedure	£1,550 to £2,878	£6,270/QALY	DCB dominant
Cost of POBA/DCB procedure with BMS bailout	£1,550 to £2,878	£6,312/QALY	DCB dominant
Cost of both PTA/DCB with and without BMS bailout	£1,550 to £2,878	£11,916/QALY	DCB dominant
Cost of pre-operative workup for any procedure	£257 to £477	£2,528/QALY	DCB dominant
Proportion of POBA index procedures that receive bailout stenting	0% to 40%	£5,539/QALY	DCB dominant
Proportion of DCB index procedures that receive bailout stenting	0% to 25%	DCB dominant	£7,512/QALY
Proportion of TLR procedures that receive bailout stenting	0 to 40%	£4,121/QALY	DCB dominant
Time horizon	48 months		DCB dominant
Discount Rate	0% to 5%	DCB dominant	£1,599/QALY
Cost basis	2017-18 Tariffs	£11,937/QALY	

9.5.7 Present results of deterministic multi-way scenario sensitivity analysis described in table C10.2.

	36-month Proportion of TLR for DCB 15.5%	36-month Proportion of TLR for DCB 19.8%

36-month Proportion of TLR for POBA 30.0%	£446	£554
36-month Proportion of TLR for POBA 66.6%	-£492	-£385

	36-month Proportion of TLR for DCB 15.5%	**36-month Proportion of TLR for DCB 19.8%**
36-month Proportion of TLR for POBA 30.0%	£58,584/QALY	£103,217/QALY
36-month Proportion of TLR for POBA 66.6%	DCB dominant	DCB dominant

	1.0 DCB devices	**2.0 DCB devices**
1.0 BMS devices	-£188	£415
2.0 BMS devices	-£242	£361

	1.0 DCB devices	**2.0 DCB devices**
1.0 BMS devices	DCB dominant	£25,286/QALY
2.0 BMS devices	DCB dominant	£21,966/QALY

	1.0 DCB devices	2.0 DCB devices
DCB price £550	-£268	£282
DCB price £650	-£168	£482

	1.0 DCB devices	2.0 DCB devices
DCB price £550	DCB dominant	£17,183/QALY
DCB price £650	DCB dominant	£29,367/QALY

9.5.8 Present results of the probabilistic sensitivity analysis described in table C10.3.

No probabilistic sensitivity analysis was conducted (see justification above)

9.5.9 What were the main findings of each of the sensitivity analyses?

The main findings of the sensitivity analyses are the following

- The model is relatively robust
- The largest impact model is associated with the cost of the DCB IN.PACT device (between cost-saving to £298 incremental costs and dominant to £18K/QALY)
- A likewise large impact was found when varying both the POBA/DCB procedure costs and the costs for a procedure with BMS bail-out (between cost-saving to £219 and dominant to £13K/QALY)

9.5.10 What are the key drivers of the cost results?

The key drivers are cost of the DCB device, incremental clinical performance in terms of TLR between DCB and POBA, and the number of DCB devices used.

Miscellaneous results

9.5.11 Describe any additional results that have not been specifically requested in this template. If none, please state.

DCB avoids 0.316 TLRs per case. In other words, for each 1,000 treatments, DCB avoids 316 TLRs. The cost per TLR avoided is £35 per TLR avoided.

The QALY gain associated with the DCB strategy in the discounted base case analysis was quantified as 0.0167 QALYs.

The comparison analysis using other DCB (non-Medtronic) considered the pooled TLR performance of the following six studies: BIOLUX P-I, LEVANT 1, LEVANT 2, THUNDER, FEM-PAC, and ILLUMENATE FIH. Using the same approach outlined earlier, a 36-month TLR proportion of **30.8%** was obtained (as compared to **17.8%** for IN.PACT DCB). An average device cost of £512 for these other DCB (per Katsanos, 2016), yielded a 36-month cost increase of £210 compared to POBA. Hence, despite lower assumed device costs, NHS incurred a cost increase based on higher percentage of TLR procedures that need to be performed.

9.6 Subgroup analysis

For many technologies, the capacity to benefit from treatment will differ for patients with differing characteristics. Sponsors are required to complete section 9.6 in accordance with the subgroups identified in the scope and for any additional subgroups considered relevant.

Types of subgroups that are not considered relevant are those based solely on the following factors.

- Subgroups based solely on differential treatment costs for individuals according to their social characteristics.
- Subgroups specified in relation to the costs of providing treatment in different geographical locations within the UK (for example, if the costs of facilities available for providing the technology vary according to location).

9.6.1 Specify whether analysis of subgroups was undertaken and how these subgroups were identified. Cross-reference the response to the decision problem in table A1 and sections 3.2 and 7.4.4.

We conducted a subgroup analysis (or rather a new analysis) for the subgroup of patients with in-stent restenoses.

9.6.2 Define the characteristics of patients in the subgroup(s).

We assumed that the subgroup of in-stent restenosis patients would have different target-lesion revascularization. Analogous to the main analysis for patients with *de novo* lesions, we pooled the available studies (if there was more than one study available) in random effects models for each time horizon (12, 24, or 36 months). We then converted all proportions to rates, transformed them to 36-month rates, and converted the rates back to proportions. Finally, we weighted the aggregate 36-month TLR proportions by the aggregate sample size. The following table details this process.

Tables: Studies examining in-stent restenoses

DCB IN.PACT	Year	36m prob	24m prob	12m prob	36m rate	24m rate	12m rate	36 prob	sample size
Grotti	2016	40.9%			0.525939262			40.9	144
Virga	2014		14.3%		0.231476041	0.15431736		20.7%	39
RE Model (Bague, 2017 and Krankenberg, 2015)				7.1%	0.445500025		0.148500008	35.9%	117
Fixed effects estimate								**34.1%**	

POBA	Year	36m prob	12m prob	36m rate	12m rate	36 prob	sample size
Grotti	2016	42.9%		0.49758		39.2%	242
Krankenberg	2015		47.7%	1.944521	0.648174	85.7%	57
Fixed effects estimate						**67.5%**	

9.6.3 Describe how the subgroups were included in the cost analysis.

The subgroup of in-stent restenosis patients was not included in the main cost analysis as their TLR rates were deemed to be different from *de novo* lesions.

9.6.4 What were the results of the subgroup analysis/analyses, if conducted? The results should be presented in a table similar to that in section 9.5.1 (base-case analysis).

We conducted a separate cost analysis and cost-effectiveness analysis for in-stent restenoses.

	Incremental costs	Incremental cost-effectiveness ratio
In-stent restenosis subgroup	-£49	DCB dominant
Main analysis: *de novo* lesions	£11	£665/QALY

9.6.5 Were any subgroups not included in the submission? If so, which ones, and why were they not considered?

No other subgroups were singled out and therefore no other subgroup was omitted in the submission.

9.7 Validation

9.7.1 Describe the methods used to validate and cross-validate (for example with external evidence sources) and quality-assure the model. Provide references to the results produced and cross-reference to evidence identified in the clinical and resources sections.

Two research analysts reviewed the final de novo cost analysis model independently. A face validity test was conducted by the sponsors. Robust assessment was performed during model development to test the effects of parameter variation and ensure the model responded appropriately to changes in parameter inputs.

9.8 Interpretation of economic evidence

9.8.1 Are the results from this cost analysis consistent with the published economic literature? If not, why do the results from this evaluation differ, and why should the results in the submission be given more credence than those in the published literature?

The results of this cost analysis are mostly consistent with the findings of the identified published economic studies. However, a number of these studies report analyses for other countries, with different underlying cost. The results of the current cost analysis is consistent with the Katsanos et al. 2016 study. Studies that examined other DCB systems (e.g., NHS HTA Simpson et al.) also found DCB to be cost-effective.

9.8.2 Is the cost analysis relevant to all groups of patients and NHS settings in England that could potentially use the technology as identified in the scope?

Yes, the cost analysis is relevant to all groups of patients and NHS settings in England that could potentially use the technology. However, in certain complex lesions (i.e., severe calcification) where there is no optimal treatment solution, there might be emerging technologies not on the market or not reimbursed by the NHS that could become adjunctive to the technology assessed here (DCB) versus the status quo (POBA).

9.8.3 What are the main strengths and weaknesses of the analysis? How might these affect the interpretation of the results?

The main strength of the analysis is that it leverages all data available – in that it uses a combination of random and fixed effects meta-analysis (or, rather, “pooling” of TLR rates) to make use of all available high-quality evidence. In addition, a cost-effectiveness analysis has been conducted.

The main weakness is the relative scarcity of evidence in the in-stent restenosis subgroup.

9.8.4 What further analyses could be undertaken to enhance the robustness/completeness of the results?

The best type of analysis to undertake would be a validation study with external data once more evidence is available – this particularly pertains to in-stent restenosis. The other type of analysis to conduct would we a probabilistic sensitivity analysis although the remaining amount of uncertainty *a priori* is judged to be low.

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10 Appendices

10.1 Appendix 1: Search strategy for clinical evidence (section 7.1.1)

The following information should be provided:

10.1.1 The specific databases searched and the service provider used (for example, Dialog, DataStar, OVID, Silver Platter), including at least:

- Medline
- Embase

- Medline (R) In-Process
- The Cochrane Library.

The databases used for the systematic review were Medline (via Pubmed) and Embase. An additional search on the Cochrane Library was conducted but not further publications were selected.

10.1.2 The date on which the search was conducted.

The search was conducted on 19th July 2017.

10.1.3 The date span of the search.

Articles published from 1995 to the 19th July 2017 have been included in the search.

10.1.4 The complete search strategies used, including all the search terms: textwords (free text), subject index headings (for example, MeSH) and the relationship between the search terms (for example, Boolean).

#1 - **'percutaneous transluminal'** NEAR/2 **balloon*** OR (**'percutaneous transluminal'** NEAR/5 **angioplast*** AND **balloon***) OR (**pta** AND **balloon***)

#2 - #1 AND ((**popliteal** OR **sfa** OR **femoropopliteal** OR **infrapopliteal**) NEAR/5 **arter*** OR **superficial** NEAR/2 **femoral** NEAR/5 **arter***)

#3 - #2 AND (**deb** OR **dcb** OR **peb** OR **elut*** NEAR/2 **balloon*** OR (**coat*** OR **drug*** OR **paclitaxel**) NEAR/5 (**balloon*** OR **inflat***))

#4 - **inpact** OR **'in pact'** OR **admiral*** OR **pacific*** AND (**deb** OR **drug** NEAR/2 **elut*** OR **peb** OR **elut*** NEAR/2 **balloon***) OR (**inpact** OR **'in pact'** OR **admiral*** OR **pacific*** AND (**medtronic*** OR **invatec***)) OR (**inpact** OR **'in pact'** OR **admiral*** OR **pacific***) NEAR/2 (**trial*** OR **stud***) AND **balloon***

#5 - paclitaxel* OR **paclitaxel** AND (**deb** OR **dcb** OR **peb** OR **elut*** NEAR/2 **balloon*** OR (**'drug coated'** OR **'drug coating'**) NEAR/2 **balloon*** OR **coat*** NEAR/2 **balloon***)

#6 - #3 OR #4 OR #5

Filters

Article Type: NOT (**'conference abstract'**/it OR **'conference paper'**/it OR **'editorial'**/it OR **'letter'**/it OR **'note'**/it OR **'conference paper'**/exp OR **'symposium'**/exp OR **'workshop'**/exp OR **'abstract report'**/exp OR **'book'**/exp OR **'editorial'**/exp OR **'letter'**/exp OR **'note'**/exp OR [conference abstract]/lim OR [conference paper]/lim OR [conference review]/lim OR [editorial]/lim OR [letter]/lim OR [note]/lim OR **patent***:de,ti OR **letter**:ti OR **editorial**:ti OR **note**:ti OR **book**:ti OR **book**:it OR **book**:pt OR **symposia**:ti OR **symposium**:ti OR **congress**:ti OR (**poster** NEXT/1 **session**):ti OR **poster**:ti OR **posters**:ti OR **comment**:ti OR **comments**:ti OR **'trade journal'**:pt OR **interview**:ti OR **interviews**:ti OR **meeting**:ti)

Publication Dates: From 1995/1/1 to date
Languages: English

10.1.5 Details of any additional searches, such as searches of company or professional organisation databases (include a description of each database).

Not applicable

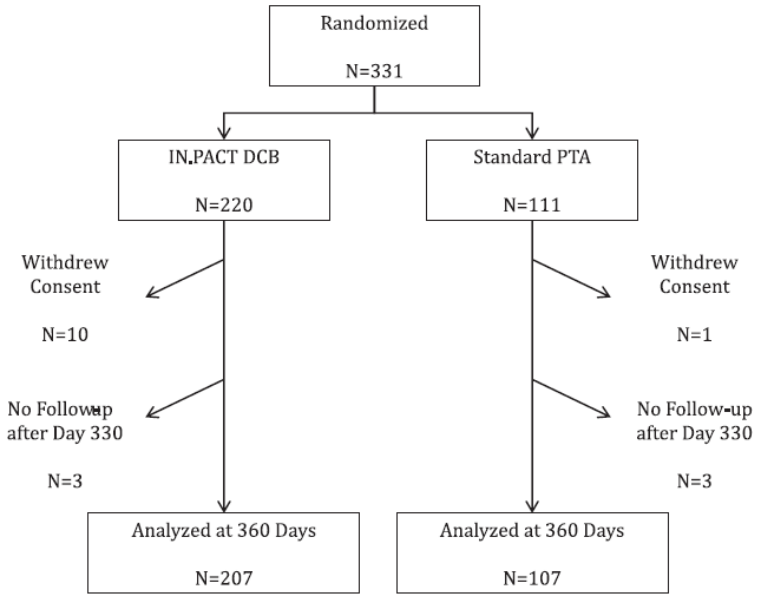
10.1.6 The inclusion and exclusion criteria.

Inclusion criteria

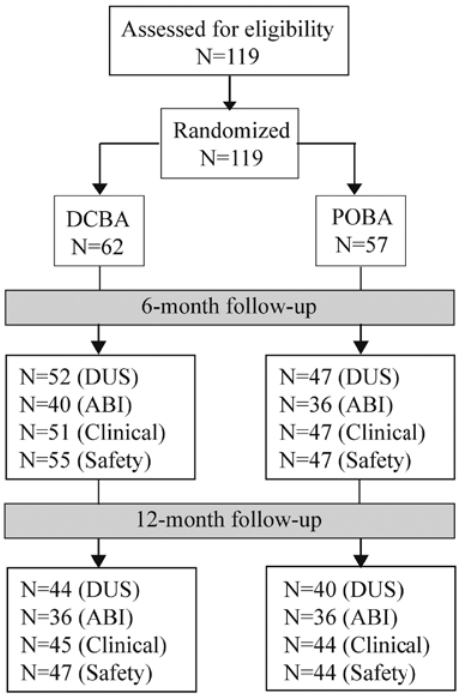
Population	Patients with peripheral arterial disease with intermittent claudication as an indication for invasive treatment.
Interventions	Percutaneous Transluminal Angioplasty (PTA) with IN.PACT™ Admiral™ or IN.PACT™ Pacific™ Paclitaxel-coated Balloon Catheter
Outcomes	The outcome measures to consider include: • Primary Patency • Target Lesion Revascularization (TLR) • Target Vessel Revascularization (TVR) • Thrombosis • Restenosis • Target limb major amputation • Procedure or device-related adverse events • Survival
Study design	Randomized Clinical Trials (RCTs) Observational Studies Case series
Language restrictions	English only
Search dates	1995 - Current
Exclusion criteria	
Population	• Patients without Peripheral Artery Disease • Patients with below-the-knee lesion (BTK)
Interventions	• Patients NOT treated with DCB or • Patients treated with DCB but not with IN.PACT™ Admiral or IN.PACT™ Pacific • Mixed population
Outcomes	None of the following are reported: • Primary Patency • Target Lesion Revascularization (TLR) • Target Vessel Revascularization (TVR) • Thrombosis • Restenosis • Target limb major amputation • Procedure or device-related adverse events • Survival
Study design	Case report, in-vitro studies, not human studies
Language restrictions	Non-English
Search dates	Prior to 1995

8.9.7 Study flowcharts to show number of patients in each arm:

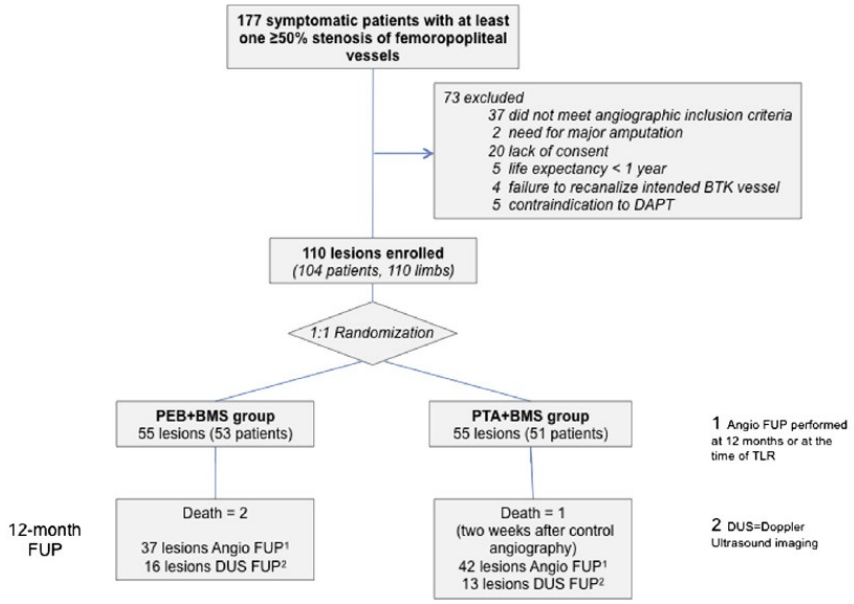
<u>Tepe et al., 2015</u> (Laird et al. - 24-months follow-up missing):



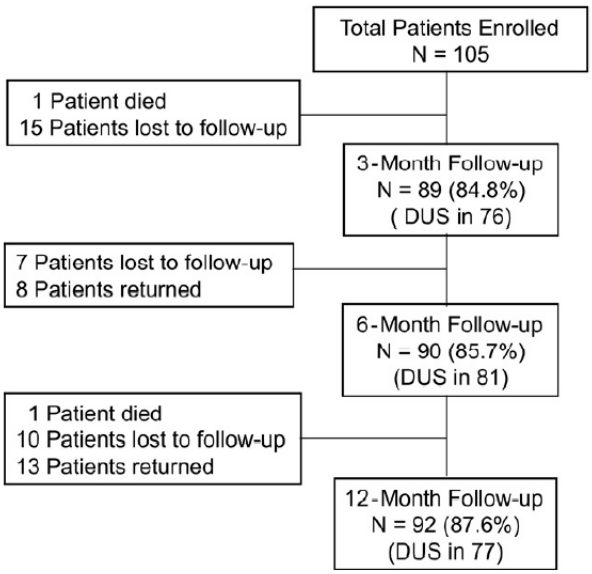
Krankenberg et al., 2015 :



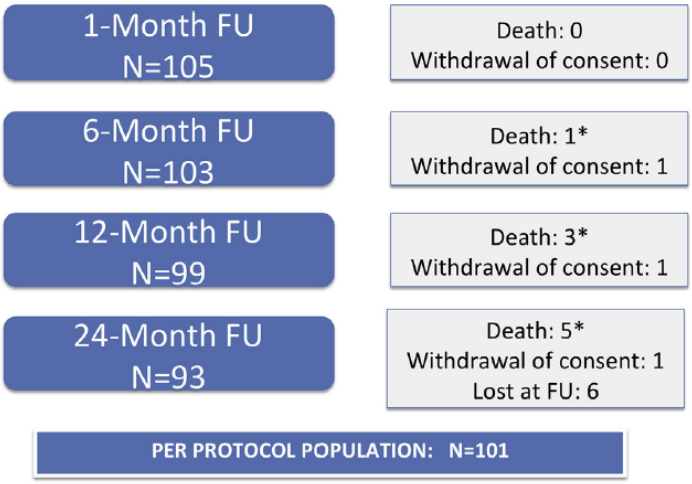
Liistro et al. 2013 :



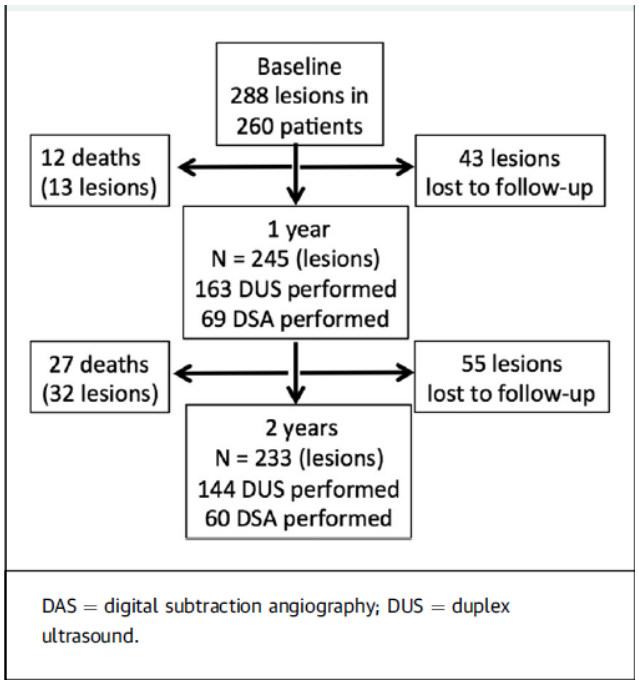
<u>Micari et al. 2012</u>(2013 - 24-months follow-up missing):



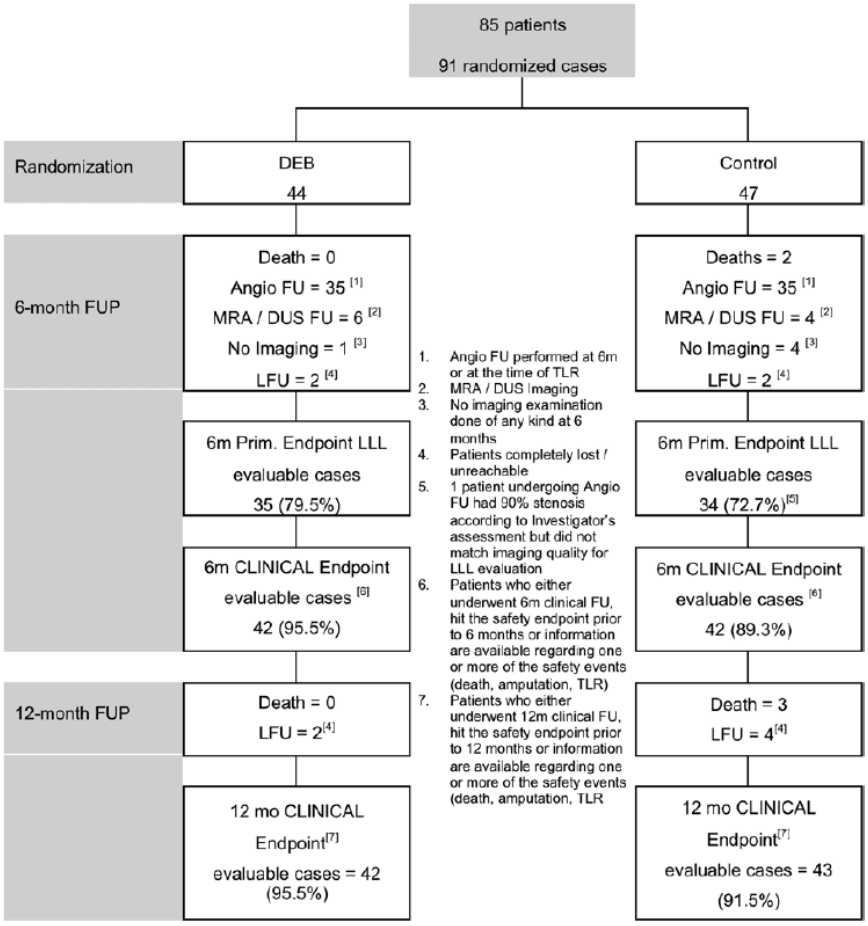
Micari et al. 2016, 2017:



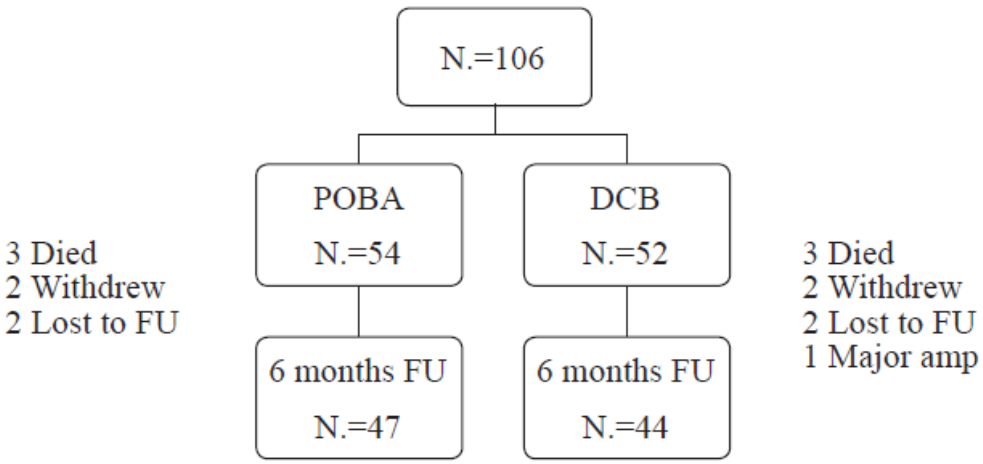
Schmidt et al. 2016 :



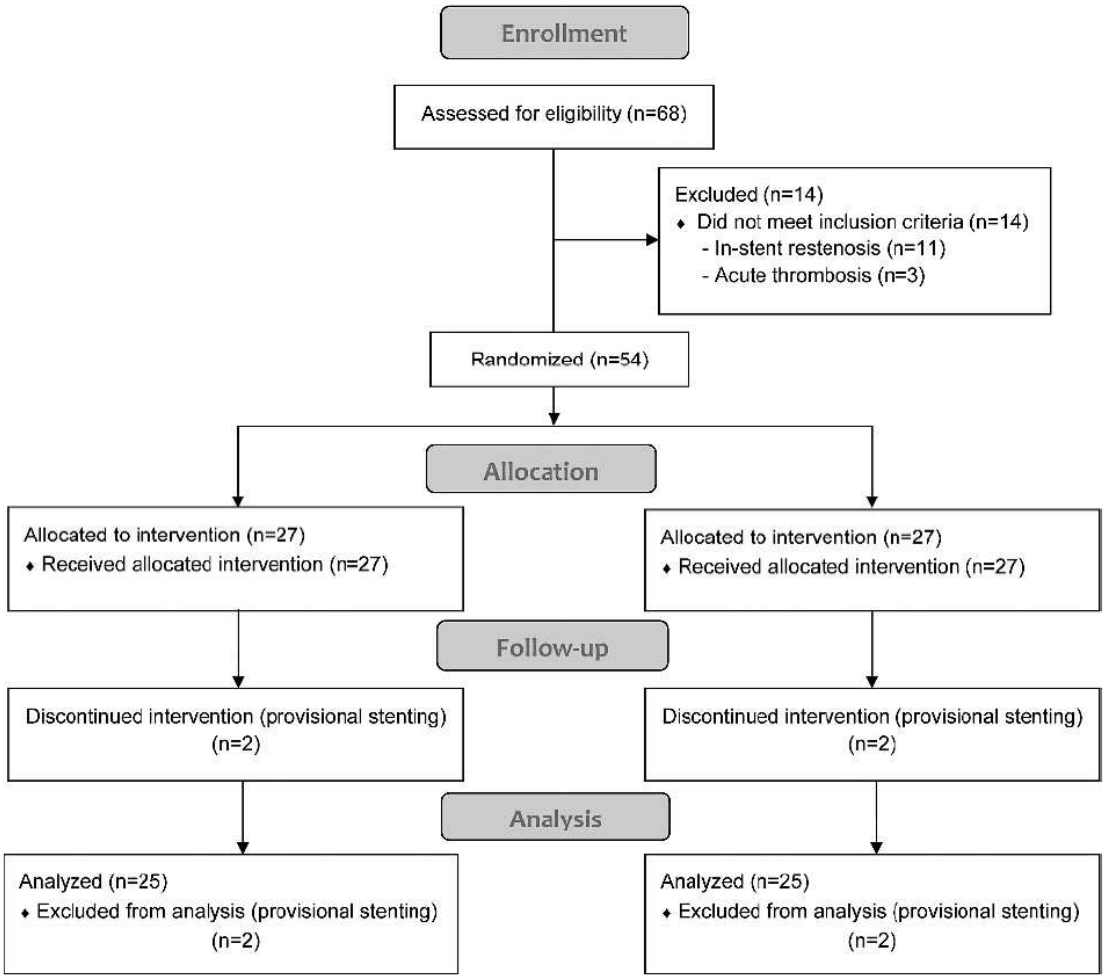
Werk et al. 2012 :



Debing et al. 2016 :



Fanelli et al. 2012 :



10.1.7 The data abstraction strategy.

Not applicable

10.2 Appendix 2: Search strategy for adverse events (section 7.7.1)

The following information should be provided.

10.2.1 The specific databases searched and the service provider used (for example, Dialog, DataStar, OVID, Silver Platter), including at least:

- Medline
- Embase
- Medline (R) In-Process
- The Cochrane Library.

The databases used for the systematic review were Medline (via Pubmed) and Embase. An additional search on the Cochrane Libray was conducted but not further publications were selected.

10.2.2 The date on which the search was conducted.

The Medline (via Pubmed) and Embase search was conducted on 19th July 2017.

10.2.3 The date span of the search.

The Medline (via Pubmed) and Embase search included articles published from 1995 to the 19th July 2017.

10.2.4 The complete search strategies used, including all the search terms: textwords (free text), subject index headings (for example, MeSH) and the relationship between the search terms (for example, Boolean).

Medline (via Pubmed) and Embase search: same strategy reported in 10.1.4 has been used. No specific filters were used.

10.2.5 Details of any additional searches (for example, searches of company databases [include a description of each database]).

Not applicable

10.2.6 The inclusion and exclusion criteria.

Medline (via Pubmed) and Embase search: Same as 10.1.6

10.2.7 The data abstraction strategy.

Not applicable

10.3 Appendix 3: Search strategy for economic evidence (section 8.1.1)

The following information should be provided.

10.3.1 The specific databases searched and the service provider used (for example, Dialog, DataStar, OVID, Silver Platter), including at least:

- Ovid
- Embase
- Ovid MEDLINE (R) Epub Ahead of Print, In-Process & Other Non-Indexed Citations
- Ovid MEDLINE(R) Daily
- Ovid MEDLINE(R)

10.3.2 The date on which the search was conducted

25th August 2017.

10.3.3 The date span of the search.

Articles published from 2004 to current have been included in this search.

10.3.4 The complete search strategies used, including all the search terms: textwords (free text), subject index headings (for example, MeSH) and the relationship between the search terms (for example, Boolean).

#	Searches	Results
1	((((coat* or elut* or cover* or releas*) adj4 balloon*) or ((angioplast* or angio plast*) adj3 (catheter* or microcatheter*))) and ((drug* or medicine* or medication* or medicament* or Paclitaxel* or Taxol* or Abraxane* or Capxol* or Cyclopax* or Cyclo pax* or Ebetaxel* or Genetaxyl* or Genexol* or Intaxel* or LipoPac* or Lipo Pac* or Mitotax* or Mito tax* or Nabpaclitaxel* or OncoGel* or Onco Gel* or Onxol* or On xol* or Paxceed* or Paxene* or Plaxicel* or Taxel* or TaxAlbin* or Tax Albin* or Taxus* or Yewtaxan* or Yew taxan*) adj5 (balloon* or catheter* or microcatheter*)) and ((drug* or medicine* or medication* or Paclitaxel* or Taxol* or Abraxane* or Capxol* or Cyclopax* or Cyclo pax* or Ebetaxel* or Genetaxyl* or Genexol* or Intaxel* or LipoPac* or Lipo Pac* or Mitotax* or Mito tax* or Nabpaclitaxel* or OncoGel* or Onco Gel* or Onxol* or On xol* or Paxceed* or Paxene* or Plaxicel* or Taxel* or TaxAlbin* or Tax Albin* or Taxus* or Yewtaxan* or Yew taxan*) adj5 (angioplast* or angio plast* or coat* or elut* or cover* or releas*))).ti,ab.	3264
2	(DEB or DEBs or DEBC or DEBCs or DCB or DCBs or DCBC or DCBCs).ti,ab.	6541
3	(balloon* adj5 (coat* or elut*)).af.	6447
4	(((peripher* adj4 (arter* or vascular*)) and (peripher* adj4 disease*) and ((arter* or vascular*) adj4 disease)) or femoropopliteal-occlusive-disease*).ti,ab.	58483
5	((PAD or PADs or PAOD or PAODs or PVD or PVDs) and ((peripher* adj4 (arter* or vascular*)) and (peripher* adj4 disease*) and ((arter* or vascular*) adj4 disease))).ti,ab.	16549
6	((arter* or branch* or intervention* or profunda* or profundi* or profundus* or tributar* or vascul* or vein* or vessel*) adj4 (femora* or femori* or femoro* or fibular* or genicular* or groin* or iliac* or iliofemor* or infrapoplit* or inguina* or malleolar* or pedis* or peripheral* or peroneal* or plantar* or popliteal* or renal* or sural* or tibia* or tibio* or arm or arms or leg or legs or brach*)).ti,ab.	409077

7	(cost* or economic* or 'economic impact*' or reimburs* or payment* or copayment* or icer or icers or qaly or qol or hrqol or 'quality adjusted life years' or 'quality of life' or 'economic evaluation*' or payers or fee or fees or price or prices or pricing or expenditure* or 'technology assessment*' or 'economic model*' or medicare or medicaid or drg or drgs or 'diagnosis related group*' or hcfa or 'health care finance administration*' or 'length of stay').ti,ab.	2575151
8	(1 or 2 or 3) and (4 or 5 or 6) and 7	200
9	(conference* or congress* or meeting* or poster* or symposia* or symposium* or (oral* and (abstract* or presentation* or session*)) or (scientific* and session*) or comment* or editorial* or letter* or note* or patent*).dt,pt.	9203083
10	8 not 9	150
11	limit 10 to english	145
12	remove duplicates from 11	90
13	limit 12 to yr="2004-current"	88

10.3.5 Details of any additional searches (for example, searches of company databases [include a description of each database]).

Not applicable

11 Related procedures for evidence submission

11.1 Cost models

An electronic executable version of the cost model should be submitted to NICE with the full submission.

NICE accepts executable cost models using standard software – that is, Excel, TreeAge Pro, R or WinBUGs. If you plan to submit a model in a non-standard package, NICE should be informed in advance. NICE, in association with the External Assessment Centre, will investigate whether the requested software is acceptable, and establish if you need to provide NICE and the External Assessment Centre with temporary licences for the non-standard software for the duration of the assessment. NICE reserves the right to reject cost models in non-standard software. A fully executable electronic copy of the model must be submitted to NICE with full access to the programming code. Care should be taken to ensure that the submitted versions of the model programme and the written content of the evidence submission match.

NICE may distribute the executable version of the cost model to a consultee if they request it. If a request is received, NICE will release the model as long as it does not contain information that was designated confidential by the model owner, or the confidential material can be redacted by the model owner without producing severe limitations on the functionality of the model. The consultee will be advised that the model is protected by intellectual property rights, and can be used only for the purposes of commenting on the model's reliability and informing comments on the medical technology consultation document.

Sponsors must ensure that all relevant material pertinent to the decision problem has been disclosed to NICE at the time of submission. NICE may request additional information not submitted in the original submission of evidence. Any other information will be accepted at NICE's discretion.

When making a full submission, sponsors should check that:

- an electronic copy of the submission has been given to NICE with all confidential information highlighted and underlined
- a copy of the instructions for use, regulatory documentation and quality systems certificate have been submitted
- an executable electronic copy of the cost model has been submitted
- the checklist of confidential information provided by NICE has been completed and submitted.

- A PDF version of all studies (or other appropriate format for unpublished data, for example, a structured abstract) included in the submission have been submitted

11.2 Disclosure of information

To ensure that the assessment process is as transparent as possible, NICE considers it highly desirable that evidence pivotal to the Medical Technologies Advisory Committee's decisions should be publicly available at the point of issuing the medical technology consultation document and medical technology guidance.

Under exceptional circumstances, unpublished evidence is accepted under agreement of confidentiality. Such evidence includes 'commercial in confidence' information and data that are awaiting publication ('academic in confidence').

When data are 'commercial in confidence' or 'academic in confidence', it is the sponsor's responsibility to highlight such data clearly, and to provide reasons why they are confidential and the timescale within which they will remain confidential. The checklist of confidential information should be completed: if it is not provided, NICE will assume that there is no confidential information in the submission. It is the responsibility of the manufacturer or sponsor to ensure that the confidential information checklist is kept up to date.

It is the responsibility of the sponsor to ensure that any confidential information in their evidence submission is clearly underlined and highlighted correctly. NICE is assured that information marked 'academic in confidence' can be presented and discussed during the public part of the Medical Technologies Advisory Committee meeting. NICE is confident that such public presentation does not affect the subsequent publication of the information, which is the prerequisite allowing for the marking of information as 'academic in confidence'.

Please therefore underline all confidential information, and highlight information that is submitted under 'commercial in confidence' in blue and information submitted under 'academic in confidence' in yellow.

NICE will ask sponsors to reconsider restrictions on the release of data if there appears to be no obvious reason for the restrictions, or if such restrictions would make it difficult or impossible for NICE to show the evidential basis for its guidance. Information that has been put into the public domain, anywhere in the world, cannot be marked as confidential.

Confidential information submitted will be made available for review by the External Assessment Centre and the Medical Technologies Advisory Committee. NICE will at all times seek to protect the confidentiality of the information submitted, but nothing will restrict the disclosure of information by NICE that is required by law (including in particular, but without limitation, the Freedom of Information Act 2000).

The Freedom of Information Act 2000, which came into force on 1 January 2005, enables any person to obtain information from public authorities such as NICE. The Act obliges NICE to respond to requests about the recorded information it holds, and it gives people a right of access to that information. This obligation extends to submissions made to NICE. Information that is designated as 'commercial in confidence' may be exempt under the Act. On receipt of a request for information, the NICE secretariat will make every effort to contact the designated company representative to confirm the status of any information previously deemed 'commercial in confidence' before making any decision on disclosure.

11.3 Equality

NICE is committed to promoting equality and eliminating unlawful discrimination, including paying particular attention to groups protected by equalities legislation. The scoping process is designed to identify groups who are relevant to the evaluation of the technology, and to reflect the diversity of the population. NICE consults on whether there are any issues relevant to equalities within the scope of the evaluation, or if there is information that could be included in the evidence presented to the Medical Technologies Advisory Committee to enable them to take account of equalities issues when developing guidance.

Evidence submitters are asked to consider whether the chosen decision problem could be impacted by NICE's responsibility in this respect, including when considering subgroups and access to recommendations that use a clinical or biological criterion.

For further information, please see the NICE website (www.nice.org.uk/aboutnice/howwework/NICEEqualityScheme.jsp).

NICE National Institute for Health and Care Excellence

Medical Technologies Evaluation Programme

MT336 –The IN.PACT drug-coated balloon for peripheral arterial disease

Specialist commentator questionnaire responses

Name of Specialist Commentator	Job title	Organisation
Dr James Lenton	Vascular & Interventional Radiology Consultant	Leeds Teaching Hospitals NHS Trust
Dr Trevor Cleveland	Consultant Vascular Radiologist	Sheffield Teaching Hospitals NHS Trust
Prof Andrew Bradbury	Consultant Vascular and Endovascular Surgeon	Heart of England NHS Foundation Trust, Birmingham
Ms Jane Todhunter	Vascular Nurse Practitioner	North Cumbria University Hospitals NHS Trust
Dr Peter Holt	Reader/Consultant Vascular Surgeon	St George's University NHS Foundation Trust
Dr Nadeem Shaida	Consultant Vascular & Interventional Radiologist	Cambridge University Hospitals NHS Foundation Trust
Mr Dan Carradice	Consultant Vascular & Endovascular Surgeon	Hull York Medical School
Mr Kevin Varty	Consultant Vascular Surgeon	Addenbrooke's Hospital NHS Foundation Trust
Dr Robert Morgan	Specialist vascular and interventional radiologist	St George's University NHS Foundation Trust
Dr Stephen Butterfield	Consultant Vascular Interventional Radiologist	University Hospital of South Manchester
Ms Janice Tsui	Consultant Vascular Surgeon	UCL, Royal Free Campus

NICE National Institute for Health and Care Excellence

Comments on specific sections of the draft briefing

Dr James Lenton	Page/section Page 3 Page 10 Page 11	Response DCB needs to be inflated for at least 1 minute All-cause mortality was greater in the DCB arm (8 Vs 1 %) at 2 yrs. This was discussed in the publication – felt not to be device or procedure related – does this need to be commented upon in the summery Comment that Amphirion balloon has now been withdrawn & why
Dr Trevor Cleveland	Page/section N/A Page 4/5 Page 5 Page 10-12	Please take note of my previously declared authorship of the systematic review, referred to in the Topic Briefing. I have no on-going financial relationship with Medtronic (the manufacturer) As noted, NICE has recently issued updated Guidance (CG147) which makes no recommendation for the use or otherwise of DEBs (from any manufacturer). The inclusion of aorto-iliac indications/disease in this briefing is confusing, as the IN.PACT assessment is for femoro-popliteal disease. Given that NICE were aware of the data contained in this submission (including the systematic review) it would seem a difficult conflict to have a technology review, based on just about the same evidence, that recognises that DEBs offer an advantage over the present standard of care (recently reiterated). My personal understandings of the data are that DEBs do offer a benefit to both patients and the overall healthcare system. In addition in other third world countries such devices are in more routine use. The Innovation Briefing for the Lutonix DCB is largely predicated on the Levant Trials. These were a large part of the comparator data for the IN.PACT device, and form the basis of the reviews of a better marginal outcome for IN.PACT compared with Lutonix. It is repeatedly noted that none of the trial centres were in the UK. There is no reason to expect that EU or USA patients have different disease than in the UK. Thus it would seem reasonable to expect that extrapolating the results to the UK is a justifiable proposal. Further the "real world registry" inevitably would not include the UK, where there is NICE guidance, which recommends an alternative strategy. The BASIL-3 Trial is referred to, and is an important trial (please note that I was a co-applicant for tis trial funding through the HTA). However, the BASIL-3

	Page 12 Page 6 Page 8	Trial is one that is recruiting patients with Severe Limb Ischaemia (SLI). Many of the patients reviewed in the briefing literature are patients with claudication, and so is a different cohort. CG147 places a high reliance on the outcome from BASIL-3 but ultimately this is not a trial for patients with claudication, which is a significant group for which IN.PACT is proposed (RCC 2 and 3 as well as 4 in the IN.PACT Trial) Medtronic state that 35 Trusts are using the IN.PACT DCB. It would seem likely that these are being used for a mixture of indications including restenosis, dialysis fistulae as well as femoro-popliteal disease. The Cochrane review found no evidence for improvement in "clinical outcomes" such as amputation or death. One would not expect to find such outcomes, given that the devices are often being studied in a population who rarely undergo either of those end-points, i.e. patients with claudication. For patients with critical limb ischaemia this might be a more regular endpoint, but they do not appear to have discriminated. Clinically driven target lesion revascularisation (CD-TLR) does appear to be a clinical endpoint, the briefing suggests that it is not. CD-TLR is seen in the data to be improved by the use of DEBs
Prof Andrew Bradbury	None	NICE has examined the evidence for drug eluting technologies (such as the IN.PACT drug coated balloon, DCB) on two occasions (PAD guidelines 2012 https://www.nice.org.uk/guidance/cg147; up-dated 2017) and have correctly concluded that there is insufficient evidence of clinical and cost-effectiveness to justify recommending its use in the NHS until such time as the NIHR HTA-funded BASIL-2 trial reports its findings (https://www.journalslibrary.nihr.ac.uk/programmes/hta/138102#/). The problem is that although these drug technologies, including IN.PACT DCB, have been shown to reduce restenosis in industry-funded trials they have not been shown to improve clinical outcomes; and they are many time more expensive than standard (pain) balloons and stents.
Ms Jane Todhunter	None	Blank
Dr Peter Holt	None	Blank
Dr Nadeem Shaida	None	Blank

Mr Dan Carradice	Summary Key uncertainties	I think that it may be contentious to say that "the current standard of care for people with PAD (is) plain balloon PTA (with or without stenting)". NICE guidelines state that the standard of care for intermittent claudication is risk factor modification, best medical therapy, supervised exercise and Naftidrofuryl Oxalate. Revascularisation should be limited to those with lifestyle limiting claudication who fail to respond to these measures. With regard to critical ischaemia (rest pain and/or tissue loss), the Basil trial suggests that in patients expected to survive more than 2 years, overall survival is better following surgical bypass than with PTA in the fem pop segment. The Basil 2 trial is recruiting and will tell us about the infrapopliteal segment. I would suggest changing the wording to " The intended place in therapy would be to replace the current standard of care for people with PAD who are selected to receive endovascular revascularisation of the femoropopliteal ateries, plain balloon PTA (with or without stenting)". I suggest expanding to include the comments below
Mr Kevin Varty	None	Blank
Dr Robert Morgan	None	Blank
Dr Stephen Butterfield	None	Blank
Ms Janice Tsui	Page 4, last line P 12, Schmidt et al, study size, design & location P12, Ongoing studies	Suggest clarifying that in intermittent claudication, angioplasty (or indeed any intervention) is only offered when exercise has not shown improvement AND claudication is limiting 'Retrospective observational study…. In X centres in Germany' – need to insert number of centres Would be useful to include where sites are for the studies listed (e.g. like for BASIL3: 60 sites in uk; similar for the rest)

Your opinion on how this technology would be used in practice

Question 1: How do you rate this technology's level of innovation? Is it a minor variation on existing technologies or does it represent a novel concept/design?

Dr James Lenton	No longer novel as around for some time, but new concept when first introduced. Only minor variation in procedure.
Dr Trevor Cleveland	The IN.PACT DEB is one of a class of devices, as noted in the Briefing. Each device in this class uses a different excipient, which the manufacturers regularly describe as a reason for their unique nature, at the time of sales. A similar argument is put forward in the Lutonix innovation briefing. As such the IN.PACT is a minor variation on existing technologies, which the company consider translates into a significant improvement in benefits (and this is supported in the systematic review – although in this all other DEBs are considered as a single class of device).
Prof Andrew Bradbury	The IN.PACT DCB is one of several drug technologies (balloons and stents) marketed for the treatment of PAD. They are all made somewhat differently but, despite the marketing 'hype' from the manufacturers, there is no reason to believe that one works better than any other
Ms Jane Todhunter	Variation of existing technology
Dr Peter Holt	DCB are an established part of the vascular surgeon's practice now. The clinical effectiveness is becoming more understood and their use is becoming routine
Dr Nadeem Shaida	One of a number of existing drug eluting balloons on the market – this technology has been available for a number of years now
Mr Dan Carradice	Overall, drug eluting technology is an exciting innovation with early evidence suggesting promising results, especially for this particular device
Mr Kevin Varty	Drug coating of balloons (DCB) for angioplasty is a significant innovation. The evidence to date, for femoropopliteal disease, mainly in claudicants, shows that restenosis and repeat intervention is less likely with DCB compared to plain balloon angioplasty. Approximately a 30-50% reduction. The main question is how it performs against drug eluting stents. Also the place of atherectomy.
Dr Robert Morgan	This is a novel development compared with the current standard of care – i.e. non drug-coated balloon angioplasty.
Dr Stephen Butterfield	Drug coated angioplasty balloons represent a significant change from standard (uncoated) angioplasty balloons. There are variations in use and type of excipients and dose density of the active agent, paclitaxel between different drug coated balloon manufacturers. The variation in drug coated balloon composition may contribute to variations in published outcomes between different drug coated balloons.

Ms Janice Tsui	This technology contributes to current range of drug eluting balloons which aims to improve upon current treatment, rather than a completely new innovation.

Question 2: Would users of this technology require any special training?

Dr James Lenton	No
Dr Trevor Cleveland	No
Prof Andrew Bradbury	Some but not a lot as performing angioplasty with IN.PACT DCB is very similar to performing angioplasty with a plan balloon
Ms Jane Todhunter	Unlikely to require further training
Dr Peter Holt	Yes, but if they have an endovascular practice of peripheral angioplasty this is short (can be paper based of face-to-face) and related to minor technical aspects of use rather than prolonged training courses
Dr Nadeem Shaida	None other than the usual with any new device ie.may need a company rep to be present for the first few cases
Mr Dan Carradice	No
Mr Kevin Varty	No significant additional training required
Dr Robert Morgan	A small amount of additional specific training would be required to use these devices.
Dr Stephen Butterfield	Minimal or no extra training.
Ms Janice Tsui	No

Your experience with this technology

Question 3: Are you familiar with the technology?

Dr James Lenton	Yes
Dr Trevor Cleveland	Yes
Prof Andrew Bradbury	Yes, very
Ms Jane Todhunter	Not as a user, but as part of the vascular team
Dr Peter Holt	Yes
Dr Nadeem Shaida	Yes

Mr Dan Carradice	Yes
Mr Kevin Varty	Yes
Dr Robert Morgan	Yes
Dr Stephen Butterfield	Yes
Ms Janice Tsui	Yes

Question 4: Have you used this technology before? Do you use it currently?

Dr James Lenton	Yes & yes
Dr Trevor Cleveland	Yes I have used it. Our department uses these balloons for the treatment of restenosis and in-stent restenosis, for primary disease we follow the NICE Guidance.
Prof Andrew Bradbury	We are using drug coated balloons (DCB) and drug eluting stents (DES) in the NIHR HTA-funded BASIL-3 trial. In keeping with NICE CG 147 we do not use DCB/DES outside trial. BASIL-3 is currently recruiting in over 30 UK NHS Trusts with the aim of increasing that to around 50 by the end of tis year. BASIL-3 is currently recruiting on target.
Ms Jane Todhunter	Never used it
Dr Peter Holt	Yes
Dr Nadeem Shaida	Yes – Also use currently along with a number of competitor products
Mr Dan Carradice	Yes
Mr Kevin Varty	It has been used on many of my patients, and I have seen them at follow up with scans and symptom changes. I have not performed the angioplasty myself
Dr Robert Morgan	Yes- I use it currently
Dr Stephen Butterfield	I have been using drug coated balloons since 2013 and the IN.PACT drug coated balloon since approximately 2014. I continue to use the IN.PACT DCB in my current practice.
Ms Janice Tsui	Yes, this range of technology but not this exact DCB

Question 5: If so how regularly and how many times?

Dr James Lenton	Regularly, numbers unknown but likely <100
Dr Trevor Cleveland	As noted above, my practice is to use these for recurrent disease, and I have used the IN.PACT balloon on approximately 10-20 occasions
Prof Andrew Bradbury	When patients are randomised to DCB
Ms Jane Todhunter	Blank
Dr Peter Holt	<50
Dr Nadeem Shaida	1-2x/week
Mr Dan Carradice	Once or twice per month
Mr Kevin Varty	In the last 2 years I would estimate 50 of my patients have been treated with a DCB
Dr Robert Morgan	I use it for a large proportion of femoropopliteal angioplasty procedures. Approximately three times per week.
Dr Stephen Butterfield	Regular use on a weekly (case dependant) basis.
Ms Janice Tsui	Blank

Question 6: Were you involved in the development/testing of this technology?

Dr James Lenton	No
Dr Trevor Cleveland	No
Prof Andrew Bradbury	The clinical and cost-effectiveness DCB and DES are being evaluated in BASIL-3 which is large, multicentre pragmatic UK-based trial funded by NIHR-HTA.
Ms Jane Todhunter	Blank
Dr Peter Holt	No
Dr Nadeem Shaida	No
Mr Dan Carradice	No
Mr Kevin Varty	**No**
Dr Robert Morgan	**No**
Dr Stephen Butterfield	**No**

Ms Janice Tsui	No

Question 7: Has this technology been superseded or replaced already?

Dr James Lenton	No
Dr Trevor Cleveland	Not to my knowledge
Prof Andrew Bradbury	DCB and DES are not currently recommended by NICE for use in the NHS.
Ms Jane Todhunter	Blank
Dr Peter Holt	No- this balloon is the current industry standard
Dr Nadeem Shaida	No
Mr Dan Carradice	No
Mr Kevin Varty	The data against plain balloon angioplasty is persuasive that DCB performs better, and will be an overall benefit for the patient and the NHS (reduced re-interventions). This is for femoropopliteal disease where lesions can be crossed. Much of the data is in claudicants with lesions up to 20 cms few beyond that. This technology is challenged by drug eluting stents(DES). We need more data on the costs and benefits of DCB versus DES in treating fem pop disease of differing lengths and in claudicants and critical ischaemia. In my opinion, there is a place for DCB over plain angioplasty in fem-pop disease, but we do not know yet, the optimal treatment if we also consider DES, and covered stents.
Dr Robert Morgan	No
Dr Stephen Butterfield	No. Drug coated stents continue to develop.
Ms Janice Tsui	No

Patient impact

Question 8: How could this technology improve patient health outcomes? Are there any groups of people who would particularly benefit?

Dr James Lenton	Yes – improvement in outcome in treatment. May benefit younger patients more given longer term improvements
Dr Trevor Cleveland	As noted in the briefing, the intention of these devices is to reduce the likelihood of restenosis. The assumption is that restenosis would result in recurrence of the symptoms (or risk of the segment completely blocking) and the need for repeat treatment (or even threat to limb viability). The evidence presented would indicate that CD-TLR (Clinically Driven Target Lesion Revascularisation) is reduced by these devices, thus giving the patient a similar level of outcome to plain balloons, but with the need for less re intervention (and thus inconvenience, morbidity from recurrent symptoms, and reduced healthcare costs of retreatment). It would seem likely that the devices would be appropriate to consider for patients with both claudication and critical limb ischaemia who have femoro-popliteal disease deemed suitable for angioplasty.
Prof Andrew Bradbury	DCB and DES may improve clinical outcomes in patients with PAD. However, as yet, there is no evidence that they do. Hence the research recommendation by NICE to undertake the BASIL-3 trial which has been funded by NIHR HTA.
Ms Jane Todhunter	May reduce the need for re-intervention
Dr Peter Holt	DCB use is the current best practice for peripheral angioplasty
Dr Nadeem Shaida	The idea is that the drug prevents restenosis. Numerous papers exist demonstrating improved primary patency rates v plain balloon angioplasty. Less clear is the actual clinical advantage to patients over other therapies eg. Supervised exercise programmes in claudicants. Critical limb ischaemia patients would probably benefit from this over plain balloon but with the caveat that the vessel is non-calcified as there is evidence that drug balloons do not work well in calcified vessels. Drug balloons v stents (plain or drug eluting) in CLI is also a controversial area. Another key role for DEB is in the treatment of in-stent restenosis.
Mr Dan Carradice	If this technology proves to increase the durability of angioplasty, without an increase in complications then this is likely to be associated with improved quality of life and limb salvage. Trials are underway to study whether this is the case and whether this device is cost effective. All patients with peripheral arterial occlusive disease in the femoropopliteal segment may benefit and it may be that this technology finds a place in the infrapopliteal and aorto iliac segments as well.
Mr Kevin Varty	Claudicants who remain with significant symptoms after exercise programmes and risk factor modification will benefit from this in comparison to plain balloon angioplasty. NICE 147 guidance should remain, DCB should not be used without exercise and risk factor interventions first. We do not have evidence of the benefit of DCB in patients with critical limb ischaemia yet.

Dr Robert Morgan	There are proven significant improvements in patency rates for femoropopliteal occlusive lesions as far as three years follow-up post procedure. The majority of patients with lower limb claudication and critical limb ischaemia would theoretically benefit from the use of these devices.
Dr Stephen Butterfield	Improve sustained symptoms of pain and functional walking distance in claudicants. Improve rest pain and improve tissue healing in patients with critical ischaemia. This technology has shown benefit in patients with peripheral vascular disease, including patients with diabetes and patients who have had recurrence of disease / symptoms from previous endovascular interventions.
Ms Janice Tsui	This technology would reduce restenosis and reintervention rates which would be of benefit to patients. Current data on clinical and patient-specific outcomes are limited, however, reducing re-intervention alone would be of benefit in a group of patients which consists of high risk patients. Patients with severe peripheral arterial disease (PAD) would benefit.

Question 9: How could it change patient experience? Would it lead to fewer hospital visits, less invasive treatment or other benefits for patients?

Dr James Lenton	Reduction in need for re intervention. Improved symptom control.
Dr James Lenton	The procedure of DEB or plain balloon/stent is almost the same. The benefit for patients would be in less regular symptomatic recurrence, and a reduced likelihood of needing to seek further medical attention, and hospital treatment.
Dr Trevor Cleveland	Not possible to say as yet as no evidence of clinical and cost-effectiveness. We await the results of BASIL-3.
Prof Andrew Bradbury	May mean fewer hospital visits/ less intervention from angiosuite / may reduce the need for surgical intervention.
Ms Jane Todhunter	This will reduce the mid-late term failure rate of angioplastyand so despite there being an upfront cost it will improve patency and reduice readmissions in the longer term. There may also be a reduction in major amputations if the effect is prolonged
Dr Peter Holt	Potentially less chance of coming back for reintervention (there is some evidence for this) or of delaying the time to reintervention
Dr Nadeem Shaida	It could lead to improved quality of life, a lower rate of amputation, less visits to hospital and less time as an inpatient.
Mr Dan Carradice	In the selected group for DCB treatment you would expect fewer re-interventions compared to plain balloon angioplasty (30-50% reduction)
Mr Kevin Varty	The improved patency rates up to three years post procedure should reduce the need for repeat endovascular or surgical interventions. This would be expected to translate into fewer hospital visits.

Dr Robert Morgan	The initial procedure is essentially the same from the patients perspective with no influence on its ability to be performed as a day case or in-patient stay. Current date suggests that use of this technology will reduce number of reinterventions required to maintain successful outcomes for patients with associated healthcare savings and reduced pain and inconvenience to patients. Our own audit on DCB use v standard balloon angioplasty (submitted for BARD Lutonix review) supports the reduction in reinterventions.
Dr Stephen Butterfield	Few restenosis would mean few reinterventions (and associated complications) and fewer hospital visits for most patients. In particular for a group of patients at risk of progressive renal impairment, reducing need for contrast exposure would be of benefit.
Ms Janice Tsui	

Question 10: Are you aware of any safety alerts for this technology?

Dr James Lenton	No
Dr Trevor Cleveland	No It should be noted that the below the knee balloon (IN.PACT Amphirion) was withdrawn (as noted in the Briefing) following a study which showed unfavourable outcomes. It should also be noted that my understanding is that this study was not statistically significant in terms of the poor outcome, but indicated a trend towards that.
Prof Andrew Bradbury	Medtronic recalled and stop selling the IN.PACT Amphirion drug-eluting balloon after results from the IN.PACT DEEP clinical study indicated a trend towards a higher rate of major amputation in the drug-eluting balloon arm in patients with below-the-knee disease. The study also showed no benefit with the drug-eluting balloon compared to standard balloon angioplasty in terms of re-intervention and late lumen loss. J Am Coll Cardiol. 2014 Oct 14;64(15):1568-76. doi: 10.1016/j.jacc.2014.06.1198. Drug-eluting balloon versus standard balloon angioplasty for infrapopliteal arterial revascularization in critical limb ischemia: 12-month results from the IN.PACT DEEP randomized trial. Zeller T1, Baumgartner I2, Scheinert D3, Brodmann M4, Bosiers M5, Micari A6, Peeters P7, Vermassen F8, Landini M9, Snead DB9, Kent KC10, Rocha-Singh KJ11; IN.PACT DEEP Trial Investigators. Author information Abstract BACKGROUND: Drug-eluting balloons (DEB) may reduce infrapopliteal restenosis and reintervention rates versus percutaneous transluminal angioplasty (PTA) and improve wound healing/limb preservation. OBJECTIVES: The goal of this clinical trial was to assess the efficacy and safety of IN.PACT Amphirion drug-eluting balloons (IA-DEB) compared to PTA for infrapopliteal arterial revascularization in patients with critical limb ischemia (CLI). METHODS: Within a prospective, multicenter, randomized, controlled trial with independent clinical event adjudication and angiographic and wound core laboratories 358 CLI patients were randomized 2:1 to IA-DEB or PTA. The 2 coprimary efficacy endpoints through 12 months were clinically driven target lesion revascularization (CD-TLR) and late lumen loss (LLL). The primary safety endpoint through 6 months was a composite of all-cause mortality, major amputation, and CD-TLR. RESULTS: Clinical characteristics were similar between the 2 groups. Significant baseline differences between the IA-DEB and PTA arms included

	mean lesion length (10.2 cm vs. 12.9 cm; p = 0.002), impaired inflow (40.7% vs. 28.8%; p = 0.035), and previous target limb revascularization (32.2% vs. 21.8%; p = 0.047). Primary efficacy results of IA-DEB versus PTA were CD-TLR of 9.2% versus 13.1% (p = 0.291) and LLL of 0.61 ± 0.78 mm versus 0.62 ± 0.78 mm (p = 0.950). Primary safety endpoints were 17.7% versus 15.8% (p = 0.021) and met the noninferiority hypothesis. A safety signal driven by major amputations through 12 months was observed in the IA-DEB arm versus the PTA arm (8.8% vs. 3.6%; p = 0.080). CONCLUSIONS: In patients with CLI, IA-DEB had comparable efficacy to PTA. While primary safety was met, there was a trend towards an increased major amputation rate through 12 months compared to PTA. (Study of IN.PACT Amphirion™ Drug Eluting Balloon vs. Standard PTA for the Treatment of Below the Knee Critical Limb Ischemia [INPACT-DEEP]; NCT00941733). Copyright © 2014 American College of Cardiology Foundation. Published by Elsevier Inc. All rights reserved.
Ms Jane Todhunter	No
Dr Peter Holt	Not for this specific device
Dr Nadeem Shaida	In 2013 the IN.PACT DEEP industry sponsored trial of DEB v plain balloon angioplasty for BELOW KNEE disease was stopped early and the below knee DEB withdrawn. Medtronic have now just launched a new BTK study with the In.Pact balloon. Also worth mentioning that although unusual some patients are allergic to Paclitaxel (which they may have had as part of cancer treatment)
Mr Dan Carradice	No
Mr Kevin Varty	No
Dr Robert Morgan	None
Dr Stephen Butterfield	**No**
Ms Janice Tsui	**No**

System impact

Question 11: How would use of this technology impact on NHS services?

Dr James Lenton	Potential reduction in re intervention rates with cost saving. Unknown overall impact on costs – greater up front costs Vs reduction in re intervention
Dr Trevor Cleveland	As noted in the Briefing, there are a large number of primary angioplasties performed in the UK for PVD in the femoro-popliteal segment. If there were to be a large-scale transference of the present NICE guidance (plain balloon angioplasty with bail-out bare metal stents) to DEBs, then there would be a significant up front cost for the purchase of the devices. The potential benefit (assessed in the cost effectiveness analysis) would be the better quality outcome for patients, and the reduced need for resources to perform re-intervention.
Prof Andrew Bradbury	Use of DCB, including IN.PACT, could represent a serious misuse of NHS resources they are much more expensive than plain balloons and with no evidence of clinical benefit
Ms Jane Todhunter	More expensive to purchase however may prove cost effective.
Dr Peter Holt	Higher up front cost, but reduced readmission and reintervention
Dr Nadeem Shaida	Increased cost of DEB over plain balloon. This is two-fold – firstly the balloon itself is costlier, secondly if the lesion being treated is long (which is often the case) then more than one balloon is needed whereas with plain balloon angioplasty the same balloon can be reused. The DEB are usually slightly larger than plain balloon (5/6F v 4F) – depending on unit set up this may impact on bedrest time etc.
Mr Dan Carradice	Improved durability of angioplasty would lead to less re-attendances / re-admissions, less repeat procedures, less minor and major amputations.
Mr Kevin Varty	Currently, this is for selected claudicants only. Reducing the nuber of interventions and clinic visits for recurrent symptoms.
Dr Robert Morgan	The reduced requirement for reinterventions should free up financial and staffing resources for other work in the NHS.
Dr Stephen Butterfield	Although this technology has a higher initial cost in comparison to standard angioplasty balloons it has the potential to reduce reintervention rates with the associated savings in reduced clinic visits and reintervention. Patient satisfaction has the potential to be increased by producing better primary sustained clinical outcomes with a reduced need for secondary interventions
Ms Janice Tsui	Reducing re-interventions would reduce the burden on resources including beds, procedural slots and interventional expertise.

Question 12: Would any changes in facilities or infrastructure be needed for this technology to be used?

Dr James Lenton	No
Dr Trevor Cleveland	The procedure for using a DCB is very similar to the present standard of care (angioplasty and stenting)
Prof Andrew Bradbury	NICE have decided that DCB and DES should not be use in the NHS (outside the BASIL-3) trial until such time as BASIL-3 reports it results
Ms Jane Todhunter	No
Dr Peter Holt	No
Dr Nadeem Shaida	No
Mr Dan Carradice	No
Mr Kevin Varty	No
Dr Robert Morgan	None
Dr Stephen Butterfield	No
Ms Janice Tsui	No

Question 13: Do you think that use of this technology could lead to cost savings for the NHS?

Dr James Lenton	Possibly- see below
Dr Trevor Cleveland	The systematic review would indicate this to be the case, and that is the best evidence that we have available (note my conflict in this regard)
Prof Andrew Bradbury	Unlikely based on current evidence
Ms Jane Todhunter	Possibly
Dr Peter Holt	Yes through reduced readmission and reintervention
Dr Nadeem Shaida	Unclear – although some authors have published on potential savings, as above the heterogeneity of the population and lack of real long term clinical outcome data makes it difficult to be certain
Mr Dan Carradice	Yes

Mr Kevin Varty	Some minor saving overall
Dr Robert Morgan	Yes
Dr Stephen Butterfield	Yes by reducing reinterventions foir patients.
Ms Janice Tsui	Yes in the longer term

Any other comments or opinions on this technology (optional)

Dr James Lenton	Economic modelling provided by the company is based on only using one balloon per patient- in the real world many patients have multi level disease and would require more than one balloon for treatment. The comparison Vs plain balloon costs (p5 & 17) are a lot less attractive in that setting. The potential savings due to a reduction in re intervention and improvement in outcome will be very hard to model.
Dr Trevor Cleveland	My overall view is that DEBs offer a significant benefit over plain balloons in terms of recurrence of symptoms and need for further treatment. It was a surprise that the recent update of CG147 did not recognise what was was noted in the CG147 data review, and that the guidance was not changed. There was a reliance on expert comment, and the BASIL-3 Trial. As noted above this trail should provide very useful data, but in the context of severe limb ischaemia not intermittent claudication . The briefing indicates that this guidance will not be updated until 2021. In the meantime data such as reviewed in this briefing will challenge that guidance, and potentially generate a conflict of information, particularly as these data were available at the CG147 review.
Prof Andrew Bradbury	I see no reason why NICE should change its currently held view on the use of DCB / DES fr PAD
Ms Jane Todhunter	Blank
Dr Peter Holt	Blank
Dr Nadeem Shaida	I believe DEB have a role to play but it is not quite clear in what capacity. I think definitely they are useful in in-stent restenosis cases. For claudicants it depends on whether your centre treats claudicants with angioplasty (against prior NICE guidance) or not. The freedom from target lesion revascularisation is often quoted as a “pseudo”clinical endpoint and DEB appears to confer a benefit here. As above in calcified vessels it is unlikely to be helpful. In CLI the debate is whether the goal of treatment (eg. Treat ulcer) would be achieved with plain balloon or stent alone and whether DEB adds any additional benefit. Diabetic patients with their mixed macro and microvascular disease are another difficult group to treat and again DEB effect is unclear here. Finally all above comments relate to SFA/popliteal disease. The evidence for DEB below the knee is minimal at best.

Mr Dan Carradice	This technology has shown very promising results to date, however it is important to note the following weaknesses in the evidence: Many of the trials on this topic do not give clear information regarding the quality and compliance of the other aspects of care, such as smoking cessation, best medical therapy and supervised exercise. Best practice with regard to these measures may reduce the additional benefit of the new technology over plain balloon angioplasty. Much of the evidence is based upon the treatment of claudicants rather than those with limb threatening ischaemia, and the results may differ. The evidence has a very high level of industry involvement with the associated potential for bias. The studies tend to focus on surrogate technical outcomes rather than clinically meaningful ones. The economic study estimates quality of life based upon a single small study which was looking at a completely different issue (the role of stenting). This may impact upon the validity of the results. Despite heavy industry involvement in the studies and the opportunity for producing plain and drug eluting balloons which are indistinguishable, operator blinding is rare. The presented registry data shows less impressive 2 year results. This is to be expected, but the size of the deficit should be noted. It is crucial that high quality independent studies with clinically important endpoints are completed.

CONFLICTS OF INTEREST

PERSONAL FINANCIAL INTERESTS

Specialist commentators	Consultancies or directorships	Clinicians receiving payment for a procedure	Fee-paid work	Shareholdings	Financial interest in a company's product	Expenses and hospitality	Funds Personal non-pecuniary interest
Dr James Lenton	No	No	No	No	No	No	No
Dr Trevor Cleveland	No	No	**Yes**	No	No	No	No
Prof Andrew Bradbury	No	No	No	No	No	No	No
Ms Jane Todhunter	No	No	No	No	No	No	No
Dr Peter Holt	No	No	No	No	No	No	No
Dr Nadeem Shaida	No	No	No	No	No	No	No
Mr Dan Carradice	No	No	No	No	No	No	No
Mr Kevin Varty	No	No	No	No	No	No	No
Dr Robert Morgan	No	No	**Yes**	No	No	No	No
Dr Stephen Butterfield	No	No	No	No	No	No	No
Ms Janice Tsui	No	No	No	No	No	No	No
Conflict(s) declared							
Dr Trevor Cleveland	**I have received a one off payment from Medtronic for Consultancy on their product range at a single meeting and have received a payment for additional work done as a part of a presentation at a symposium at the British Society of Interventional Radiologists Annual Scientific Meeting. I do not have any ongoing financial relationship with Medtronic nor do I have any financial or other interest in the IN.PACT balloon range.**						

Specialist commentators	Consultancies or directorships	Clinicians receiving payment for a procedure	Fee-paid work	Shareholdings	Financial interest in a company's product	Expenses and hospitality	Funds Personal non-pecuniary interest
Dr Robert Morgan	I am a proctor and occasional speaker for the Medtronic company in connection with their embolization product ONYX. Medtronic is the manufacturer of the IN.PACT balloon, so taking this project on may conceivably be a conflict of interests.						

PERSONAL NON-FINANCIAL INTERESTS

Specialist commentators	Expressed a clear opinion reached as a conclusion of a research project or in a published statement	Been an author on a document submitted as an evidence publication to a NICE advisory committee	Hold office in a professional organisation, charity or advocacy group with a direct interest in the topic	Have any other reputational risks in relation to the topic
Dr James Lenton	No	No	No	No
Dr Trevor Cleveland	Yes	Yes	Yes	Yes
Prof Andrew Bradbury	Yes	Yes	Yes	Yes
Ms Jane Todhunter	No	No	No	No
Dr Peter Holt	Yes	Yes	Yes	Yes
Dr Nadeem Shaida	No	No	No	No
Mr Dan Carradice	No	No	No	No
Mr Kevin Varty	No	No	No	No
Dr Robert Morgan	No	No	No	No
Dr Stephen Butterfield	Yes	Yes	Yes	Yes
Ms Janice Tsui	No	No	No	No

Specialist commentators	Expressed a clear opinion reached as a conclusion of a research project or in a published statement	Been an author on a document submitted as an evidence publication to a NICE advisory committee	Hold office in a professional organisation, charity or advocacy group with a direct interest in the topic	Have any other reputational risks in relation to the topic
Conflict(s) declared				
Dr Trevor Cleveland	**I worked on a paper, published in the BMJ which received support from Medtronic personnel in the formulation and writing of the publication. This was declared to the Journal Editors prior to publication.**			
Prof Andrew Bradbury	**I was the Chief Investigator on the NIHR HTA funded BASIL-1 trial and the results of this trial were used to inform recommendation in the NICE PAD guideline**			
Dr Peter Holt	**I acted as an expert opinion on the same topic for NICE for the Bard Lutonix balloon appraisal**			
Dr Stephen Butterfield	**I contributed to NICE review of BARD Lutonix drug eluting balloon and submitted a presentation of our work using the BARD Lutonix balloon**			

CONFLICTS OF INTEREST (cont.)

NON-PERSONAL INTERESTS

Specialist commentators	Grant for the running of a unit	Grant or fellowship for a post or member of staff	Commissioning of research	Contracts with or grants from NICE
Dr James Lenton	No	No	No	No
Dr Trevor Cleveland	No	No	No	No
Prof Andrew Bradbury	No	**Yes**	No	**Yes**
Ms Jane Todhunter	No	No	No	No
Dr Peter Holt	No	**Yes**	No	No
Dr Nadeem Shaida	No	No	No	No
Mr Dan Carradice	No	No	No	No
Mr Kevin Varty	No	No	No	No
Dr Robert Morgan	No	No	No	No
Dr Stephen Butterfield	No	No	No	No
Ms Janice Tsui	No	No	No	No
Conflict(s) declared				
Prof Andrew Bradbury	**I am Chief Investigator of the NIHR HTA-funded BASIL2 and BASIL-3 trial and a co-investigator on the NIHR HTA-funded EVRA and GAPS trial** **I am Chairing the NICE national guideline committee on AAA**			
Dr Peter Holt	**A statistician at St George's is paid in part through a research grant from the aortic arm of Medtronic. This is unrelated to the current topic of appraisal.**			

LINKS/FUNDING FROM THE TOBACCO INDUSTRY

Specialist commentators	Yes or No?	*Conflict(s) declared*
Dr James Lenton	No	Blank
Dr Trevor Cleveland	No	Nil
Prof Andrew Bradbury	No	Blank
Ms Jane Todhunter	No	Blank
Dr Peter Holt	No	Blank
Dr Nadeem Shaida	No	None
Mr Dan Carradice	No	N/A
Mr Kevin Varty	No	None
Dr Robert Morgan	No	None
Dr Stephen Butterfield	No	None
Ms Janice Tsui	No	N/A

OTHER COMPETING INTERESTS BELIEVED TO BE RELEVANT BUT NOT LISTED ABOVE

None.

NICE National Institute for Health and Care Excellence

National Institute for Health and Care Excellence

Centre for Health Technology Evaluation

Pro-forma Response

External Assessment Centre Report factual check

The IN.PACT drug-coated balloon for femoro-popliteal peripheral arterial disease

Please find enclosed the assessment report prepared for this assessment by the External Assessment Centre (EAC).

You are asked to check the assessment report from [insert EAC] to ensure there are no factual inaccuracies contained within it. If you do identify any factual inaccuracies you must inform NICE by 12pm, **4 December 2017** using the below proforma comments table. All your comments on factual inaccuracies will receive a response from the EAC and when appropriate, will be amended in the EAC report. This table, including EAC responses will be presented to the Medical Technologies Advisory Committee and will subsequently be published on the NICE website with the Assessment report.

29 November 2017

NICE National Institute for Health and Care Excellence

Issue 1

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
The assessment report states that our submission was only partially aligned with the scope issued by NICE and states that "the EAC can conclude that the Sponsor has not performed a meta-analysis based on the scope" which we agree is somewhat accurate, however the report is not sensitive to the fact that we were constrained by the time restraints of the MTEP process, specifically the publication of the final scope.	We respectfully request that the assessment report is sensitive to the fact that the scope was changed significantly at a very late stage.	We apologise that the clinical submission did not fully comply with the scope, especially as it seems to have resulted in significant workload for KiTEC. We would however like to flag that our clinical submission was aligned with the draft scope that was issued on 31st August 2017. The final scope, which was restricted to patients with intermittent claudication, was not shared (in accordance with the MTEP process) with us until the 20th September; this was only 2 weeks before submission deadline; regrettably too late to re-write and commission a new submission. We politely suggest that future iterations of the MTEP process take issues such as this into account in order to prevent avoidable workload and costs for the EAC, NICE and the sponsor.	Thank you for your response. The issue regarding the appropriateness of the meta-analysis relates to the fact that the sponsor did not meta-analyse comparative arms of the included studies. This is not influenced by changes to the scope on the inclusion or exclusion of intermittent claudication.

Issue 2

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
"The definition of intermittent claudication is mainly depended on clinical criteria, the most important of which is the Rutherford score. The score takes values from 1-7, and stages 1-3 refer to claudication (mild to severe), stages equal or above 4 refer to CLI. The EAC asked the clinical experts further clarifications on this criterion. The majority confirmed that Rutherford score equal or above 4 should be categorised as CLI and therefore excluded from the report. As a result of the above, the EAC excluded from the report all studies that included more than 10% population with CLI."	Medtronic believe the assessment report should not have excluded all the studies that included patients with a score of Rutherford 4.	As peripheral arterial disease is a progressive disease, there is no clear cut-off point between IC and CLI and so there is of course a point where the differentiation between the two is difficult to define. Most, if not all, intermittent claudication clinical trials include patients with Rutherford Class 4. Medtronic believes that it is appropriate to include these patients in the analysis. In addition, the inclusion of these studies in the submission is important for the decision-making committee to see. Usually RCC 5&6 would define the CLI population. It is also important to add that including patient data with Rutherford score of 4 is more likely to increase the TLR rate. Therefore, including these studies is in fact a conservative measure. The fact that the results are not improved by the inclusion of Rutherford 4 leads us to believe that the EAC should not have excluded many of the studies. We also feel that an explanation of the rationale behind the decision to exclude all studies that included more than 10% population with CLI would be helpful.	The patient population included in an assessment report is defined by the final scope. As per the final scope the eligible patient population was patients with intermittent claudication. The EAC asked the clinical experts with regards to the definition of CLI and intermittent claudication based on the Rutherford score and the majority of them replied that Rutherford category 4 refers to patients with ischaemic rest pain, which falls within the critical limb ischaemia definition. According to NHS choices section about peripheral artery disease (PAD) (link) "intermittent claudication" is defined as a painful ache in the legs when people with PAD walk, which usually disappears after a few minutes' rest. Furthermore, in the same section it is clarified that

			symptoms of CLI include 'a severe burning pain in your legs and feet that continues even when you're resting'. In addition, NICE's MIB72 defines CLI as resting pain, or the presence of ulcers or gangrene. Based on the above the EAC accepted that patients with Rutherford score equal or higher than 4 should be categorised as CLI. With regards to the points about clinical trials investigating patients with intermittent claudication and a rationale to a cut-off of 10% population with CLI, the EAC asked the clinical experts if the population included in the IN.PACT SFA trial is representative of other SFA trials. There was agreement between the experts that this was the case. The trial included a 5% population with Rutherford score ≥4. In addition, a similar trial the LEVANT 2 had 8% patient population with Rutherford score 4. We therefore based on the above, considered a cut-off of 10% to be in alignment with studies representative of this patient population.

Issue 3

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
Page 18: The sponsor's search did not include 'IN.PACT' as a keyword. There were inconsistencies in the sponsor's PRISMA flow diagram relating to the number of studies removed by de-duplication.	We suggest the sentence "The sponsor's search did not include 'IN.PACT' as a keyword" is corrected. We believe the PRISMA flow diagram is correct considering the explanation provided.	The search did in fact include IN.PACT as a keyword in addition to other keywords that could define a study where IN.PACT DCB was used. Please see Appendix. 1 below. As discussed previously, EMBASE was used as primary search database while Pubmed and the Cochrane Library have been used only to manually search for additional publications looking at the list of references mentioned in the already selected studies. Therefore, since only one main data base has been used, no duplications have been found.	In the sponsor submission and in the screen shot attached here, the keyword 'IN.PACT' is not included. The sponsor did include 'inpact' and 'in pact' but some search databases are sensitive to the full-stop and it is best practice to include it as a variant spelling. The sponsor submission states that "Medline (via PubMed) and Embase"

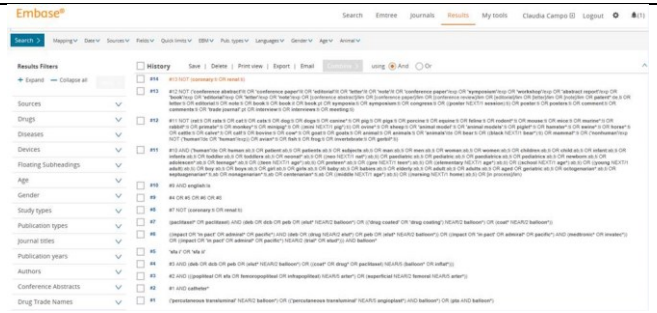
			were searched and the PRISMA does not specify which databases were searched.

Issue 4

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
The Sponsor's meta-analysis included RCT, retrospective and prospective cohort study results, which is not advisable (Higgins et al. 2011).	We suggest rephrasing the section noting that also subgroup analysis regarding the type of study (RCT vs. cohort studies) have been presented.	We would like to note that subgroup meta-analyses have been conducted considering separately RCT from retrospective and prospective cohort studies at 12 and 24 months. Results have been considered comparable in nature (see tables B17 and B18 of the submission). At 24 months only one RCT has been identified and therefore only a global analysis could be conducted. We would also like to take this opportunity to acknowledge the other methodological concerns regarding the meta-analysis. We will ensure that the methodology explained by KiTEC is followed in any future MTEP submissions. We would however like to note that, despite the methodological differences, the IN.PACT TLR result used in our model (17.8%) was very similar to that used in the EACs model (18.6%) and believe that this would have been more similar had the studies excluded by KiTEC been included (please see issue 2). We hope this confirms that there were no perverse intentions in selecting the methodology for our meta-analysis.	The meta-analysis conducted by the sponsor does not retain the randomisation employed by the trials which ensures balance of characteristics between comparator groups. The sponsor's meta-analysis sub-group analysis synthesises information within treatment allocations, but does not explicitly compare the groups.

Issue 5

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
"The full search strategy (sent following a request from the EAC) was labelled 'EMBASE search' but the syntax used is a mixture of Cochrane and Ovid Embase, with filters from a PubMed search, meaning the search would not function in any database."	We suggest the statement "The full search strategy (sent following a request from the EAC) was labelled 'EMBASE search' but the syntax used is a mixture of Cochrane and Ovid Embase, with filters from a PubMed search, meaning the search would not function in any database." is removed from the report.	Medtronic apologise for the difficulty experienced in replicating our search however we would like to note that the search criteria provided was exactly the one used in EMBASE. We have replicated and provided a screen shot of the use of it in EMBASE to show that we were able to replicate at our end (larger screenshot provided in appendix A):	The EAC accepts this amendment; this platform for searching EMBASE is unfamiliar to the EAC.

Issue 6

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
In reference to Laird 2015, the EAC considered that "this RCT, which was fully funded by the sponsor, was subject to some potential sources of bias" and "With regard to the performance bias the EAC would like to note the higher rates of predilation rates in the intervention group compared to standard PTA."	Medtronic would like to provide some further detail to ease any concerns the EAC have flagged in regards to potential sources of bias. We feel that inclusion of these explanations may help the MTAC in their decision making.	We thank the reviewers for their feedback. Regarding the potential bias, Medtronic would like to further explain in detail how bias was controlled. It is unlikely that the study investigators would intentionally over-treat or under-treat patients based on their assigned treatments. Regardless, the study endpoints were designed to minimize the impact of any possible subjectivity in investigators' clinical decision-making. To mitigate the risk of "over-treating" bias, the blinded CEC adjudicated all TLR events for their "clinically-driven" status. Specifically, all patients were required to have been symptomatic or have had a protocol-defined drop in ABI to count as an endpoint failure. There were only two DCB subjects and 1 PTA subject that had only non-clinically-driven TLR events at two years, confirming no significant over-treating bias in the trial. To mitigate the risk of "under-treating" bias, the primary patency endpoint was designed to include any instances of restenosis assessed by the blinded core labs, regardless of whether the patient received an intervention. The rates of predilation were different in the two groups because in subjects enrolled outside the US, predilation was not mandatory and was left up to the discretion of the treating physician per their standard practice. In the case of PTA patients, predilation and treatment can be viewed as the same procedure since the same balloon can be used for multiple dilatations (i.e. both for pre-dilatation and treatment). However, since a DCB can be used only for a single application, predilation with a plain balloon is typically performed (and was mandatory in US subjects in the study) prior to treatment with DCB.	Thank you for your response. In accordance with the NICE proposed tool for methodological quality assessment, performance biases are the systematic differences between groups in the care provided, apart from the intervention under investigation. In this case, the intervention group had higher rates of predilation in comparison with the comparator group. As a result we flagged in our report the presence of this imbalance. The EAC did not suggest that these patients were intentionally over or under-treated but highlighted the presence of the imbalance (the intervention group had more predilation per lesion than the comparator group) and the fact that there may be some risk of bias on the observed treatment effect, however, this is unknown and difficult to quantify.

NICE National Institute for Health and Care Excellence

Issue 7

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
No factual inaccuracy as such, Medtronic would simply like to provide some further information regarding the mortality rates in Laird 2015 in relation to the following comments from the EAC: • This response suggests no obvious conflicts of interest. The other study outcomes, such as thrombosis and primary patency, had denominator values of which the EAC were unable to reproduce. The EAC concludes that this study is at unclear risk of attrition bias. • Whilst the findings in Laird et al. 2015 are concerning, the EAC accepts the assumption of no additional mortality risk.	Whilst the assessment report is accurate in stating that, in relation to the Independent Clinical Events Adjudication Committee "this response suggests no obvious sources of conflict/bias", Medtronic would nevertheless like to provide some further clarification to ease any concerns the EAC and/or MTAC may have regarding the mortality risk.	<u>All-cause mortality not limb-related:</u> o The 2-year mortality rate in the DCB group was 8.1% (16/198) compared to 0.9% (1/106) in the PTA group (p=0.008). While this was a statistically significant result, after a thorough investigation, there is no substantial evidence of treatment limb-related causes. o All deaths were adjudicated by an independent and blinded CEC, and none of the deaths were assessed as device- or procedure-related. <u>PTA mortality rate unusually low</u> o When compared to other published series in a similar patient population, the 2-year mortality rate in the PTA group of the trial was unusually low (0.9%). Typical mortality rates in these trials range from 3.5-11%. On the other hand, the mortality rate of 8.1% for IN.PACT Admiral DCB at two years is consistent with these results. As a comparison, the two-year mortality rate in the DCB arm of the LEVANT 2 Study was 6.9% (19/277). The two-year mortality rate in the LEVANT 2 Study's PTA arm has not been reported. [Laurich, SVS 2015] o The 95% confidence interval for the IN.PACT SFA Trial 2-year mortality rate was [4.7%, 12.8%]. In comparison, the 95% confidence interval for the LEVANT 2 Study was [4.2%, 10.5%]. These data indicate that the observed death rates were similar. o Of note, the differential mortality rate was driven primarily by the US phase, where there were 13 DCB deaths and 0 PTA deaths. In comparison, the mortality rate was more balanced in the European phase of the trial, with 3 DCB deaths and 1 PTA death. Deaths occurred late, with varied causes o The deaths occurred relatively late in the study follow-up, with the median time to death in the DCB group approximately 1.5 years after the index procedure (564.5 days) and at 397 days in the PTA group. o Note that nominal dose pre-clinical testing has shown that no quantifiable drug is identified in the targeted tissue area at 320 days. There were also no instances of CEC-adjudicated paclitaxel-related distal embolic events through 12 months. o The site-reported causes of death were varied and included cardiac arrest (2), CAD, CHF, ischemic cardiomyopathy, respiratory failure (2), sepsis (2), perforated transverse colon secondary to cecal volvulus, cancer, infarction of the right cerebral hemisphere in the anterior and medial flow region, dementia, deterioration of general condition, sudden death, and unknown. The cause of death in the PTA subject was cancer. Mortality rate to be monitored throughout the trial.	The EAC acknowledges the extent to which Medtronic and their independent assessors have explored different mortality rates that were observed, nevertheless, different rates were observed, and the EAC would be remiss not to highlight this. We also would like to highlight the fact that in our conclusions we have stated that 'People treated with IN.PACT SFA had a statistically significant higher mortality at 2 years, however, based on the independent committee that assessed this outcome and the views of the clinical experts, this was not attributed to the intervention.'

		o The differential mortality rate between treatment groups will continue to be monitored in the full five-year follow-up of the IN.PACT SFA Trial.	

Issue 8

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
Page 61 in reference to Laird (2015): The other study outcomes, such as thrombosis and primary patency, had denominator values of which the EAC were unable to reproduce.	Medtronic would like to further explain how different calculations were used for different endpoints in the hope that it may provide some factual support in relation to the statement "The other study outcomes, such as thrombosis and primary patency, had denominator values of which the EAC were unable to reproduce."	We thank the reviewers for their feedback. Please look at issue 6 above, for how potential sources of bias were controlled in the study. Medtronic would like to further explain how different calculations were used for different endpoints. Medtronic used two different calculations approaches, Kaplan Meier survival estimates and proportion rates within the study. In the Kaplan Meier method, the effect of the intervention is assessed by measuring the number of subjects survived (saved) or succeed (not having an event) after that intervention over a period of time. All subject's information are used for the survival rate estimate, which can be affected by subjects under study that are uncooperative and refused to remain in the study or when some of the subjects may not experience the event or death before the end of the study although they would have experienced or died if observation continued, or we lose touch with them midway in the study (censored). The Kaplan-Meier estimate is the simplest way of computing the survival over time in spite of all these difficulties associated with subjects or situations and it doesn't use subject's clinical compliance status directly. For the proportion rates, the rate is calculated using number of subjects had an event divided by number of subjects that were considered as evaluable. The evaluable subjects were those who had an event at any time up to the follow-up window and were included in the numerator and denominator, even if they withdrew or had died prior to the follow-up window or at some point during the 30 day follow up window, therefore, the denominators in these outcome measures were higher than the total patients that remained at 24 months. The subjects' clinical compliance status was not part of the consideration when the event rate is calculated.	Whilst Kaplan-Meier plots are presented, hazard rates; the appropriate effect estimand for survival analyses, are not reported.

Issue 9

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
"The base case costs are generated after selecting the model parametrization which does not distinguish TLR rates for patients undergoing bailout stenting."	We suggest that this sentence is amended to say "The base case costs are generated after selecting the model parametrization which assumes that the TLR rates for patients undergoing bailout stenting is already captured by the TLR rate of POBA and DCB because these patients were not excluded from the included RCTs."	Our base case does distinguish TLR rates for patients undergoing bailout however it makes the qualified assumption that the data already captures this and patients with bailout BMS were not excluded from the RCTs used to give the TLR rates inputted for POBA and DCB.	The EAC are happy to amend the text to provide additional clarity on the modelling in the sponsor's submission as follows "The base case costs are generated after selecting the model parametrization which assumes that the TLR rates for patients undergoing bailout stenting are already captured by the TLR rate estimated for POBA and DCB patients."

Issue 10

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
The EAC applied the sponsor's model with the option enabled in which TLR rates are estimated separately for patients who require bailout stenting. This assumes that the data used to parameterize TLR with either IN.PACT DCB or PTA applies to patients who did not undergo bailout stenting. This reflects the population in Laird et al. 2015 providing the data on RR for TLR with IN.PACT, who were randomised to treatment or control after successful dilatation.	We suggest that the original assumption (without option for separate consideration of TLR after bailout stenting – in line with our original submission) is used for base case computations, as opposed to the EAC's choice to enable the option. We believe the latter should be explored in sensitivity analysis rather than as a base case assumption. This would result in the following Expected cost of technology and comparator (36 months): **PTA with BMS bailout**: Index cost £2,694; TLR cost £1,242; Total cost £3,936 **IN.PACT DCB with BMS bailout**: Index cost £3,504; TLR cost £463; Total cost £3,967 **Difference**: Total cost £31	While it is true that patients in Laird et al, 2015 were randomised to treatment after successful dilatation, the actual provisional (or, "bailout") stenting occurred after randomization. Successful dilatation only refers to successful initial dilatation with a plain balloon. The decision to perform bailout stenting was made after treatment with the randomized therapy, to treat flow-limiting dissections that resulted from use of the index therapy. This is evidenced by the fact that a total of n=220 DCB patients and n=111 POBA patients got treated (see Laird Table 1 – this is after randomization). Per Table 1, 16 of the 220 DCB patients received provisional stenting, and 14 of the 111 POBA patients. Note further that the study-reported TLR rates (Table 2) are in reference to the n=220 and n=111 index treatments, i.e. the reported TLR rate includes, for the DCB strategy, those patients treated with DCB only, AND the patients treated with DCB who received bailout stenting. Same for the POBA strategy. In addition, please note that when physicians perform bail-out stenting, they only stent the segment of the lesion with either recoil or flow-limiting dissection. In most cases, they do not stent the entire length of the target lesion. Therefore, the long-term clinical outcome still depends on DCB, rather than the bail-out stent used to repair the dissection.	The EAC was advised that the use of a drug coated balloon would be unlikely to provide additional benefit in patients for whom bailout stenting was indicated. Consequently, the EAC chose to apply a single TLR rate to all patient receiving bailout stenting (through selecting this option in the sponsor's model). The EAC accepts that the relative risk (taken from Laird et al., 2015) includes patients who received bailout stenting. However, the EAC interpreted the methodology described in Laird et al. to indicate that a significant proportion of patients requiring bailout stenting did not progress to randomisation. On this basis, the EAC opted to apply the RR determined from Laird et al. only to patients for whom bailout stenting was not required. The EAC accepts that this is a conservative assumption. However, if patients requiring bailout stenting after dilatation were excluded from randomisation in Laird et al., the alternative

<table>
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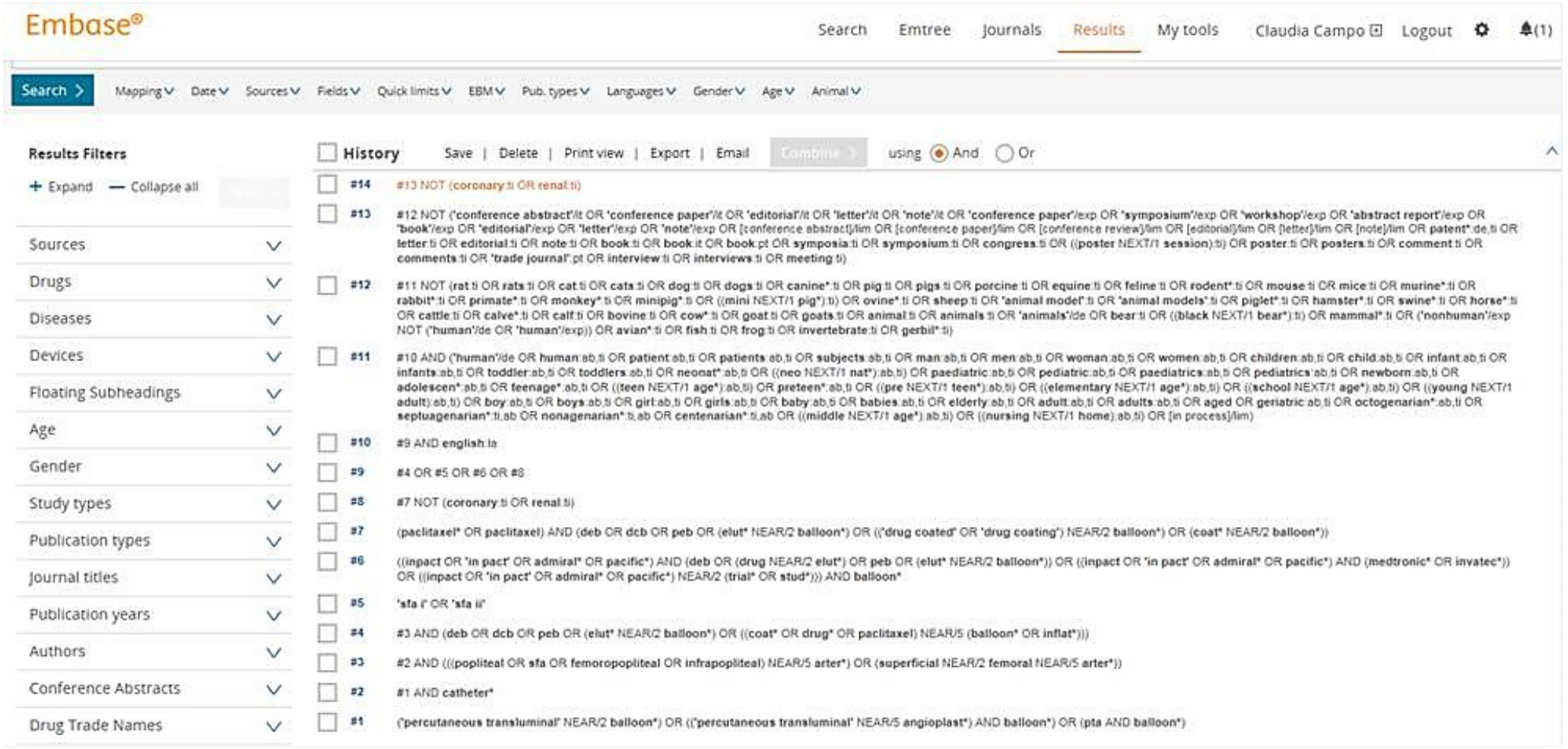
<td>Expected cost of technology and comparator (48 months):
<table>
<tr><th></th><th>Index cost</th><th>TLR cost</th><th>Total cost</th></tr>
<tr><td>PTA with BMS bailout</td><td>£2,694</td><td>£1,456</td><td>£4,150</td></tr>
<tr><td>IN.PACT DCB with BMS bailout</td><td>£3,504</td><td>£575</td><td>£4,080</td></tr>
<tr><td>Difference</td><td></td><td></td><td>-£71</td></tr>
</table>
</td>
<td>As a result, it would be incorrect to apply BMS TLR performance for the stratum of bailout patients, as the EAC did in their revised analysis. This could only be considered if the TLR rates for patients reported with DCB only and POBA only would be available. However, these data are not available from Laird et al, 2015.

The option to consider BMS TLR rates for patients treated with bailout stenting was only embedded in the model to facilitate sensitivity analysis calculations, where the percentage of bailout stenting varies.</td>
<td>approach of applying the RR to all patients regardless of whether bailout stenting occurs would be anti-conservative.</td>
</tr>
</table>

Issue 11

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
The model assigns a utility tariff to estimate QALYs and ICERs. Whilst this is the approach for most technology appraisals, a cost-consequences approach is often adopted for evaluating medical technology programmes (NICE 2011). For this report, the EAC has considered only the cost of the technology and comparators and the resulting cost savings from the sponsor's submission.	We propose that the assessment report does state the ICERs according to the model where the EACs TLR rate for IN.PACT DCB has been adjusted.	Whilst the MTEP Methods guide states that "given the remit of the Programme, the approach expected to be appropriate for most technologies is cost-consequence analysis", we feel it would be within scope and useful for the decision makers on the committee to see that the model estimates an ICER that is well below £10,000/QALY even at a short time horizon.	The EAC have undertaken additional analysis and presented results consistent with the scope of the MTEP Methods guide. The EAC have reported the ICERs estimated using the sponsor's model. The EAC will amend their report to emphasise that these ICERs fall well below traditionally accepted cost-effectiveness thresholds. The following was included in page 71 of the assessment report ''In scenarios where IN.PACT DCB did not dominate PTA, ICERs for IN.PACT DCB all fell below the threshold of £20,000-£30,000 per QALY considered acceptable within the UK NHS.''

Appendix A:



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- Diseases
- Devices
- Floating Subheadings
- Age
- Gender
- Study types
- Publication types
- Journal titles
- Publication years
- Authors
- Conference Abstracts
- Drug Trade Names

History Save | Delete | Print view | Export | Email | Combine > using And Or

#14	#13 NOT (coronary:ti OR renal:ti)
#13	#12 NOT ('conference abstract'/it OR 'conference paper'/it OR 'editorial'/it OR 'letter'/it OR 'note'/it OR 'conference paper'/exp OR 'symposium'/exp OR 'workshop'/exp OR 'abstract report'/exp OR 'book'/exp OR 'editorial'/exp OR 'letter'/exp OR 'note'/exp OR [conference abstract]/lim OR [conference paper]/lim OR [conference review]/lim OR [editorial]/lim OR [letter]/lim OR [note]/lim OR patent*:de,ti OR letter:ti OR editorial:ti OR note:ti OR book:ti OR book:it OR book:pt OR symposia:ti OR symposium:ti OR congress:ti OR ((poster NEXT/1 session):ti) OR poster:ti OR posters:ti OR comment:ti OR comments:ti OR 'trade journal':pt OR interview:ti OR interviews:ti OR meeting:ti)
#12	#11 NOT (rat:ti OR rats:ti OR cat:ti OR cats:ti OR dog:ti OR dogs:ti OR canine*:ti OR pig:ti OR pigs:ti OR porcine:ti OR equine:ti OR feline:ti OR rodent*:ti OR mouse:ti OR mice:ti OR murine*:ti OR rabbit*:ti OR primate*:ti OR monkey*:ti OR minipig*:ti OR ((mini NEXT/1 pig*):ti) OR ovine*:ti OR sheep:ti OR 'animal model':ti OR 'animal models':ti OR piglet*:ti OR hamster*:ti OR swine*:ti OR horse*:ti OR cattle:ti OR calve*:ti OR calf:ti OR bovine:ti OR cow*:ti OR goat:ti OR goats:ti OR animal:ti OR animals:ti OR 'animals'/de OR bear:ti OR ((black NEXT/1 bear*):ti) OR mammal*:ti OR ('nonhuman'/exp NOT ('human'/de OR 'human'/exp)) OR avian*:ti OR fish:ti OR frog:ti OR invertebrate:ti OR gerbil*:ti)
#11	#10 AND ('human'/de OR human:ab,ti OR patient:ab,ti OR patients:ab,ti OR subjects:ab,ti OR man:ab,ti OR men:ab,ti OR woman:ab,ti OR women:ab,ti OR children:ab,ti OR child:ab,ti OR infant:ab,ti OR infants:ab,ti OR toddler:ab,ti OR toddlers:ab,ti OR neonat*:ab,ti OR ((neo NEXT/1 nat*):ab,ti) OR paediatric:ab,ti OR pediatric:ab,ti OR paediatrics:ab,ti OR pediatrics:ab,ti OR newborn:ab,ti OR adolescen*:ab,ti OR teenage*:ab,ti OR ((teen NEXT/1 age*):ab,ti) OR preteen*:ab,ti OR ((pre NEXT/1 teen*):ab,ti) OR ((elementary NEXT/1 age*):ab,ti) OR ((school NEXT/1 age*):ab,ti) OR ((young NEXT/1 adult):ab,ti) OR boy:ab,ti OR boys:ab,ti OR girl:ab,ti OR girls:ab,ti OR baby:ab,ti OR babies:ab,ti OR elderly:ab,ti OR adult:ab,ti OR adults:ab,ti OR aged OR geriatric:ab,ti OR octogenarian*:ab,ti OR septuagenarian*:ti,ab OR nonagenarian*:ti,ab OR centenarian*:ti,ab OR ((middle NEXT/1 age*):ab,ti) OR ((nursing NEXT/1 home):ab,ti) OR [in process]/lim)
#10	#9 AND english:la
#9	#4 OR #5 OR #6 OR #8
#8	#7 NOT (coronary:ti OR renal:ti)
#7	(paclitaxel* OR paclitaxel) AND (deb OR dcb OR peb OR (elut* NEAR/2 balloon*) OR (('drug coated' OR 'drug coating') NEAR/2 balloon*) OR (coat* NEAR/2 balloon*))
#6	((inpact OR 'in pact' OR admiral* OR pacific*) AND (deb OR (drug NEAR/2 elut*) OR peb OR (elut* NEAR/2 balloon*)) OR ((inpact OR 'in pact' OR admiral* OR pacific*) AND (medtronic* OR invatec*)) OR ((inpact OR 'in pact' OR admiral* OR pacific*) NEAR/2 (trial* OR stud*))) AND balloon*
#5	'sfa i' OR 'sfa ii'
#4	#3 AND (deb OR dcb OR peb OR (elut* NEAR/2 balloon*) OR ((coat* OR drug* OR paclitaxel) NEAR/5 (balloon* OR inflat*)))
#3	#2 AND (((popliteal OR sfa OR femoropopliteal OR infrapopliteal) NEAR/5 arter*) OR (superficial NEAR/2 femoral NEAR/5 arter*))
#2	#1 AND catheter*
#1	('percutaneous transluminal' NEAR/2 balloon*) OR (('percutaneous transluminal' NEAR/5 angioplast*) AND balloon*) OR (pta AND balloon*)

National Institute for Health and Care Excellence

External Assessment Centre correspondence

MT336 IN.PACT DCB

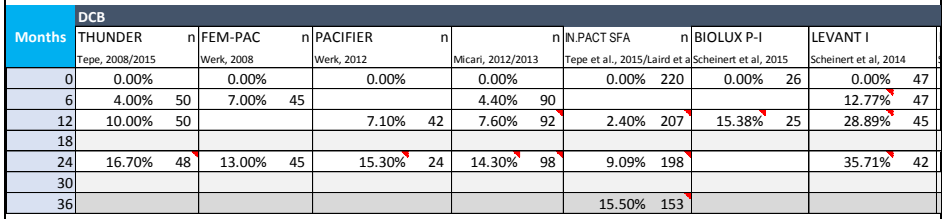
The purpose of this table is to show where the External Assessment Centre relied in their assessment of the topic on information or evidence not included in the sponsors' original submission. This is normally where the External Assessment Centre:

a) become aware of additional relevant evidence not submitted by the sponsor
b) need to check "real world" assumptions with NICE's expert advisers, or
c) need to ask the sponsor for additional information or data not included in the original submission, or
d) need to correspond with an organisation or individual outside of NICE

These events are recorded in the table to ensure that all information relevant to the assessment of the topic is made available to MTAC. The table is presented to MTAC in the Assessment Report Overview, and is made available at public consultation.

Submission Document Section/Sub-section number	Question / Request *Please indicate who was contacted. If an Expert Adviser, only include significant correspondence and include clinical area of expertise.*	Response *Attach additional documents provided in response as Appendices and reference in relevant cells below.*
Clinical evidence section	**Initial questions sent to manufacturer – 09.10.17** 1. The sponsor has submitted clinical evidence from 2 registries located in Italy (the Italian registry and the Prospective registry) is there any overlap between the populations included in these two registries? 2. In section 2.1, page 8, the sponsor claims that: '*The IN.PACT DCB Technology encompasses two DCBs, IN.PACT Admiral DCB and IN.PACT Pacific DCB. The primary difference between IN.PACT Admiral and IN.PACT Pacific is the guidewire compatibility: IN.PACT Admiral is compatible with a 0.035" guidewire and IN.PACT Pacific is compatible with a 0.018" guidewire. This difference provides the physician with expanded options to increase the likelihood of successfully reaching the targeted lesion without impacting the device performance or drug delivery at the target lesion. The clinical evidence generated with IN.PACT Admiral can be convincingly used to demonstrate the safety and effectiveness of IN.PACT Pacific to deliver paclitaxel to the target lesion in the peripheral artery.'* Can the sponsor explain the reasoning for suggesting that the clinical evidence generated for IN.PACT Admiral are generalisable to IN.PACT Pacific? 3. In section 2.2, the sponsor states '*As a result, the efficacy of these devices varies significantly, with some even proven to have no difference in efficacy in comparison to plain balloon angioplasty.'* Can you please provide references for this claim? 4. In section 3.3, the sponsor states that '*This submission recommends the primary use of IN.PACT DCB in place of PTA with or without*	**Responses from manufacturer – 16.10.17** • These are not Medtronic studies, they were performed by physicians independently. We therefore contacted the authors directly who confirmed they are two completely different sets of patients as it is prohibited by Italian law to enroll the same patients for different studies. • The CE marked product IN.PACT Pacific was used for the PACIFIER trial. The main difference between the two platforms is the guidewire compatibility that is 0.035" for IN.PACT Admiral and 0.018" for IN.PACT Pacific. IN.PACT Pacific is coated with the identical FreePac formulation as IN.PACT Admiral. Furthermore the balloon components of the two catheter platforms are composed of identical materials and dimensions, and the FreePac coating is applied to the identical drug dose and volume per balloon surface. Critical IN.PACT Pacific design features which are identical to the IN.PACT Admiral design features: Balloon material, diameters and working lengths Balloon coating formulation (FreePac) Applied coating volume Drug coating procedure and related parameters Paclitaxel drug dose and drug dose density for all sizes Analytical specifications Sterilization method and parameters

Submission Document Section/Sub-section number	Question / Request *Please indicate who was contacted. If an Expert Adviser, only include significant correspondence and include clinical area of expertise.*	Response *Attach additional documents provided in response as Appendices and reference in relevant cells below.*
	bailout BMS, which is currently recommended within the treatment section of the clinical guideline.' Can the sponsor clarify what they mean by '*in place of PTA'*? Our understanding is that the only difference in the scope between the intervention and the comparator is the use of a drug-coated balloon vs. a non-drug coated one. The procedure which is PTA otherwise remains the same. 5. In section 7.1.1 the sponsor states '' *The search terms that have been used individually or combined include "Percutaneous Transluminal Angioplasty", "popliteal", "femoral", "balloon", "in.pact", "paclitaxel" and a string of words previously proposed.''* Can you please clarify if these words are already included in appendix 1 and the reference of previously proposing using these keywords? 6. Can the sponsor provide the full outline of their search strategy for all the databases they searched? Currently, the submission includes the search strategy for Cochrane but not for the other databases used. 7. In section 7.1.2, can the sponsor please provide more detail of how the unpublished material was found e.g. which databases or trials registries were searched and the keywords used. 8. In section 7.2.1, table B1, the sponsor lists the following exclusion criteria under the 'intervention' subheading: a. Patients NOT treated with DCB or b. Patients treated with DCB but not with IN.PACT Admiral or IN.PACT Pacific c. Mixed population	The differences between the two products are considered minor in nature. The two products can be considered substantially equivalent. • The below references show studies where DCBs showed no significant difference in TLR rate versus PTA: **Trial Name** / **DCB** / **Trial Design** / **DCB 12M TLR** / **PTA 12M TLR** / **P-Value** LEVANT 2 / Lutonix / DCB vs. PTA / 12.3% / 16.8% / 0.21 RAPID Trial / Legflow / DCB+Stent vs. Stent / 17% / 22.2% / 0.277 Biolux P1 / Passeo-LUX / DCB vs. PTA / 15.4% / 41.1% / 0.064 The following table shows the TLR rates reported in different studies for different DCBs, as you can see there is variability in the reported TLR rate for different DCBs. Section C, the economic analysis will provide more detail on this.

Submission Document Section/Sub-section number	Question / Request *Please indicate who was contacted. If an Expert Adviser, only include significant correspondence and include clinical area of expertise.*	Response *Attach additional documents provided in response as Appendices and reference in relevant cells below.*
	Can the sponsor please explain what they mean with the term 'mixed population'? 9. Also in section 7.2.1, table B1, can the sponsor explain why they chose to restrict the literature search to English language only and why the date limits are set to 1995? 10. In section 7.2.2, the numbers reported in the PRISMA flowchart the sponsor reports that there were no duplicates as part of their search strategy. How is this possible if both Embase and PubMed were searched? 11. In section 7.2.3, table B2, different search dates were used for the unpublished studies search. Can you please provide the reason for this choice? 12. In section 7.6.7, the sponsor states '*Every study analysed reported superiority in these two clinical end-points across the DCB population.'* Is this in comparison to PTA? 13. Please provide access to the criteria used for methodological quality assessment of the studies included in the clinical evidence submission for both the RCT and observational studies. 14. In section 7.6.6, the sponsor states that 'Fo*r the comparator arm it was not considered appropriate to carry out a meta-analysis using the studies identified via the IN.PACT DCB search criteria because this would exclude some key studies that should be used to calculate pooled estimates of the clinical endpoints for PTA (with or without bailout BMS).'* Can the sponsor provide more details on	 DCB Months / THUNDER Tepe, 2008/2015 / n / FEM-PAC Werk, 2008 / n / PACIFIER Werk, 2012 / n / Micari, 2012/2013 / n / IN.PACT SFA Tepe et al., 2015/Laird et a / n / BIOLUX P-I Scheinert et al, 2015 / LEVANT I Scheinert et al, 2014 0 0.00% 0.00% 0.00% 0.00% 0.00% 220 0.00% 26 0.00% 47 6 4.00% 50 7.00% 45 4.40% 90 12.77% 47 12 10.00% 50 7.10% 42 7.60% 92 2.40% 207 15.38% 25 28.89% 45 18 24 16.70% 48 13.00% 45 15.30% 24 14.30% 98 9.09% 198 35.71% 42 30 36 15.50% 153 • Your understanding is correct. The procedure does remain the same and the only difference between the intervention and the comparator is the use of a drug-coated balloon vs. a non-drug coated one. The term PTA is widely used to mean "PTA with a non-drug coated balloon" and throughout the submission this is what we mean by "PTA". • The words mentioned in qu.5 are included in Appendix 1. They have been selected considering the aim of the project and using the publication of Katsanos et al as reference (Reference 1) • The search strategy included in Appendix 1 is for EMBASE. Pubmed and the Cochrane Library have been used only to manually search for additional publications looking at the list of references mentioned in the already selected studies. • We used an internal record of data that has been presented but as yet has not been published in a peer-reviewed journal. Medtronic keep an internal record of presentations from major conferences

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	their search strategy for retrieving evidence on the comparator if a different search strategy from the intervention was used? 15. Can the sponsor please explain why the pooled estimates for Percutaneous transluminal angioplasty (PTA) from published studies (Katsanos et al 2014, Katsanos et al 2016, Herten et al 2016 and Giacoppo et al 2016) were used as a comparator outside of the meta-analysis? I.e. No meta-analysis included the comparator of PTA with a non-drug coated balloon. 16. Can the sponsor please explain why these studies (Katsanos et al 2014 etc) 'would be appropriate for use for the comparator'? 17. Can the sponsor advise whether Katsanos (2016) assessed the quality of information that it used to determine a pooled estimate and clarify whether the pooled estimates were obtained using a random effect approach? 18. Can the sponsor provide the summary of methodology of the studies which provided pooled estimates for PTA and used to compare to the results of the sponsor s meta-analyses? Ie. Katsanos et al 2014, Katsanos et al 2016, Herten et al 2016, Giacoppo et al 2016. 19. Did the sponsor explore the influence of selection bias in the meta-analysis statistically? i.e. with funnel plots. 20. The report describes that a sensitivity analysis was done according to the type of lesion. Did the sponsor mean to report that this was a subgroup analysis rather than a sensitivity analysis?	where high quality Medtronic- or physician-generated data for IN.PACT DCB was presented. • Mixed population means articles where more than one device model has been used (i.e. articles where bot IN.PACT Admiral and another DCB has been used) • We decided to set a year limit because we wanted to avoid presence of very old articles that could be screened erroneously. Only publications in English were considered since we believed that other languages would have been not comprehensible for all and they are, in many cases, published in local journal with a low impact factor. • Please see answer to question 6 • No database was searched, we used an internal record of data that has been presented but as yet has not been published in a peer-reviewed journal. Medtronic keep an internal record of presentations from major conferences where data from high quality Medtronic- or physician-generated studies for IN.PACT DCB was presented. From these presentations we chose to include only those that presented data which has not yet been published. Any data presented from high quality studies prior to 2009 will now be published and therefore will be included in the published studies. • Yes, it was in comparison with PTA. • We used the checklist proposed by NICE. For RCTs, we then followed the "CRD's guidance for undertaking reviews in health

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	21. Cochrane advises that meta-regression should not be used if there are less than 10 studies contributing to a meta-analysis. Overall, the report has sufficient studies for a meta-regression, but not for the sub-groups. Can the sponsor give a rationale for the meta-regression for the sub-groups as they all have less than 10 studies in each? 22. Can the sponsor confirm that Micari et al 2016 used different patients to Micari et al 2012 (page 76)? 23. What the sponsor means by 'the heterogeneity in the true effects is not related to some of the predictors/moderators included in the model' (page 77)? 24. What the sponsor means by '*as results of the meta-regression model the heterogeneity in the true effects is related to hyperlipidaemia'* (page 78)? 25. An I-square of >50% indicates considerable inconsistency between study estimates. Can the sponsor provide a rationale for meta-analysing with large I-square values? 26. Can the sponsor provide a rationale for the choice of covariates in the meta-regression? 27. On page 86, the sponsor states that '*every study analysed reported superiority'*, when making this statement are the authors comparing their pooled effect estimate against the comparator effect estimate? If this is the case how are they adjusting for differences in characteristics of the populations being compared (bearing in mind that this is not a randomised comparison)?	care" from the Centre for Reviews and Dissemination, University of York, 2008 and in particular Chapter 1, section 1.3.4. For the observational studies we followed the CASP guidelines. • The analyses that have been flagged were pulled from the same search strategy used for the published evidence section and no other analyses that estimated the pooled estimates of PTA were found (i.e. no exclusions). Their search strategies are detailed within the publications. PTA has been the procedure for 30 years and so to do our own meta-analysis for the comparator would have been extensive (well over the 100 pages allocated for the submission). The pooled estimate for PTA will be explored further in section C, the economic analysis. Jan to explain the search strategy used for Katsanos 2016 and how this is being updated for the purpose of the economic section. See Table 3. • Because the search strategy for the published studies was limited to trials including IN.PACT DCB only. We decided it would be more appropriate to use external meta-analyses that included a wider search criteria. As mentioned in question 5, our search criteria was based on the search criteria used in Katsanos 2014 which makes this an appropriate meta-analysis to use for the comparator. Katsanos 2014 is a detailed MA, published in a high-quality peer-reviewed journal, Journal of Vascular Surgery. PTA is the term used for PTA with a non-drug coated balloon. This term is equivalent to Balloon Angioplasty (BA), Plain Balloon (PB), Plain Old Balloon Angioplasty (POBA) and other similar abbreviations. • See qu.15

	Question to manufacturer – 20.10.17 In the sponsor's submission, the exclusion criteria listed in page 14 state that studies including 'Patients with below-the-knee lesion (BTK)' were excluded'. Can you please clarify in what context you list BTK disease as an exclusion as a few of the submitted studies have included populations with BTK disease. For example 42% of the population included in the IN.PACT Global study had BTK disease. In studies where concomitant BTK disease was present do you have additional data on whether these patients received treatment for their BTK in addition to the femoropopliteal lesions?	• The quality of information was not formally assessed in the Katsanos (2016) paper. The pooling estimates for each time period were determined by weighted pooling (i.e., a fixed effect approach). For the current submission, we can apply a random effects approach. Note that we still need to combine the pooled estimates for each follow-up time point by conversion through rates (assuming constant hazard). • Katsanos 2016 explained by Jan Pietzsch Please see Table 2 below for summary. Medtronic are happy to provide a summary of each analysis in a format preferred by NICE if desired? • The conventional proposed methods for evaluation of asymmetry of funnel plot, such as the Egger's linear regression method or the Begg's rank correlation test are not reliable on a set of 11 or less studies (Ref: Higgins JPT, Green S (editors). Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 [updated March 2011]. The Cochrane Collaboration, 2011), also considering that this is a meta-analysis of proportion, the funnel plot was not an accurate method of assessing publication bias. So that, we conducted a univariate meta-regression analysis to investigate whether clinical heterogeneity of studies was associated with the year • Yes, correct. We mean a subgroup analysis of de-novo and ISR patients. •  We had a sample size greater than 10 only considering the overall set of studies and Freedom from TLR at 12 months outcome. It would be preferable to have a sample size greater than it was, but

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		mainly for the health economic analysis, we needed to consider at least a 2-yrs horizon (TLR and Primary patency at 24 months). In order to have a more detailed picture and taking into account important elements such as the nature of the study (RCTs, Prospective and Retrospective Cohort studies) or the characteristics of the lesions (De novo or ISR) we performed a univariate meta-regression analysis. We showed all the results, but obviously, the small sample size must always be considered. • Yes • We conducted a univariate meta-regression analysis to investigate whether clinical heterogeneity of study was associated with the covariates reported in the papers, in particular: the lesion length, age, gender (male), smoking habit, hyperlipidemia, hypertension and diabetes. When some of the covariates were statistically associated with the outcome, the p-value was reported. In this case, no statistically significant variables were found. • According to the previous answer, in this case the variable hyperlipidemia was statistically significant. (Again, always considering the small sample). • Cochrane (Ref: Higgins JPT, Green S (editors). Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 [updated March 2011]. The Cochrane Collaboration, 2011)) reports the following thresholds as a rough guide to interpretation of I2: 0% to 40%: might not be important, 30% to 50%: may represent moderate heterogeneity,

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		60% to 90%: may represent substantial heterogeneity, 75% to 100%: considerable heterogeneity. We performed meta-analysis to evaluate the I2 for each set of studies and only a couple of models had an I2 greater than 75%. We showed all the results to present a complete picture. • The covariates selected for the meta-regression were the most known risk factors and consequently more frequently reported in the considered papers. • This statement was based on the results reporting on the selected RCTs comparing DCB with PTA. A direct comparison has not been conducted through the meta-analysis since we only selected studies where IN.PACT DCB were used without taking in consideration which was the comparator. **Response from manufacturer – 20.10.17** • In all studies, when we say BTK patient is excluded, we meant that if the **target lesion** is in BTK (meaning that the primary lesion indicated for treatment), they are excluded from the study. • However, many PAD patients have multi-level disease, meaning they have lesions in both SFA and BTK. • In IN.PACT Global, 42% of patients have concurrent BTK disease, meaning that in addition to SFA lesions, they also have BTK lesions. However, none of these BTK lesions were the target lesions, and none were treated with IN.PACT DCB. • I believe in the IN.PACT Global (as well as other IN.PACT studies), it is required to have at least 1 vessel run-off to the foot, this means

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		at least 1 BTK vessel needs to be patent – otherwise if there is no patent distal run-off, it will thrombose the treated segment proximal to it. • With regards to whether these concurrent BTK lesions were treated with PTA, I do not know if we collect that data. Awaiting clarification from the US team in Eric's absence. • Based on the IN.PACT Global CRF, what we can get is how many of subjects had BTK disease in the past, and some of these subjects may have been treated in the past, but none of these data can be identified as directly related to the subjects treated during the index procedure, in other words, the subjects were enrolled with intention to treat SFA lesions, and any subjects with intention of treating the BTK lesions during the index procedure should be excluded:

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Risk Factors

Hypertension:	O Yes	O No	O Unknown
Hyperlipidemia:	O Yes	O No	O Unknown
Diabetes Mellitus[13]:	O Yes	O No	O Unknown
If yes, is subject insulin dependent:	O Yes	O No	
Smoking:	O Active	O Previous	O Never
Renal Insufficiency[14]:	O Yes	O No	O Unknown
If yes, is subject on dialysis:	O Yes	O No	
Carotid Artery Disease:	O Yes	O No	O Unknown
Coronary Heart Disease:	O Yes	O No	O Unknown
Below the knee vascular disease, Right limb:	O Yes	O No	O Unknown
Below the knee vascular disease, Left limb:	O Yes	O No	O Unknown

Previous Revascularization and Amputation

Previous peripheral revascularization in a location listed below[15]: O Yes O Yes, however, location is not listed O No

If Yes:

Location:	Revascularization
Right Superficial femoral:	☐ PTA ☐ DEB ☐ BMS ☐ DES ☐ Surgery ☐ Other, specify:_____
Left Superficial femoral:	☐ PTA ☐ DEB ☐ BMS ☐ DES ☐ Surgery ☐ Other, specify:_____
Right Popliteal:	☐ PTA ☐ DEB ☐ BMS ☐ DES ☐ Surgery ☐ Other, specify:_____
Left Popliteal:	☐ PTA ☐ DEB ☐ BMS ☐ DES ☐ Surgery ☐ Other, specify:_____
Right Iliac:	☐ PTA ☐ DEB ☐ BMS ☐ DES ☐ Surgery ☐ Other, specify:_____
Left Iliac:	☐ PTA ☐ DEB ☐ BMS ☐ DES ☐ Surgery ☐ Other, specify:_____
Right Common femoral:	☐ PTA ☐ DEB ☐ BMS ☐ DES ☐ Surgery ☐ Other, specify:_____
Left Common femoral:	☐ PTA ☐ DEB ☐ BMS ☐ DES ☐ Surgery ☐ Other, specify:_____
Right Femoral profunda:	☐ PTA ☐ DEB ☐ BMS ☐ DES ☐ Surgery ☐ Other, specify:_____
Left Femoral profunda:	☐ PTA ☐ DEB ☐ BMS ☐ DES ☐ Surgery ☐ Other, specify:_____
Right BTK arteries:	☐ PTA ☐ DEB ☐ BMS ☐ DES ☐ Surgery ☐ Other, specify:
Left BTK arteries:	☐ PTA ☐ DEB ☐ BMS ☐ DES ☐ Surgery ☐ Other, specify:_____

Previous limb amputation[16]: O Yes O No

Right limb:	O None	O Toe	O Transmetatarsal	O Below the knee	O Above the knee
Left limb:	O None	O Toe	O Transmetatarsal	O Below the knee	O Above the knee

- For the published studies, Claudia has responded with the following:

  In the DEBELLUM Study patients with BTK lesions received the same treatment of patients with SFA lesions (that sometimes had a primary stenting before DEB implant) however IN.PACT Admiral was used for femoropopliteal lesions and the IN.PACT Amphirion for BTK lesions. When data allow, results have been reported only

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		for SFA (**i.e. "Primary Endpoint – Lumen Loss" on pag. 62 is only for SFA lesions**). A note is reported when results included both SFA and BTK lesions.
	Questions to experts advisers – 24.10.17 1. The sponsor claims that from a technical point of view, ''the clinical evidence generated with IN.PACT Admiral can be convincingly used to demonstrate the safety and effectiveness of IN.PACT Pacific to deliver paclitaxel to the target lesion in the peripheral artery.'' Do you think this statement is correct? 2. The sponsor included a number of studies with patients having a Rutherford score of equal or more than 4. Is that representative of a patient with intermittent claudication or critical limb ischaemia? 3. Is the population included in the IN.PACT SFA trial representative of other SFA trials? 4. In the IN.PACT SFA trial randomization occurred after successful crossing of the lesion in the IN.PACT SFA I phase and after successful crossing and pre-dilatation with a standard PTA balloon in II phase. How can this difference affect the results of the study? 5. Can patient populations with in-stent restenosis be regarded as similar to patients with de novo stenosis if all other baseline characteristics are the same? As the sponsor submitted a number of studies that looked at only patients with in-stent restenosis we are trying to clarify whether we can pool this data together into a meta-analysis. 6. What is the impact of concomitant below-the knee disease in patients with femoropopliteal lesions?	**Response from Dr Paul Scott – 24.10.17** 1. The sponsor claims that from a technical point of view, ''the clinical evidence generated with IN.PACT Admiral can be convincingly used to demonstrate the safety and effectiveness of IN.PACT Pacific to deliver paclitaxel to the target lesion in the peripheral artery.'' Do you think this statement is correct? Yes. 2. The sponsor included a number of studies with patients having a Rutherford score of equal or more than 4. Is that representative of a patient with intermittent claudication or critical limb ischaemia? Critical limb ischaemia. 3. Is the population included in the IN.PACT SFA trial representative of other SFA trials? Yes. 4. In the IN.PACT SFA trial randomization occurred after successful crossing of the lesion in the IN.PACT SFA I phase and after successful crossing and pre-dilatation with a standard PTA balloon in II phase. How can this difference affect the results of the study? This is standard practise. However it is a potential source of bias if the control group received only single balloon inflation. 5. Can patient populations with in-stent restenosis be regarded as similar to patients with de novo stenosis if all other baseline characteristics are the same? As the sponsor submitted a number of studies that looked at only patients with in-stent restenosis we

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		are trying to clarify whether we can pool this data together into a meta-analysis. No different groups. 6. What is the impact of concomitant below-the knee disease in patients with femoropopliteal lesions? Severe below the knee disease is an independent predictor of fem-pop revascularisation. **Response from Dr James Lenton – 24.10.17** 1. The sponsor claims that from a technical point of view, ''the clinical evidence generated with IN.PACT Admiral can be convincingly used to demonstrate the safety and effectiveness of IN.PACT Pacific to deliver paclitaxel to the target lesion in the peripheral artery.'' Do you think this statement is correct? Yes 2. The sponsor included a number of studies with patients having a Rutherford score of equal or more than 4. Is that representative of a patient with intermittent claudication or critical limb ischaemia? 4 is sever claudication, >4 is critical limb ischemia. Patients in class 4 though may some develop CLI 3. Is the population included in the IN.PACT SFA trial representative of other SFA trials? Yes 4. In the IN.PACT SFA trial randomization occurred after successful crossing of the lesion in the IN.PACT SFA I phase and after successful crossing and pre-dilatation with a standard PTA balloon in II phase. How can this difference affect the results of the study? Not sure it does, the limiting step is usually crossing the lesion therefore if the same patient was in the phase I or II trial they should both get to randomisation. Thus probably this same provided a. No patients were then excluded in the phase II trial on

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		the basis of the outcome of pre-dilation and b. patients in Phase II randomised to POBA got a further normal sized PTA. 5. Can patient populations with in-stent restenosis be regarded as similar to patients with de novo stenosis if all other baseline characteristics are the same? As the sponsor submitted a number of studies that looked at only patients with in-stent restenosis we are trying to clarify whether we can pool this data together into a meta-analysis. I do not think so as the pathology is potentially different - Atherosclerotic disease Vs neo intimal hyperplasia. 6. What is the impact of concomitant below-the knee disease in patients with femoropopliteal lesions? Patients with CLI may not get clinical improvement if femoropoplital disease is treated in isolation in the presence of significant below the knee disease. **Response from Dr Trevor Cleveland – 25.10.17** 1. The sponsor claims that from a technical point of view, ''the clinical evidence generated with IN.PACT Admiral can be convincingly used to demonstrate the safety and effectiveness of IN.PACT Pacific to deliver paclitaxel to the target lesion in the peripheral artery.'' Do you think this statement is correct? I would have thought that the CE marking studies are those that show that the device is safe, and that it effectively transfers drug to the artery wall. The clinical data confirms the safety. The data indicates the clinical outcomes, which are sufficiently robust, to my mind, to show an improvement in success and reduce the clinically driven target revascularisation, which is a reflection of patient requirements. To that end the data do show effectiveness

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		measures. The cost effectiveness analysis (in the BMJ Open) would suggest that this is within the level that would usually be considered reasonable (I am conflicted as I was an author of this paper). 2. The sponsor included a number of studies with patients having a Rutherford score of equal or more than 4. Is that representative of a patient with intermittent claudication or critical limb ischaemia? Rutherford 4 is defined as "rest pain" and therefore is critical limb ischaemia. A score of greater than 4 is more profound ischaemia, including tissue loss. 3. Is the population included in the IN.PACT SFA trial representative of other SFA trials? SFA disease is notoriously variable, but from my understanding it is a similar group of patients to other studies. 4. In the IN.PACT SFA trial randomization occurred after successful crossing of the lesion in the IN.PACT SFA I phase and after successful crossing and pre-dilatation with a standard PTA balloon in II phase. How can this difference affect the results of the study? I don't think that this is definitely any different, it is very rare for a balloon not to inflate in the SFA. The point, I think of the requirement in the phase II trial, is that the distribution of drug is better if there has been predilatation, and the phase I trial "allowed" a window for investigators to omit the predilatation. This is not the practice indicated in the IFU. 5. Can patient populations with in-stent restenosis be regarded as similar to patients with de novo stenosis if all other baseline characteristics are the same? As the sponsor submitted a number of studies that looked at only patients with in-stent restenosis we

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		are trying to clarify whether we can pool this data together into a meta-analysis. No, in-stent restenosis (neointimal hyperplasia) is a different pathological process than de-novo disease (atheroma). 6. What is the impact of concomitant below-the knee disease in patients with femoropopliteal lesions? It is generally accepted, and there is evidence from many years ago (Wayne-Johnston et al if I recall), that for such lesions the inflow and outflow affect the success of SFA treatments. Thus most trials will require that the inflow has been maximised and that there is at least 1 runoff vessel (without a significant stenosis within it). Treatment of the runoff may be allowed at the same time in some trials. Thus there are many variables in the success and durability of SFA treatments, which makes studies very difficult to construct to remove all but one variable, and to have sufficient patients to complete the trial. **Response from Dr Peter Holt – 29.10.17** 1. The sponsor claims that from a technical point of view, ''the clinical evidence generated with IN.PACT Admiral can be convincingly used to demonstrate the safety and effectiveness of IN.PACT Pacific to deliver paclitaxel to the target lesion in the peripheral artery.'' Do you think this statement is correct? Yes – it is just a different wire platform (0.035 vs 0.018)

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		2. The sponsor included a number of studies with patients having a Rutherford score of equal or more than 4. Is that representative of a patient with intermittent claudication or critical limb ischaemia? CLI. The evidence for DCBs in CLI is unproved in terms of preventing amputation 3. Is the population included in the IN.PACT SFA trial representative of other SFA trials? Broadly yes. Mainly claudicants with short lesions (8cm) and most stenotic rather than occlusions (up to 30%). The extent to which this reflects clinical practice requires investigation as really most are CLI rather than claudication. 4. In the IN.PACT SFA trial randomization occurred after successful crossing of the lesion in the IN.PACT SFA I phase and after successful crossing and pre-dilatation with a standard PTA balloon in II phase. How can this difference affect the results of the study? Yes – if you randomise after pre-dilation you have already removed those cases that have not responded well to POBA and need stenting, which will exaggerate the benefit of the DCB 5. Can patient populations with in-stent restenosis be regarded as similar to patients with de novo stenosis if all other baseline characteristics are the same? As the sponsor submitted a number of studies that looked at only patients with in-stent restenosis we are trying to clarify whether we can pool this data together into a meta-analysis. No, they are very different, and should be analysed separately

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		6. What is the impact of concomitant below-the knee disease in patients with femoropopliteal lesions? BTK disease is more indicative of CLI, and diabetic vascular disease. Disease progression, clinical progression and amputation are far more likely with BTK, or combined BTK/SFA disease. **Response from Ms Janice Tsui – 30.10.17** 1. The sponsor claims that from a technical point of view, ''the clinical evidence generated with IN.PACT Admiral can be convincingly used to demonstrate the safety and effectiveness of IN.PACT Pacific to deliver paclitaxel to the target lesion in the peripheral artery.'' Do you think this statement is correct? ○ The technology in terms of drug delivery and formulation is the same for both the Admiral and Pacific balloons, so I think it is a reasonable statement to make. 2. The sponsor included a number of studies with patients having a Rutherford score of equal or more than 4. Is that representative of a patient with intermittent claudication or critical limb ischaemia? ○ Rutherford category 4 refers to patients with ischaemic rest pain – which falls within the critical limb ischaemia definition. 3. Is the population included in the IN.PACT SFA trial representative of other SFA trials? ○ Yes, similar in that more patients had claudication then ischaemic rest pain.

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		4. In the IN.PACT SFA trial randomization occurred after successful crossing of the lesion in the IN.PACT SFA I phase and after successful crossing and pre-dilatation with a standard PTA balloon in II phase. How can this difference affect the results of the study? o I think as this was a planned difference and no significance difference in outcome was identified in the 2 phases, there was probably minimal effect on the results. 5. Can patient populations with in-stent restenosis be regarded as similar to patients with de novo stenosis if all other baseline characteristics are the same? As the sponsor submitted a number of studies that looked at only patients with in-stent restenosis we are trying to clarify whether we can pool this data together into a meta-analysis. o I think in-stent restenosis is not the same as de novo stenosis. The former is becoming increasingly significant due to increased used of stents. So the pooled data as well as separate data would be important. 6. What is the impact of concomitant below-the knee disease in patients with femoropopliteal lesions? o I think this becomes more relevant when talking about Rutherford 4,5,6 (rest pain and tissue loss) where patients will have concomitant disease that need to be treated for clinical benefit. **Response from Dr Stephen Butterfield – 31.10.17** 1. The sponsor claims that from a technical point of view, ''the clinical evidence generated with IN.PACT Admiral can be convincingly used to demonstrate the safety and effectiveness of IN.PACT Pacific to

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		deliver paclitaxel to the target lesion in the peripheral artery.'' Do you think this statement is correct? YES 2. The sponsor included a number of studies with patients having a Rutherford score of equal or more than 4. Is that representative of a patient with intermittent claudication or critical limb ischaemia? Rutherford 4, 5 & 6 represent critical limb ischaemia 3. Is the population included in the IN.PACT SFA trial representative of other SFA trials? Yes in that it contains predominantly patients with claudication. BASIL 3 Trial which is currently recruiting is looking at patients with critical limb ischaemia only. 4. In the IN.PACT SFA trial randomization occurred after successful crossing of the lesion in the IN.PACT SFA I phase and after successful crossing and pre-dilatation with a standard PTA balloon in II phase. How can this difference affect the results of the study? Randomisation technique was chosen to minimise use of bail-out stenting which could have biased outcomes. This strategy may limit its effectiveness when rolled out to general use outside of clinical trial parameters as device may be used in patients who don't have successful / any predilatation. IN.PACT Global Registry results may support this point. 5. Can patient populations with in-stent restenosis be regarded as similar to patients with de novo stenosis if all other baseline characteristics are the same? As the sponsor submitted a number of studies that looked at only patients with in-stent restenosis we are trying to clarify whether we can pool this data together into a meta-analysis. In-stent restenosis isn't usually considered as similar to de-novo stenosis.

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		6. What is the impact of concomitant below-the knee disease in patients with femoropopliteal lesions? Poor / no outflow vessels below the knee is generally considered to have an adverse impact on outcomes following femoropopliteal intervention. **Response from Dr Nadeem Shaida – 01.11.17** 1. The sponsor claims that from a technical point of view, ''the clinical evidence generated with IN.PACT Admiral can be convincingly used to demonstrate the safety and effectiveness of IN.PACT Pacific to deliver paclitaxel to the target lesion in the peripheral artery.'' Do you think this statement is correct? They have laboratory data which demonstrates the drug is delivered to the artery. The clinical data is less convincing because there is no way of knowing how much of the clinical improvement is due to the angioplasty and how much is due to the drug. Competitor products like the Ranger balloon from Boston scientific claim to be "drug eluting" rather than "drug coated" with prolonged drug dispersion profile but again it is virtually impossible to clinically verify this. 2. The sponsor included a number of studies with patients having a Rutherford score of equal or more than 4. Is that representative of a patient with intermittent claudication or critical limb ischaemia? Rutherford 1-3 includes intermittent claudication patients. Patients with 5 and 6 have ulceration (CLI). Patients with Rutherford 4 have rest pain which is in between – some studies count these as CLI, some will include them in the IC group.

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		3. Is the population included in the IN.PACT SFA trial representative of other SFA trials? yes 4. In the IN.PACT SFA trial randomization occurred after successful crossing of the lesion in the IN.PACT SFA I phase and after successful crossing and pre-dilatation with a standard PTA balloon in II phase. How can this difference affect the results of the study? Some operators will base their decision algorithm on how the artery responds to plain angioplasty – if it looks bad (dissection or vessel recoil) after plain angioplasty the theory is that drug balloon will still be suboptimal and the patient is better off with stenting. This may have influenced decision making between the phases 5. Can patient populations with in-stent restenosis be regarded as similar to patients with de novo stenosis if all other baseline characteristics are the same? As the sponsor submitted a number of studies that looked at only patients with in-stent restenosis we are trying to clarify whether we can pool this data together into a meta-analysis. No – having restenosed the patient is on a path to worse outcomes generally. Sometimes external factors eg. smoking status can be related to chance of restenosis. Essentially the presence of a foreign body changes the baseline to make comparison with de novo stenosis unhelpful.

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		6. What is the impact of concomitant below-the knee disease in patients with femoropopliteal lesions? Unclear – again decision making varies – if significant SFA/pop disease, some operators will treat these first and see what happens. Others will aggressively treat all disease. Huge variation in practice makes it very difficult to understand what the effect is. On the other hand there is evidence demonstrating that if there is iliac and SFA/pop disease, treating the iliac disease first helps. **Response from Mr Kevin Varty – 01.11.17** 1. The sponsor claims that from a technical point of view, ''the clinical evidence generated with IN.PACT Admiral can be convincingly used to demonstrate the safety and effectiveness of IN.PACT Pacific to deliver paclitaxel to the target lesion in the peripheral artery.'' Do you think this statement is correct? I think the safety and ability to deliver some Paclitaxel to the artery wall is accepted. 2. The sponsor included a number of studies with patients having a Rutherford score of equal or more than 4. Is that representative of a patient with intermittent claudication or critical limb ischaemia? Rutherford 4 – claudication. Rutherford 5/6 critical ischaemia. So the numbers of 5/6 are important in terms of establishing outcome for critical ischaemia. 3. Is the population included in the IN.PACT SFA trial representative of other SFA trials? Yes other SFA trial include similar patients. 4. In the IN.PACT SFA trial randomization occurred after successful crossing of the lesion in the IN.PACT SFA I phase and after successful crossing and pre-dilatation with a standard PTA balloon

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		in II phase. How can this difference affect the results of the study? I don't feel this makes a large difference to the trial. When lesions cannot be crossed and dilated they will not be treated with any angioplasty so that subgroup is not relevant to the question plain balloon or drug balloon better outcome? 5. Can patient populations with in-stent restenosis be regarded as similar to patients with de novo stenosis if all other baseline characteristics are the same? As the sponsor submitted a number of studies that looked at only patients with in-stent restenosis we are trying to clarify whether we can pool this data together into a meta-analysis. In stent restenosis is pathologically different and I would not want to see those studies combined with the outcomes for denovo lesions. 6. What is the impact of concomitant below-the knee disease in patients with femoropopliteal lesions? More extensive below the knee run off disease will reduce patency in the SFA segment. So this should be similar in the groups being compared. Alternatively the below knee disease should be treated at the same time as the SFA disease – which is often what occurs in reality for critical limb ischaemia pateints less so for claudicants.

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	Question to manufacturer – 24.10.17 I have a follow-up question about IN.PACT Global, although the exclusion criteria list Rutherford 5-6, the patient baseline characteristics include score 5. Do you have further information on this?	**Response from manufacturer – 26.10.17** RC5 patients were considered protocol deviations as only patients with RC2-4 were allowed. However, at the moment the patient signed and dated informed consent and when the guidewire crossed the lesion, we kept the subject in the study. Therefore you will also see I&E violations.
	Question to manufacturer – 30.10.17 Do you have any information regarding the synthesis of the independent committee that assessed outcomes in the IN.PACT SFA trial and whether or not they declared any conflicts of interest?	**Response from manufacturer – 30.10.17** Attached is the language from the CEC MOP, I specifically highlighted the conflict of interest piece: **'**Each member shall not have any other real or potential conflicts of interest and shall not be involved in the conduct of the study except through their role on the CEC. Each member shall have no undisclosed financial or other significant connections to Medtronic Inc. or its Affiliates, including Invatec SpA ("Medtronic Invatec") or other study organizers, and shall not be affiliated with said bodies, associated, core laboratories, the data coordinating center, the principal investigators or any related entity participating in Study.'
Economic evidence section	**Questions to manufacturer – 06.11.17:** 1. According to a 2014 conference abstract by Werk et al. entitled 'The PACIFIER trial. A randomized multicenter trial evaluating prevention of restenosis with paclitaxel-coated PTA balloon catheters in stenosis or occlusion of femoropopliteal arteries: first report of the 3 year follow up results', 3 year follow up results were	**Response from manufacturer – 10.11.17** 1. Because this is a physician-sponsored study, Medtronic has no control over when the physicians ultimately decide to publish or present the results. Eric has searched our internal database of presentations and manuscripts and has not been able to find the data, he only has the PACIFIER 6 month VIVA presentations and 12 month CircCV paper. He did

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	made available in September 2014, however, we could not locate them. Do you have a copy of these results? 2. The economic model included in the submission allows the selection of Bare Metal Stenting. Can I confirm first that this option refers to bailout stenting for the primary procedure? Selecting the option reduces the trimonthly risk of TLR for POBA – this would appear appropriate. However, selecting the option increases the risk of TLR with DCB. Can the company explain the logic behind this?	send over this link however it unfortunately does not provide an answer to your question: http://www.endovascularmagazine.eu/articles/2015-01/IN.PACT-drug-coated-balloon-for-femoropopliteal-revascularization/index.htm. **Response from manufacturer – 09.11.17** Yes, this option refers to bailout stenting in the index procedure. We incorporated this choice for sensitivity analyses, as one could argue that, once a stent has been placed, the TLR performance of BMS should apply. Under this assumption, the POBA results indeed get better, and the DCB results worse, as the BMS TLR rates are higher than the DCB TLR rates. We opted to not implement this approach in the base case, though, as the study-reported TLR rates (e.g., in IN.PACT SFA) do incorporate the performance in these stented patients in their overall reported TLR rates. Furthermore, one could argue that DCB plus stent might perform better than POBA plus stent.
	Questions to expert advisers – 07.11.17 • Is bail-out stenting routinely undertaken where the primary intervention is perceived to have been unsuccessful? • Is it biologically plausible that the use of a second drug coated balloon, in addition to the standard procedure, would lead to a reduction in the need for bail-out stenting?	**Response from Dr Stephen Butterfield – 07.11.17** • Is bail-out stenting routinely undertaken where the primary intervention is perceived to have been unsuccessful? Yes • Is it biologically plausible that the use of a second drug coated balloon, in addition to the standard procedure, would lead to a reduction in the need for bail-out stenting? The reason for bail

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	• Is an assumption of 1.4 balloons, on average, plausible? If not, how many balloons are needed on average?	out stenting is usually either failure of the angioplasty (artery lumen fails to dilate sufficiently) or a flow limiting dissection. The drug coating on the balloon isn't designed / intended to address either of these conditions so insertion of a second drug coated balloon wouldn't appear logical. Prior to wider use of bailout stenting prolonged lower pressure inflation with standard angioplasty balloon was used to try to treat flow limiting dissections but stenting produces better outcomes. • Is an assumption of 1.4 balloons, on average, plausible? If not, how many balloons are needed on average? Our centres presented data showed an average of 1.5 balloons per case – so yes. **Response from Dr Trevor Cleveland – 07.11.17** • Yes bail out stenting is the prescribed NICE guidance • Not sure I understand you scenario. If someone has done a PTA, and feels that the result is the best that they can do with a balloon, and it's not sufficient, then they need a stent (bare metal or DES) to hold the artery open. The drug is simply there to try to reduce restenosis, which happens much later. So a DEB after PTA, at the time of primary procedure would be pointless, should have used DEB first time around if drug elution is considered effective. Does that make sense? Happy to talk if I'm misunderstanding your question.

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		• At the moment the balloons are a given length. At the moment, I think the longest In-Pact balloon is 150mm long. You need to treat the entire length of the diseased artery, so often the length of disease is longer, so more than 1 balloon is needed. 1.4 is about reasonable to my mind. **Response from Dr James Lenton – 07.11.17** • Is bail-out stenting routinely undertaken where the primary intervention is perceived to have been unsuccessful? May vary with different operators. I would bail out stent in CLI if no better or looked worse post angioplasty. In Claudication I would probably only stent if appearance worse after angioplasty. • Is it biologically plausible that the use of a second drug coated balloon, in addition to the standard procedure, would lead to a reduction in the need for bail-out stenting? I don't think so - the idea behind DEB is a reduction in re stenosis rather than the immediate appearance which is due to the angioplasty alone and therefore a 2nd DEB is unlikely to improve this. • Is an assumption of 1.4 balloons, on average, plausible? If not, how many balloons are needed on average? I don't really know but 1.4 sounds about right but again would vary with individuals practice as long length treatments will need more balloons.

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		Response from Dr Peter Holt – 07.11.17 • Is bail-out stenting routinely undertaken where the primary intervention is perceived to have been unsuccessful? Stenting is used if there is residual stenosis that is resistant to reballooning, or where there is a flow limiting dissection. • Is it biologically plausible that the use of a second drug coated balloon, in addition to the standard procedure, would lead to a reduction in the need for bail-out stenting? No. The reasons for stenting are mechanical, the drug is to prevent long term recurrence. DCB and stenting are complementary not alternatives • Is an assumption of 1.4 balloons, on average, plausible? If not, how many balloons are needed on average? No. The lesion length varies hugely as do balloon lengths! **Responses from Dr Paul Scott – 09.11.17** • Is bail-out stenting routinely undertaken where the primary intervention is perceived to have been unsuccessful? Yes, in our practice. • Is it biologically plausible that the use of a second drug coated balloon, in addition to the standard procedure, would lead to a reduction in the need for bail-out stenting? No, should lead to a reduction in restenosis after successful angioplasty, but lesions which show significant recoil are likely to still show significant recoil after second ballooning making bail out with stent lilkely.

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		• Is an assumption of 1.4 balloons, on average, plausible? If not, how many balloons are needed on average? To clarify is this total balloons or DEB. If DEB this is probably reasonable per case, yes. **Response from Janice Tsui – 09.11.17** • Is bail-out stenting routinely undertaken where the primary intervention is perceived to have been unsuccessful? *Yes – or suboptimal* • Is it biologically plausible that the use of a second drug coated balloon, in addition to the standard procedure, would lead to a reduction in the need for bail-out stenting? *Possible but with the appropriate pre-dilatation times, this effect is unlikely to be significant* • Is an assumption of 1.4 balloons, on average, plausible? If not, how many balloons are needed on average? *Yes this is plausible. No. of balloons depend on length of lesion and length of balloons, but given the range of balloons available, I think this is a reasonable average* **Response from Dr Nadeem Shaida – 09.11.17** • Is bail-out stenting routinely undertaken where the primary intervention is perceived to have been unsuccessful? Yes generally - it depends on why the procedure was unsuccessful. If the lesion has

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	Question to expert advisers – 09.11.17	been crossed and angioplastied either with plain or drug balloon and there is a suboptimal result with dissection or recoil then most operators would use a stent. If the lesion was not able to be crossed the one cannot safely stent it regardless. In claudicants some operators will be reluctant to stent regardless of angioplasty result - there may then be a discussion with surgical colleagues about bypass. This discussion may relate to position of the stent - it may reduce future surgical options eg. convert a fem-above knee pop bypass to a fem-below knee pop bypass. • Is it biologically plausible that the use of a second drug coated balloon, in addition to the standard procedure, would lead to a reduction in the need for bail-out stenting? Unlikely - as above the indication is usually dissection or recoil causing suboptimal result. At this stage the patient will have had the plain balloon for pre dilatation and a prolonged inflation with the drug balloon. Further drug balloon is unlikely to help. • Is an assumption of 1.4 balloons, on average, plausible? If not, how many balloons are needed on average? 1.4 drug balloons would be a plausible figure. Lesions range from any length up to 30cm plus. The Medtronic balloons come in a range of lengths with the longest balloon 15cm - so depends entirely on length of target lesion.

Submission Document Section/Sub-section number	Question / Request *Please indicate who was contacted. If an Expert Adviser, only include significant correspondence and include clinical area of expertise.*	Response *Attach additional documents provided in response as Appendices and reference in relevant cells below.*
	• The IN.PACT SFA trial has reported a high difference in mortality rates between the drug-coated balloon and the comparator (8% vs 0.9%, respectively). The authors of the study do not provide an explanation for this difference, just that it was not device related since it didn't take place within the first month following the intervention. Can you please comment on the clinical relevance of this result?	**Response from Dr Paul Scott – 09.11.17** • It's a slight worry. It may be noise. As far as I'm aware it is not replicated in other trials. Or the group who were randomised to DEB were different i.e. not properly randomised. **Response from Janice Tsui – 09.11.17** • I would say that the 0.9% mortality rate in the PTA group is very low for this population whilst 8% is not higher than expected. I am not sure why this is, given similar baseline characteristics of the group. I think it is reasonable based on timing of deaths and individual adjudication of events, that the deaths were not device related. **Response from Dr Stephen Butterfield – 09.11.17** • It is unclear what accounts for this difference. Operative mortality is usually defined as occurring within 30 days post procedure, hence the statement that it isn't device related. Patients with peripheral vascular disease usually have a number of other comorbidities and it isn't possible to separate out the effect of the DCB from other contributing factors. It is difficult to be certain if this is a statistical quirk related to multiple comorbidities or a true device related difference. **Response from Dr Nadeem Shaida – 09.11.17**

Submission Document Section/Sub-section number	Question / Request *Please indicate who was contacted. If an Expert Adviser, only include significant correspondence and include clinical area of expertise.*	Response *Attach additional documents provided in response as Appendices and reference in relevant cells below.*
		• Difficult to explain these results - the only comment to make is that 0.9% all cause mortality is a low figure in comparison with comparative studies in a population of patients with vascular disease. **Response from Dr Trevor Cleveland – 09.11.17** • My understanding is that the additional deaths in the InPact group were unrelated to their intervention, and there is no explanation as to why they occurred in greater numbers. Quite why there was a difference is unclear, and may just be chance (although the level is such that one would be surprised). In short, I've never seen anyone put up an explanation, and they do seem unrelated. **Response from Dr James Lenton – 09.11.17** • I suspect it's a random result. I can only go on what is in the discussion of the study but reviewing the causes of death - none appear related to the device and although some may be due to vascular disease they are not limb complications. The study authors point out the 0.9% death rate in the POBA (comparator) group is unusually low when compared to other studies looking at lower limb intervention (not necessarily DCB trails) and the DCB group is within in the range of other studies.I suspect the low rate in the POBA group is the issue rather than a high rate in the DCB group.

Submission Document Section/Sub-section number	Question / Request *Please indicate who was contacted. If an Expert Adviser, only include significant correspondence and include clinical area of expertise.*	Response *Attach additional documents provided in response as Appendices and reference in relevant cells below.*
		Response from Dr Peter Holt – 09.11.17 • Yes I am aware of these data. The deaths are not procedural related, and I would say that it is very unlikely that they are linked to the DCB use. **Response from Mr Kevin Varty – 14.11.17** • The mortality difference is difficult to explain, but it is unlikely that it is related to the use of a drug eluding balloon given that there is a lot of experience with drug eluding technology in other vascular territories and devices without a mortality issue. What this does highlight is the low numbers in the studies and the risk of chance variations producing effects such as this. Higher powered studies are really needed, so we are currently making decisions based on in sufficiently robust data. When the primary angioplasty outcome is poor - failed or persistent significant stenosis a stent is a common "bail out" manoeuvre in many units now as established practice. In my experience the circumstances where a bail out stent are used would be a significant failure of the primary angioplasty and not necessarily resolved by a DEB. So I would not consider this a plausible statement. The number of balloons required is influenced by a number of factors. For more straightforward lesions in the SFA causing claudication 1.4 may be reasonable but I would expect more for more extensive disease associated with critical ischaemia

Appendix 1

Minutes of teleconference with sponsor 13.10.17:

MT336
IN.PACT_sponsor TC

Appendix 2 [Insert additional appendices as required]

Answers to questions (including appendices) received by e-mail from sponsor dated 16.10.17:

MTEP Submission
NICE Clarification Q

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MT336 additional work - Mortality rates associated with patients undergoing revascularization for intermittent claudication using PTA

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Table of Contents

Project Details

Work package reference	MT336 – Additional work
Work package name	Mortality rates associated with patients undergoing revascularization for intermittent claudication using PTA
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1. Introduction – additional work requested following draft guidance MTEP committee meeting

During the discussions at the 1st draft guidance committee on 16 February 2018, the committee noted the significantly higher levels of mortality reported in the IN.PACT SFA trial in patients who received IN.PACT drug-coated balloon (DCB) compared with those who received percutaneous transluminal angioplasty (PTA) alone. While the committee heard that the higher levels of mortality were not thought to be attributable to the IN.PACT DCB, and more likely appeared significant because of an unexpected low mortality rate in the PTA arm, the committee asked for further information to support their decision-making. This reports summarises KiTEC's findings from the literature search exploring the following questions:

- What evidence exist with regards to the long-term (≥3 years) mortality rates for patients with intermittent claudication (IC), treated with DCB, PTA or drug-eluting stent (DES)?
- What are the potential risk factors affecting future vascular and non-vascular mortality for this patient population as identified by the literature and expert elicitation?
- Further exploration of the TLR rates reported in the EAC's economic model

2. Methodology

The EAC ran two separate searches, the first to find literature on mortality rates ('Exploration of mortality rates' and 'Exploration of risk factors') and the second to find literature on target lesion revascularisation (TLR) rates ('Exploration of changes in the assumed TLR rate'). Both searches included the following databases:

- Ovid MEDLINE(R) Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) 1946 to Present
- Embase 1974 to 2018 Week 09
- Cochrane Libraries (CDSR, CENTRAL, DARE, Cochrane Methodology Register, HTA Database and NHSEED)
- PubMed
- Web of Science

Scoping searches initially comprised a hand search of the reference lists of key studies included in the original IN.PACT assessment report. Both searches shared search terms derived from the PICO elements of the systematic review carried out in the original assessment report. For the first search the population element was identical, while the intervention element was expanded to include terms for drug eluting stents, plain balloon angioplasty (POBA) and life-style modification, rehab and exercise. The comparator element was ignored. The outcome element

was restricted to mortality rates. For the second search the population and intervention elements were the same as the first search, but the outcome element was restricted to target lesion revascularisations. Both searches were restricted to results from the last 10 years (2008-Current), and animal studies, case studies, editorials and letters were excluded from the Ovid Medline and Embase searches.

The first search (mortality rates) retrieved 4914 records, which became 2941 following de-duplication. The second search (TLR rates) retrieved 1059 records, which became 503 following de-duplication. Following an initial sift of title and abstract 47 records were retained for full text review.

In cases where recent systematic reviews and meta-analyses were available the EAC included these in the report with the exception of highly relevant to the NHS setting studies which were listed additionally. In cases were included studies deviated from the inclusion criteria of the original IN.PACT SFA assessment report (such as the % of patients with CLI included in the THUNDER trial), the EAC chose to include them in the report if they were considered highly relevant to the main question.

3. Long-term mortality rates (≥3 years)

There is a lack of long-term follow-up evidence in the literature. Several systematic reviews and meta-analyses have shown that there is no statistically significant difference in the mortality rates between supervised exercise, DCB, PTA, and DES. However, the follow-up in the studies included in these reviews is maximum 2 years (Baerlocher et al. 2015; Cassese et al. 2017; Chen et al. 2018; Razavi, Mustapha, and Miller 2014; Canaud et al. 2014; Healy et al. 2015; Cui et al. 2017; Giacoppo et al. 2016; Lemor et al. 2016; Barkat, Torella, and Antoniou 2016; Vemulapalli et al. 2015).

Table 1 lists the studies identified reporting mortality rates ≥3 years. With the exception of the IN.PACT SFA trial all other studies reported a mortality rate of approximately 10% at 3 years follow-up for the PTA cohort. The trial by (Tepe et al. 2015) also investigated the difference between paclitaxel DCB and PTA. The authors reported a 9% and 14.8% mortality rate at 2 and 5 years follow-up respectively with PTA. The incidence of mortality at 5 years between DCB vs PTA was 25% vs. 14.8%, respectively. The authors attributed the difference in the different distribution of Rutherford score between the two groups. Approximately 93% of patients in the control group had baseline Rutherford stages ≤3 (7% with Rutherford 5) compared with 70% of

patients in the PCB group (30% with Rutherford 4 or 5). Table 2 lists the baseline patient and lesion characteristics for the intervention cohort of the IN.PACT SFA and the THUNDER trials. Differences were noted for the % of in-stent restenosis and provisional stenting.

Table 1: Study characteristics and mortality rates

Study	Study design	Intervention 1	Intervention 2	Mortality	Follow-up
(John et al. 2012)	RCT	BMS	PTA	10% vs. 8.3%	3 years
(Nguyen et al. 2011)	RCT	BMS	PTA	16% vs. 17%	5 years
(Laird et al. 2012)	RCT	BMS	PTA	10% vs. 8.3%	3 years
(Rocha-Singh et al. 2015)	Non-comparative	BMS	NA	10.1%	3 years
(Schneider et al. 2018)	RCT (IN.PACT SFA)	DCB (paclitaxel)	PTA	10.7% vs. 1.9% (p=0.006)	3 years
(Tepe et al. 2015)	RCT	DCB (paclitaxel)	PTA	25% vs. 14.8%	5 years
(Dake et al. 2016)	RCT	DES	PTA	10.2% vs. 16.9% (p=0.03)	5 years
BMS= bare metal stent DES= drug eluting stent PTA = percutaneous transluminal angioplasty					

Table 2: Baseline and lesion characteristics for the DCB cohorts included in the IN.PACT SFA (Schneider et al. 2018) and THUNDER trials (Tepe et al. 2015).

Characteristic	(Schneider et al. 2018) IN.PACT SFA	(Tepe et al. 2015) THUNDER
Age, y	67.5±9.5	69.0±8
Male	65%	65%
Diabetes mellitus	40.5%	52%
Hypertension	91.4%	79%
Hyperlipidaemia	84.5%	69%
Current smoker	38.6%	23%
ABI/TBI	0.769±0.228	0.5±0.3

Characteristic	(Schneider et al. 2018) IN.PACT SFA	(Tepe et al. 2015) THUNDER
Rutherford score		3.4±0.8
2	37.7	NR
3	57.3	NR
4	5.0	NR
5	0	NR
Lesion length, cm	8.94±4.89	7.5±6.2
Total occlusions	25.8%	27%
Calcification	59.3%	50%
Severe calcification	8.1%	NR
Provisional stenting	7.3%	22%
In-stent restenosis	5%	17%

4. Mortality rate for patients managed non-invasively

4.1. Evidence from single studies

The most representative study on the effect of non-invasive management on the mortality rate in patients with intermittent claudication has been reported by (Mazari et al. 2017). This RCT (CETAC trial, NCT00798850), conducted in the UK, compared the long-term outcomes of PTA, a supervised exercise programme (SEP) and combined treatment (PTA + SEP) in patients with intermittent claudication due to femoro-popliteal disease. A 5% annual mortality rate, equivalent between the 2 groups, was reported. The authors note that their findings are similar to (Fakhry et al. 2013) where a similar annual mortality rate was reported as part of a 7 year follow-up. Early outcomes from this trial (Spronk et al. 2009) were included in the meta-analyses listed below (Fakhry et al. 2018; Vemulapalli et al. 2015).

4.2. Evidence from systematic review and meta-analyses

A systematic review published in 2012 (Frans et al. 2012) reported equivalent clinical effectiveness between non-invasive management and PTA in patients with IC due to femoro-popliteal disease. However, this study had a follow-up of only 1 year. Frans et al. 2012 included evidence from three RCTs (Hobbs et al. 2006; Greenhalgh et al. 2008; Mazari et al. 2010) and all three of these studies and their subsequent updated results were included into the two subsequent meta-analyses listed below. However, no mortality rates were included in this publication.

A recent network meta-analysis looking at the comparative effectiveness of medical therapy, supervised exercise, and revascularization for patients with intermittent claudication showed that all-cause mortality was not significantly different between modalities (Vemulapalli et al. 2015). Thirty-five RCTs evaluated treatment modalities in 7475 intermittent claudication patients. Compared with standard medical treatment, only exercise training improved both maximal walking distance and initial claudication distance. All modalities were associated with improved quality of life compared with standard medical treatment, but there were no differences between treatments. There were insufficient safety data to assess treatment-related complications.

A more recent Cochrane review included ten RCTs (1087 participants) assessing the value of endovascular revascularisation vs. conservative management for people with IC (Fakhry et al. 2018). These RCTs compared endovascular revascularisation vs. no specific treatment, as well as conservative therapy or a combination therapy of endovascular revascularisation *plus* conservative therapy versus conservative therapy alone. The authors concluded that in patients with IC, endovascular revascularisation did not provide significant benefits compared with supervised exercise alone in improving functional performance or QoL. There were some evidence to suggest that a synergetic effect may occur when endovascular revascularisation is combined with a conservative therapy of supervised exercise or pharmacotherapy with cilostazol. No difference in overall mortality was observed between the different treatment modalities.

It should be noted that there was significant overlap in the studies included in the 2 meta-analyses. In addition, some of the studies included in the meta-analyses recruited patients with mixed SFA and iliofemoral lesions. Although differences in study designs were observed among the included studies, the pooled mortality rates had heterogeneity I^2=0%. Finally, as already reported in section 1 the majority of the studies had a maximum 2-year follow-up. Table 3 below lists the mortality rates from selected RCT included in the meta-analyses and the UK-based RCT by Mazari et al. 2017.

Table 3: Selected publications reporting the mortality rates in patients treated with supervised exercise

Study	Study design	Intervention 1	Control	Mortality	Follow-up
(Spronk et al. 2009)	RCT	PTA + best medical therapy	Supervised exercise + best medical therapy	Not reported in the publication (5/75 vs. 3/75 deaths* reported for the PTA and exercise group respectively based on the flow diagram)	1 year
(Greenhalgh et al. 2008)	RCT	PTA + supervised exercise + best medical therapy	Supervised exercise + best medical therapy	Not reported in the publication (2/48 vs. 2/44 deaths*)	2 years
(Mazari et al. 2017)	RCT	PTA + best medical therapy	Supervised exercise + best medical therapy	Annual mortality rate 5%	5 years
(Fakhry et al. 2013)	RCT	PTA ± stent + best medical therapy	Supervised exercise + best medical therapy	26% vs. 32%	7 years
*As reported in patient flow diagram					

5. Exploration of risk factors

5.1. Natural history of PAD

The Trans-Atlantic Inter-Society Consensus Document on Management of Peripheral Arterial Disease published originally in 2000 and updated in 2007 (TASC II) reported results from a systematic review on studies comparing mortality rates of IC patients with those of an age-matched control population (Norgren et al. 2007). The results, shown in figure 1, report a mortality rate of approximately 20% and 30% at 3 and 5 years follow-up, respectively.

A 15-year follow-up USA-based study investigating the natural history of intermittent claudication and the associated mortality risk factors identified older age, lower ankle-brachial index, diabetes requiring medication, and stroke as the independent predictors of mortality (Muluk et al. 2001). Treatment modality was not investigated as a variable affecting mortality in this study.

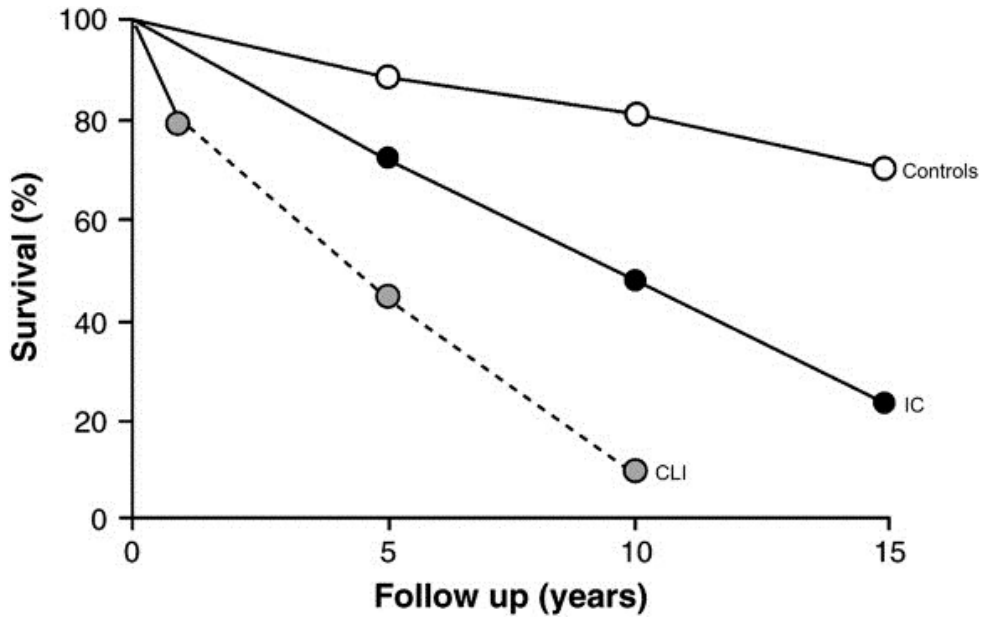


Figure 1: Survival of patients with peripheral arterial disease. IC – intermittent claudication; CLI – critical limb ischemia.

5.2. Literature

As shown by the results of our systematic review on the long-term mortality rates, the only study that showed a low mortality rate for patients with intermittent claudication treated with PTA is the IN.PACT SFA (Schneider et al. 2018). The EAC compared the patient baseline characteristics and co-morbidities of the PTA groups in the studies used to explore the mortality rates with those in the IN.PACT SFA trial. Table 4 below lists the main characteristics for each one of the included studies. No major differences that could account for the low mortality rate in the PTA arm of the IN.PACT SFA were observed.

A recent meta-analysis of the impact of diabetes on mortality in peripheral artery disease, showed that diabetes was associated with a statistically significant increased risk of all-cause mortality although the stronger effect on outcome was obtained in patients with critical limb ischemia (Vrsalovic et al. 2017). As shown by another meta-analysis (Morris et al. 2014) a shorter maximum walking distance was associated with increased 5-year cardiovascular and all-cause mortality in patients with PAD. Current evidence also suggest a positive association of total white cell count with mortality and MAEs in patients with PAD (Martin et al. 2014).

Table 4: Baseline subject and lesion characteristics for the PTA cohorts of patients included in each study.

Characteristic	(Schneider et al. 2018)	(Tepe et al. 2015)	(John et al. 2012)	(Laird et al. 2012)	(Nguyen et al. 2011)	(Dake et al. 2016)
Age, y	68.0±9.2	68.0±9	68.0±10	66.0±9	NA	67.7±10.6
Male	67.6	63%	70.9%	66.7%	65%	63.9%
Diabetes mellitus	48.6	46%	38.1%	38.9%	50%	42%
Hypertension	88.3	83%	83.6%	94.4%	91%	81.5%
Hyperlipidaemia	82.0	63%	79.9%	76.4%	75%	69.7%
Current smoker	36.0	22%	72.4% (current and past)	83.3% (current and past)	15%	84% (current and past)
ABI	0.744±0.189	0.5±0.3				
Rutherford score						
2	37.8	NA	35.8%	41.7%		NA
3	55.9	NA	61.2%	50%		90.7% (2 and 3 combined)
4	5.4	NA	NA	NA		8.5%
5	0.9	NA	NA	NA		NA
Lesion length, cm	8.81±5.12	7.4±6.7	7.0±4.3	6.4±4.0		6.3±4.0
Total occlusions	19.5%	26%	17%	18.5%		27.4%
Calcification	58.4	52%	35.3%	34.3%		95.2%
Severe calcification	6.2	NA	NA	NA		34.9%
Provisional stenting	12.6%	22%	NA	NA		NA

5.3. Specialist commentators

The EAC requested feedback from the specialist commentators participating in the assessment report. The experts highlighted the importance of general cardiovascular morbidity as a major risk factor, including diabetes and their control, highlighting the importance of prescribing and complying with best medical therapy (such as dual anti-platelet treatment). Smoking status and obesity were also noted as risk factors through their impact on cardiovascular morbidity. Because risk factors for vascular disease (such as smoking/obesity) are also risk factors for many malignancies they will be associated with non-vascular mortality in these patients. Finally the presence of other comorbidities such as renal impairment.

Other parameters identified were compliance with exercise programs, shorter maximum walking distance and the ankle-branchial index. Finally, the role of inflammation as evident of the results of recent meta-analyses (such as CRP and white blood cell count) were confirmed by the experts. In conclusion, the experts expressed the view that most of the data exist on vascular-related morbidity and mortality rather than non-cardiovascular mortality.

6. Sensitivity analysis on the rate of TLR with POBA

6.1 Available literature on the TLR rate with POBA

At the MTAC on 16th February 2018 concern was expressed by one of the expert clinicians that the economic analysis of IN.PACT utilised an underlying rate of TLR that was not representative of the typical rate for patients with intermittent claudication in the UK. The clinician indicated that the TLR rate obtained from studies in a US setting was likely to be elevated compared to that in a UK setting due to a more aggressive approach to retreatment in the US. A further concern was expressed that the TLR rate was assumed to be constant in the manufacturer's submission and in the modelling undertaken by the EAC. The EAC was requested to evaluate the evidence on the TLR rate relevant to a UK setting and to consider the impact of a time varying rate of TLR.

The EAC undertook a search of the literature with regard to any studies reporting relevant data on TLR. The search found 503 articles. None of the articles provided data on TLR based on a national registry. The available data was limited to case series and trials. The vast majority of the available data was limited to two year follow-up. The most relevant data is summarised in table

5. TLR rates at 1 year varied from 16.7% (Schroeder et al. 2017) to 54.9% (Laird et al. 2012). There was little indication that rates were systematically higher in studies undertaken in the US compared to those undertaken in Europe. Across the European studies the median TLR rate at 1 year was 30.8%; the corresponding figure for the US studies was 19.7%. It appears that the risk of TLR is elevated in the first year. The hazard in subsequent years may be decreasing over time or constant.

Table 5: summary of studies reporting TLR rate with POBA and DEB

						Percentage TLR			
Study	Size[a]	Study type	Setting	% CLI[b]	% re-inter[c]	1 year	2 years	3 years	5 years
POBA									
Dake 2016	177[d]	RCT	Mostly US	8.5	5.6	19.7	26.9	29.9	32.4
Tepe 2015	54	RCT	Germany	15	29.6	48.1	51.9	nr	55.6
Schneider 2018	111	RCT	Mostly US	6.3	5.4	20.6[e]	28.6[e]	31.2[e]	-
Laird 2012	72	RCT	Mostly US	0	2.5	54.9	58.2	58.2	-
Conrad 2006	128[f]	cohort	US	0	0	nr	15.6[g]	-	-
Rastan 2015	127	RCT	Europe	20.7	0	44.1	59.5	-	-
Laird 2015	111	RCT	Mostly US	nr	nr	nr	28.3	-	-
Schillinger 2006	53	RCT	Europe	13.2	nr	30.8	53.4	-	-
Scheinert 2014	52	RCT	Europe	7.7	0	33.3	48.8	-	-
Rosenfield 2015	160	RCT	Mostly US	8.1	17.5	16.8	-	-	-
Krankenberg 2007	121	RCT	Europe	3.5	0	18.3	-	-	-
Jia 2016	100	RCT	China	44.0	23.0	39.6	-	-	-
Krishnan 2017	100	RCT	US	5.0	18.0	16.8	-	-	-
Cejna 2001	77	RCT	Austria	24.6	0	18.2[h]	-	-	-

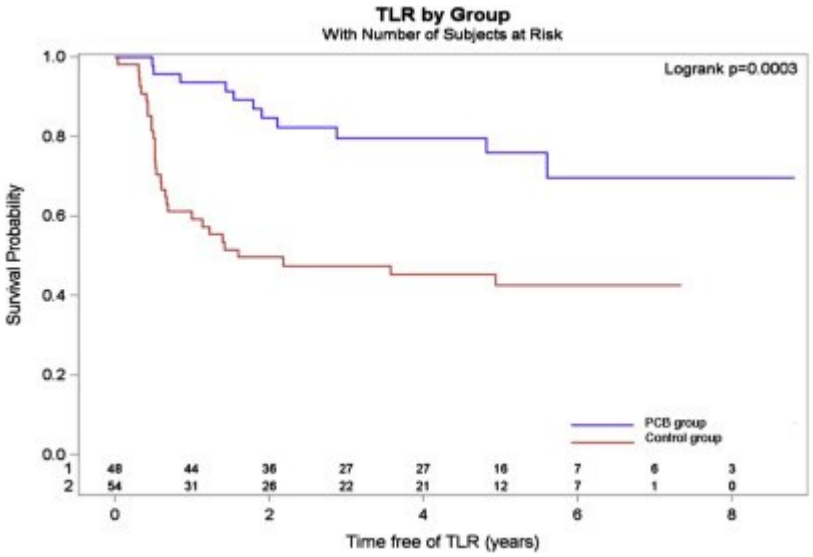
Chalmers 2013	76	RCT	UK	21.1	6.6	20.8 [e]	-	-	-
Schroeder 2017	72	RCT	Europe	1.4	10.1	16.7	-	-	-
Krankenberg 2015	57	RCT	Germany	nr	44.7	47.4	-	-	-
Liistro 2013	51	RCT	Italy	68.6	47.3	33.3	-	-	-
Werk 2012	47	RCT	Germany	nr	32.4	27.9	-	-	-
DCBs									
Tepe 2015	48	RCT	Germany	15	37.5	10.4	16.7	nr	20.8
Schmidt 2016	260	cohort	Germany	26.4	11.1	14.6	31.4	-	-
Laird 2015	220	RCT	Mostly US	nr	nr	nr	9.1	-	-
Micari 2013	105	cohort	Italy	NA	3.5	7.1	14.3[i]	-	-
Scheinert 2014	49	RCT	Europe	6.1	0	28.9	35.7	-	-
Rosenfield 2015	316	RCT	Mostly US	7.9	23.4	12.3	-	-	-
Krishnan 2017	200	RCT	US	4.0	9.5	7.9	-	-	-
Jia 2016	100	RCT	China	42.0	27.0	7.2	-	-	-
Schroeder 2017	72	RCT	Europe	1.8	9.0	5.9	-	-	-
Krankenberg 2015	62	RCT	Germany	nr	15.4	9.2	-	-	-
Bague 2017	53	cohort	France	13	nr	9.8	-	-	-
Liistro 2013	53	RCT	Italy	79.2	17.0	17.0	-	-	-
Werk 2012	44	RCT	Germany	nr	8.6	7.1	-	-	-

[a]Number of patients in relevant trial arm; [b]percentage of patients with critical limb ischaemia; [c]percentage of patients undergoing procedure for restenotic lesion; [d]data reported for cohort receiving POBA and bail-out bare metal stent (patients randomised to bail-out with drug eluting stent excluded); [e]clinically driven TLR rate; [f]limbs; [g]TLR reported at mean follow-up of 24 months; [h]TLR data include 5 bypasses; [i]two year data at 27 months

Two studies provided data over five years (Tepe et al. 2015; Dake et al. 2016). The data in Tepe et al. 2015 derived from a 3 arm RCT of POBA vs DEB vs Paclitaxel infused contrast media in a European setting (THUNDER). The number of patients in the POBA arm was modest at 54. Figure

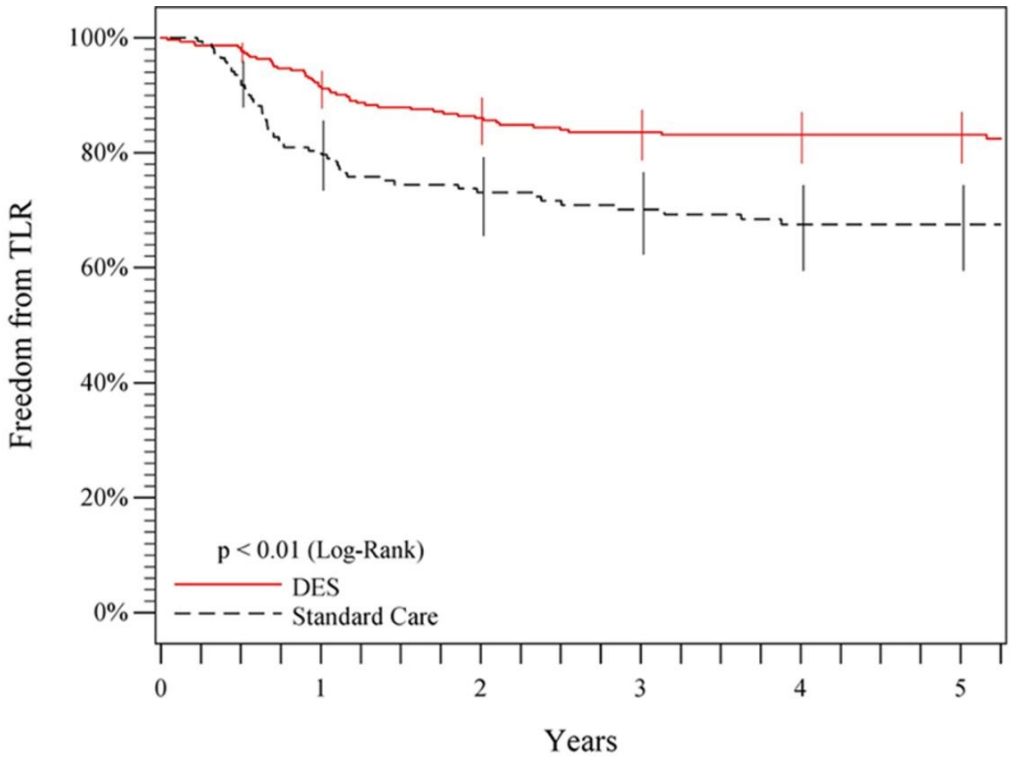
1 reproduces the Kaplan-Meier survival curve for freedom from TLR published in the paper. The trial was undertaken in Germany so practice might be considered more similar to a UK setting than that observed in the US. However, patients ranged in severity of disease with Rutherford scale scores ranging from 1 to 5 (mean of 3.1). Further, 16 of the patients in the control group received intervention for restenosis after PTA with (10) or without stenting (6). The inclusion of patients with Rutherford scores of 4 or 5 (defined as critical limb ischaemia) is likely to have increased the rate of TLR. The inclusion of patients with restenosis is also likely to have increased TLR rates.

Figure 1: Kaplan-Meier plot of time free from TLR for the POBA and DEB trial arms in THUNDER (Tepe et al. 2015).



The data in Dake et al. 2016 derived from a trial of POBA versus DES in predominantly US centres. This was a larger trial with a second randomisation of patients in the POBA arm who required bail-out stenting to either a plain stent or a DES. The data in within the table and the Kaplan-Meier curve in figure 2 refer to patients in the POBA and not receiving a DES. It is notable that just over half of patients in the POBA received a bail-out stent. The exclusion of patients randomised to a DES at bail-out is likely to lead to underestimation of the TLR rate in the POBA arm in this study. This is exacerbated by the high proportion of patients requiring bail-out stenting resulting in over one quarter of patients in the POBA receiving a DES and subsequent excluded from the TLR rates calculated (n =61).

Figure 2: Kaplan-Meier plot of time free from TLR for the POBA (successful and bare-metal stent bail-out) and DES (primary and after bail-out) trial arms in Zilver PTX (Dake et al. 2016).



Kaplan Meier Estimates of Freedom from TLR, Values Represent Patients						
Years Post-procedure	Freedom from TLR ± Standard Error		Cumulative Failed		Remaining at Risk	
	Standard Care	DES	Standard Care	DES	Standard Care	DES
0	100.0 ± 0.0%	100.0 ± 0.0%	0	0	172	305
1	80.3 ± 3.1%	91.6 ± 1.6%	33	25	125	260
2	73.1 ± 3.5%	86.0 ± 2.1%	44	40	106	220
3	70.1 ± 3.6%	83.6 ± 2.2%	48	46	88	187
4	67.6 ± 3.8%	83.1 ± 2.3%	51	47	78	164
5	67.6 ± 3.8%	83.1 ± 2.3%	51	47	69	133

Both Tepe et al. 2015 and Dake et al. 2016 indicate a falling risk of TLR over time (see Table 6). The proportion undergoing TLR in the first year is higher in 'Tepe' compared with 'Dake'. The latter reports a very similar proportion to that observed for POBA in the IN.PACT SFA trial. Whilst the initial rate is higher in 'Tepe' the gradient of the decline in TLR probability over time is steeper in 'Tepe'. The EAC judged that neither trial provided an ideal source for estimating the longer term rate of TLR with POBA for the reasons outlined above.

6.2 Modelling a declining TLR hazard informed by the literature

The EAC chose to undertake sensitivity analyses using the data from both Tepe et al. 2015 and Dake et al. 2016 to estimate the TLR rate for POBA. In each analysis the EAC retained the assumption from the base case the hazards are proportional for POBA and DCB and applied the relative risk for DCB derived from Laird et al. 2015 of 0.35 to hazards estimated for POBA from the respective data sources above. For each analysis we estimated yearly rates of TLR for POBA corresponding to the available data on survival reported in the respective studies (annually in Dake et al. 2016 and at 1, 2 and 5 years in Tepe et al. 2015). Rates with IN.PACT DEB were calculated by applying the relative risk of 0.35 from Laird et al. 2015 to these rates. The rates were then converted to a probability of TLR over 3 months for application in the model. The EAC assumed a DEB would not be used prior to bail-out stenting and the same rate of bail-out stenting in both arms. The EAC chose to apply these assumptions in the sensitivity analysis to reflect both clinical opinion and the derivation of TLR rates for IN.PACT DEB from rates for POBA which included patients receiving bail-out stenting. Table 6 reports the annual probability of TLR over years 1 to 5 applied in the original analysis which assumed 12.6% bail-out stenting in each arm and in each of the sensitivity analyses.

Table 6: Calculated annual TLR probabilities in the base case and sensitivity analyses

	Annual TLR probability				
	Year 1	Year 2	Year 3	Year 4	Year 5
POBA					
Base case	19.5	19.5	19.5	19.5	19.5
'Tepe' sensitivity analysis	48.1	7.3	2.6	2.6	2.6
'Dake' sensitivity analysis	19.7	9.0	4.1	3.6	0
IN.PACT					
Base case	7.6	7.6	7.6	7.6	7.6
'Tepe' sensitivity analysis	20.5	2.6	0.9	0.9	0.9
'Dake' sensitivity analysis	7.4	3.2	1.5	1.3	0

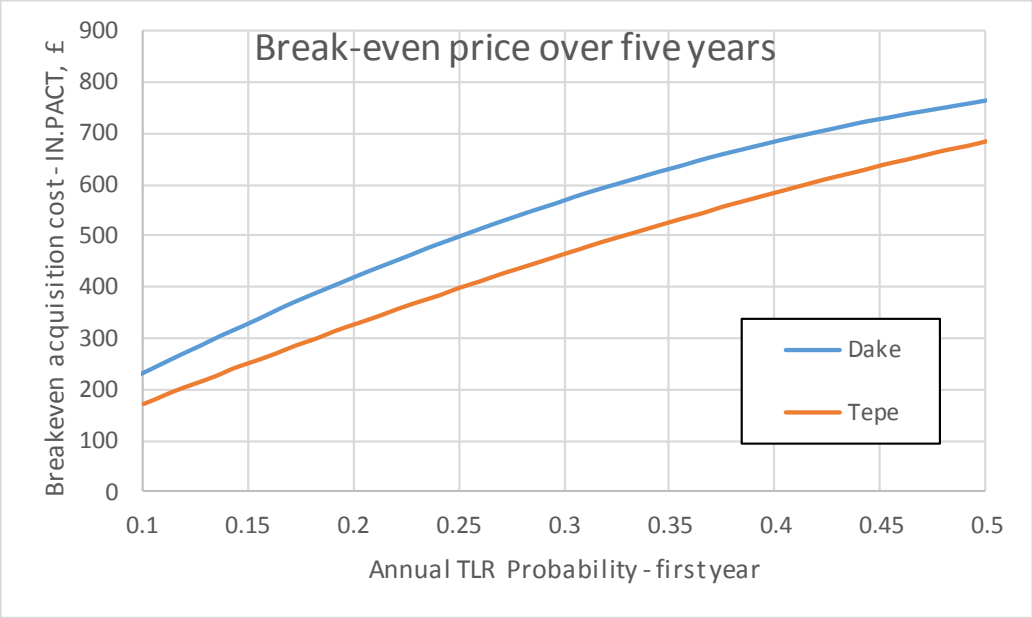
In addition to varying the TLR probability over time the EAC also varied the acquisition price for IN.PACT DEB. The results are given in table 7 for the manufacturer's suggested price of £603 and at two lower prices, £500 and £400. In the base case, IN.PACT is cost saving at four years at the price of £603 and at three years at the lower acquisition costs considered. In the sensitivity analysis in which the TLR rate for POBA is taken from Tepe et al. 2015, IN.PACT is cost saving at three years at a purchase price of £603. This is driven by the very high early re-intervention rate seen in Tepe et al. 2015. In contrast, when TLR rates with POBA are taken from Dake et al. 2016, IN.PACT does not become cost saving until the purchase price approaches £400.

Table 7: Results of sensitivity analysis on the purchase price of IN.PACT DEB with constant TLR risk (base case) or risk informed by 'Tepe' or 'Dake'.

	Additional cost for IN.PACT DEB according to time horizon		
IN.PACT purchase price	3 years	4 years	5 years
Dake model for declining TLR probability			
Base case (£603)	£264	£235	£235
£500	£138	£109	£109
£400	£15	-£13	-£13
Tepe model for declining TLR probability			
Base case (£603)	-£62	-£73	-£82
£500	-£188	-£199	-£208
£400	-£311	-£322	-£330
Base case, constant TLR risk and same bail-out rate			
Base case (£603)	£57	-£32	-£84
£500	-£69	-£158	-£210
£400	-£191	-£280	-£332

The risk of TLR in the first year varied substantially across 'Tepe' and 'Dake'. The EAC undertook further sensitivity analysis in which the shape of the TLR hazard was informed by both Tepe and Dake but the scale of the hazard was adjusted to vary the risk in the first year across the range of 10% to 50%. Across this range the breakeven acquisition price for IN.PACT was calculated over a time horizon of three and five years. Breakeven prices were plotted against the annual probability of TLR in the first year in the POBA arm. The results over a time horizon of five years are shown in Figure 3. Break-even costs rise as the probability of TLR in the first year (the scale of the hazard) increases. The curve from the model in which the shape of the hazard is informed by 'Tepe' lies below the corresponding curve generated by the data in 'Dake' because the data from 'Tepe' indicates a more rapid decline in TLR probability over time. Results for analysis over a time period of three years (not shown) are very similar to those in Figure 3, albeit with both curves shifted modestly upwards (increasing cost).

Figure 3. Breakeven acquisition costs for IN.PACT DEB at varying TLR rates assuming a falling hazard over five years.



7. Additional work requested following the additional MTAC committee meeting 23/3/2018

7.1. Modelling a declining TLR hazard using the IN.PACT SFA trial

Following the additional MTAC meeting the EAC was requested to undertake further examination of the impact of alternative assumptions on the TLR hazard using the results of the IN.PACT trial at three years (not available at the time of the original analysis). In this analysis the EAC used the probabilities reported in the IN.PACT SFA trial of TLR for patients in the POBA arm for each of the first three years to directly inform the annual risk of TLR with POBA over the first three years in the model. (Hence TLR risk was assumed constant within years but not across years). IN.PACT reported TLR probabilities very similar to those in 'Dake' over three years. Hence in this analysis the EAC took the probability of TLR in years four and five from 'Dake'. The EAC compared the results from this analysis with the results using the models in which the TLR risk was informed by the 'Tepe' or 'Dake' data after scaling the risk of TLR in the latter two models so that the risk in the first year matched that observed in the IN.PACT SFA trial.

Table 8 reports the results of this analysis in terms of the incremental cost of IN.PACT at three years and five years and the break-even acquisition cost for IN.PACT DEB at a time horizon of three and five years. Also tabulated are the assumptions regarding the use of a DEB prior to bail-out stenting, the shape of the TLR hazard and the cumulative risk of TLR at one, three and five years. The base case and the Tepe data generate break-even acquisition costs of IN.PACT DEB at three and five years of £528-£654 and £633-£672, respectively. The IN.PACT SFA and Dake scenarios, and both the Dake and Tepe scenarios rescaled to IN.PACT SFA generate lower cumulative TLR risks. The break-even acquisition costs of IN.PACT DEB at three and five years in these scenarios are £321-£402 and £336-£426, respectively.

Table 8: Results of sensitivity analysis using data from IN.PACT SFA to inform TLR risk over three years compared with results using data from 'Tepe' and 'Dake', and after rescaling the risk of TLR so that risk in the first year across all three analyses is the same.

	TLR with POBA (and bail-out stent)			Ass.	Incremental cost of IN.PACT		Break-even cost	
Data source	Risk 1st year	Cumul. risk 3 yrs	Cumul. risk 5 yrs	Bail-out after DEB*	Total at 3 yrs	Total at 5 yrs	3 years	5 years
Base case	19.5%	47.7%	66.0%	Yes	£106	-£42	£528	£633
No DEB with stent	19.5%	47.7%	66.0%	No	£57	-£84	£556	£672
Tepe	48.1%	53.2%	55.6%	No	-£62	-£82	£654	£669
Dake	19.7%	29.9%	32.4%	No	£264	£235	£387	£411
IN.PACT	20.6%	31.1%	33.6%	Yes	£318	£290	£396	£376
IN.PACT	20.6%	31.1%	33.6%	No	£246	£218	£402	£425
Tepe rescal.	20.6%	23.9%	25.9%	No	£345	£327	£321	£336
Dake rescal.	20.6%	31.1%	33.7%	No	£246	£217	£402	£426

*Either use of DEB prior to bail-out stenting and lower bail-out rate after DEB, or assumption of no DEB prior to stenting and same bail-out rate; Ass. – assumptions; yrs – years; Cumul. – Cumulative; rescal. – rescaled

Finally, the EAC undertook analysis of the break-even acquisition price for IN.PACT SFA over a time horizon of three and five years under a number of alternative scenarios regarding the assumption as to whether a DEB would be used prior to bail-out stenting, and the scale and shape of the risk of TLR over time after POBA. The results are summarised in Table 9. It is evident

that the 'Dake' data on the probability of TLR after POBA generates virtually the same results as the data from the IN.PACT SFA trial. Costs are modestly lower when an assumption is made that DEB will not be used for patients requiring bail-out stenting (and that the rate of bail-out stenting is the same regardless of the intention to use a DEB). The break-even acquisition price for IN,PACT at five years varies from £397 to £568.

Table 9: Sensitivity analysis on the break-even acquisition price for IN.PACT under alternative assumptions regarding the use of DEB prior to bail-out stenting, and the scale and shape of the risk of TLR over three and five years.

	TLR with POBA (and bail-out stent)		Assump.	Break-even cost	
Data source for TLR hazard	Shape over time	Risk 1st year	DEB with bail-out	3 years	5 years
Dake	Slow fall	20.6%	Yes	£376	£397
Dake	Slow fall	30.0%	Yes	£499	£521
Dake	Slow fall	20.6%	No	£402	£426
Dake	Slow fall	30.0%	No	£542	£568
IN.PACT	Slow fall	20.6%	Yes	£376	£396
IN.PACT	Slow fall	30.0%	Yes	£498	£519
IN.PACT	Slow fall	20.6%	No	£402	£425
IN.PACT	Slow fall	30.0%	No	£541	£566

Assump. – Assumption; yrs – years; Cumul. – Cumulative; rescal. – rescaled

8. Conclusion

According to the results of our literature search the 3-year mortality reported at the IN.PACT SFA trial (Schneider et al. 2018) is within the expected rates for patients treated with DCB and unusually low for the control group treated with PTA (assuming an annual mortality rate of 5% as reported by (Mazari et al. 2017)). The findings of the IN.PACT SFA with regards to the PTA cohort are not replicated elsewhere in the literature (as recorded in table 1). It should be noted that evidence on long-term outcomes, including mortality, are scarce.

The EAC identified further evidence from the literature that the mortality rate in studies including patients with intermittent claudication are not affected by the treatment modality used. On the contrary significant factors affecting mortality, mainly with respect to cardiovascular-associated mortality are as listed in section x. These were confirmed by the specialist experts contacted by the EAC. However, it should be noted that none of the existing studies was adequately powered to detect a difference in mortality between different treatment modalities.

In the original analysis the hazard of TLR was assumed constant. In the revised analysis the EAC considered the available evidence which, while limited, suggests a declining hazard over time. The EAC modelled a declining hazard using data for the POBA arm from two trials ('Dake' and 'Tepe') which have reported TLR rates at five year follow-up. The EAC also modelled a declining hazard of TLR with POBA using the aggregate annual data on TLR reported for the IN.PACT.SFA study. Data from the IN.PACT SFA study for the POBA arm was remarkably similar to the data from 'Dake'. Both indicate a slower decline in TLR risk over time than that indicated by 'Tepe'. This data, along with an assumption that a DEB is not used when a decision to undertake bail-out stenting is made, would indicate IN.PACT is cost neutral at five years at a purchase price of £425. This price rises if rates of TLR after POBA observed in practice in the UK are higher than those reported in the IN.PACT SFA trial and in 'Dake'.

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10. Search strategies

10.1. Search strategies for mortality rates

Total records retrieved: 4914

Total following de-duplication: 2941

- Ovid MEDLINE(R) Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) 1946 to Present
- Search date: 27th February 2018

1	popliteal.tw. or popliteal artery/	17718
2	Femoropopliteal.tw.	3107
3	(femoral adj3 arter*).tw.	22877
4	femoral artery/ or superficial femoral artery/	26874
5	or/1-4	51472
6	(claudicant* or claudication).tw. or claudication/	12557
7	((arter* or peripher*) adj3 (occlu* or reocclu* or re-occlu* or steno* or resteno* or obstruct* or lesio* or block* or harden* or stiffen* or obliter*)).tw.	105015
8	critical limb ischaemia.tw. or critical limb ischemia/	582
9	Arterial Occlusive Diseases/ or exp artery occlusion/	26355
10	or/6-9	129676
11	5 and 10	11179
12	(peripher* adj2 arter* adj2 disease*).tw. or peripheral arterial disease/ or peripheral occlusive artery disease/	15541
13	11 or 12	25542
14	(percutaneous transluminal angioplasty or pta).tw.	10165
15	exp angioplasty/	58739
16	paclitaxel.tw. or paclitaxel/	32153
17	((paclitaxel elut* or drug elut* or drug coat* or paclitaxel coat*) adj3 balloon*).tw.	967

18	dcb.tw.	1061
19	revasculari*.tw.	51928
20	drug eluting stent*.tw. or Drug-Eluting Stents/	13100
21	(non-invasive or non invasive or (lifestyle adj3 modif*) or rehab* or exercise*).tw.	448363
22	("in.pact*" or in pact* or inpact*).tw.	164
23	medtronic.af. and 12	24
24	or/14-23	586783
25	(mortality or death rate or cause of death).tw.	671863
26	mortality/	39156
27	or/25-26	686071
28	13 and 24 and 27	1131
29	limit 28 to yr="2008-Current"	752
30	animals/ not (animals/ and humans/)	4396739
31	29 not 30	748
32	(case report or editorial or letter).pt.	1429829
33	31 not 32	746

- Embase 1974 to 2018 Week 09
- Search date: 27th February 2018

1	popliteal.tw. or popliteal artery/	20376
2	Femoropopliteal.tw.	4097
3	(femoral adj3 arter*).tw.	31878
4	femoral artery/ or superficial femoral artery/	32216
5	or/1-4	62411
6	(claudicant* or claudication).tw. or claudication/	14717

7	((arter* or peripher*) adj3 (occlu* or reocclu* or re-occlu* or steno* or resteno* or obstruct* or lesio* or block* or harden* or stiffen* or obliter*)).tw.	143626
8	critical limb ischaemia.tw. or critical limb ischemia/	4013
9	Arterial Occlusive Diseases/ or exp artery occlusion/	123274
10	or/6-9	226156
11	5 and 10	14049
12	(peripher* adj2 arter* adj2 disease*).tw. or peripheral arterial disease/ or peripheral occlusive artery disease/	40626
13	11 or 12	50535
14	(percutaneous transluminal angioplasty or pta).tw.	14222
15	exp angioplasty/	80888
16	paclitaxel.tw. or paclitaxel/	93328
17	((paclitaxel elut* or drug elut* or drug coat* or paclitaxel coat*) adj3 balloon*).tw.	1983
18	dcb.tw.	1462
19	revasculari*.tw.	78409
20	drug eluting stent*.tw. or Drug-Eluting Stents/	27452
21	(non-invasive or non invasive or (lifestyle adj3 modif*) or rehab* or exercise*).tw.	620823
22	("in.pact*" or in pact* or inpact*).tw.	330
23	medtronic.af. and 12	310
24	or/14-23	869643
25	(mortality or death rate or cause of death).tw.	955823
26	mortality/	687696
27	or/25-26	1179548
28	13 and 24 and 27	2378
29	limit 28 to yr="2008-Current"	1760

30	animals/ not (animals/ and humans/)	1326617
31	29 not 30	1756
32	(case report or editorial or letter).pt.	1559214
33	31 not 32	1741

- Cochrane Libraries (CDSR, CENTRAL, DARE, Cochrane Methodology Register, HTA Database and NHSEED)
- Search date: 27th February 2018

ID	Search	Hits
#1	popliteal or [mh ^"popliteal artery"]	1203
#2	Femoropopliteal	522
#3	femoral near/3 arter*	1968
#4	[mh ^"femoral artery"] or [mh ^"superficial femoral artery"]	974
#5	[mh "lower limb"] or [mh "lower extremity"]	6694
#6	{or #1-#5}	9189
#7	claudication or [mh ^claudication]	1996
#8	claudicant*	128
#9	critical limb ischaemia or [mh ^"critical limb ischaemia"]	248
#10	[mh ^"Arterial Occlusive Diseases"] or (arter* or peripher*) near/3 (occlu* or reocclu* or re-occlu* or steno* or resteno* or obstruct* or lesio* or block* or harden* or stiffen* or obliter*)	9486
#11	((stenot* near/3 arter*) or "arterial stenosis") or [mh "artery occlusion"]	210
#12	(Rocha - Singh et al. -#11)	10951
#13	#6 and #12	1421
#14	(peripher* near/2 arter* near/2 disease*) or [mh ^"peripheral arterial disease"] or [mh ^"peripheral occlusive artery disease"]	2624
#15	#13 or #14	3586
#16	percutaneous transluminal angioplasty	845
#17	[mh Angioplasty]	4875
#18	pta	845
#19	paclitaxel or [mh paclitaxel]	6172
#20	(paclitaxel elut* or drug elut* or drug coat* or paclitaxel coat*) near/3 balloon*	410
#21	dcb	129

#22	revasculari*	9315
#23	drug eluting stent* or [mh ^"Drug-Eluting Stents"]	2935
#24	non-invasive or "non invasive" or (lifestyle near/3 modif*) or rehab* or exercise*	111002
#25	in.pact* or "in pact*" or inpact*	72
#26	#15 and medtronic	30
#27	{or #16-#26}	1292700
#28	mortality or "death rate" or "cause of death"	74880
#29	[mh ^mortality]	650
#30	#28 or #29	74880
#31	#15 and #27 and #30 Publication Year from 2008	388

- PubMed
- Search date: 27th February 2018

Search	Query	Items found
#29	Search (#12 and #23 and #26) Filters: published in the last 10 years; Humans Sort by: PublicationDate	994
#28	Search (#12 and #23 and #26) Filters: published in the last 10 years Sort by: PublicationDate	1091
#27	Search (#12 and #23 and #26)	1810
#26	Search (#24 or #25)	1111096
#25	Search ("death rate" or "cause of death")	91558
#24	Search mortality	1083641
#23	Search (#13 or #14 or #15 or #16 or #17 or #18 or #19 or #20 or #21 or #22)	919956
#22	Search (#12) AND "medtronic"	76
#21	Search (in.pact* or "in pact*" or inpact*)	90
#20	Search (non-invasive or "non invasive" or "lifestyle modif*" or rehab* or exercise*)	772041
#19	Search drug eluting stents	13386
#18	Search revascularization	51642
#17	Search "dcb"[tiab]	1076
#16	Search ((drug coated balloon) OR drug eluting balloon)	6025

#15	Search paclitaxel	32240
#14	Search "pta"[tiab]	7671
#13	Search angioplasty	73442
#12	Search (#10 or #11)	33709
#11	Search ((peripheral arterial disease) OR peripheral occlusive artery disease)	21677
#10	Search (#4 and #9)	14481
#9	Search (#5 or #6 or #7 or #8)	251256
#8	Search arterial stenosis	51420
#7	Search Arterial Occlusive Diseases	214887
#6	Search critical limb ischaemia	5123
#5	Search claudication	12552
#4	Search (#1 or #2 or #3)	45963
#3	Search femoral artery	40656
#2	Search Femoropopliteal	3122
#1	Search popliteal artery	11023

- Web of Science
- Search date: 27th February 2018

# 19	1,041	#18 AND #17 AND #8 Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI Timespan=2008-2018
# 18	497,528	TS=(mortality or "death rate" or "cause of death") Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI Timespan=2008-2018
# 17	414,006	#16 OR #15 OR #14 OR #13 OR #12 OR #11 OR #10 OR #9 Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI Timespan=2008-2018
# 16	14	#6 AND TS=(medtronic) Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI Timespan=2008-2018
# 15	161	TS=(in.pact* or "in pact*" or inpact*)

		Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI Timespan=2008-2018
# 14	347,893	TS=(non-invasive or "non invasive" or "lifestyle modif*" or rehab* or exercise*) Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI Timespan=2008-2018
# 13	13,496	TS=(drug eluting stent*) Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI Timespan=2008-2018
# 12	30,678	TS=(revasculari*) Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI Timespan=2008-2018
# 11	1,813	TS=(dcb) Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI Timespan=2008-2018
# 10	34,457	TS=(paclitaxel elut* or drug elut* or drug coat* or paclitaxel coat* NEAR/3 balloon*) Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI Timespan=2008-2018
# 9	6,389	TS=("percutaneous transluminal angioplast*" or pta) Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI Timespan=2008-2018
# 8	14,185	#7 OR #6 Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI Timespan=2008-2018
# 7	12,059	TS=(peripher* NEAR/2 arter* NEAR/2 disease*) Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI Timespan=2008-2018
# 6	2,973	#5 AND #1 Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI Timespan=2008-2018
# 5	54,780	#4 OR #3 OR #2

		Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI Timespan=2008-2018
# 4	16,022	TS=(((stenot* NEAR/3 arter*) or "arterial stenosis") or ("artery occlusion")) Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI Timespan=2008-2018
# 3	49,851	TS=((arter* or peripher*) NEAR/3 (occlu* or reocclu* or re-occlu* or steno* or resteno* or obstruct* or lesio* or block* or harden* or stiffen* or obliter*)) Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI Timespan=2008-2018
# 2	7,420	TS=(claudication OR claudicant* OR critical limb ischaemia OR Arterial Occlusive Disease*) Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI Timespan=2008-2018
# 1	12,253	TS=(popliteal artery OR Femoropopliteal OR femoral artery) Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI Timespan=2008-2018

- Hand search of selected studies
- Search date: 26th Feb. to 2nd Mar. 2018

16 studies identified from reference lists of highly relevant studies.

10.2. Search strategies for TLR rates

Total records retrieved: 1059

Total following de-duplication: 503

- Ovid MEDLINE(R) Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) 1946 to Present
- Search date: 5th March 2018

1	popliteal.tw. or popliteal artery/	17721
2	Femoropopliteal.tw.	3110
3	(femoral adj3 arter*).tw.	22894

4	femoral artery/ or superficial femoral artery/	26890
5	or/1-4	51496
6	(claudicant* or claudication).tw. or claudication/	12559
7	((arter* or peripher*) adj3 (occlu* or reocclu* or re-occlu* or steno* or resteno* or obstruct* or lesio* or block* or harden* or stiffen* or obliter*)).tw.	105046
8	critical limb ischaemia.tw. or critical limb ischemia/	583
9	Arterial Occlusive Diseases/ or exp artery occlusion/	26358
10	or/6-9	129711
11	5 and 10	11184
12	(peripher* adj2 arter* adj2 disease*).tw. or peripheral arterial disease/ or peripheral occlusive artery disease/	15552
13	11 or 12	25558
14	(percutaneous transluminal angioplasty or pta).tw.	10166
15	exp angioplasty/	58764
16	plain old balloon angioplast*.tw.	120
17	plain balloon*.tw.	97
18	POBA.tw.	185
19	(balloon* adj3 angioplast*).tw.	9058
20	or/14-19	67854
21	target lesion revasculari?ation*.tw.	3235
22	TLR.tw.	17754
23	or/21-22	19679
24	13 and 20 and 23	215
25	limit 24 to yr="2008-Current"	203
26	animals/ not (animals/ and humans/)	4398339
27	25 not 26	203
28	(case report or editorial or letter).pt.	1429995

29	27 not 28	203
30	from 29 keep 1-203	203

- Embase 1974 to 2018 Week 09
- Search date: 5th March 2018

1	popliteal.tw. or popliteal artery/	20388
2	Femoropopliteal.tw.	4100
3	(femoral adj3 arter*).tw.	31904
4	femoral artery/ or superficial femoral artery/	32239
5	or/1-4	62457
6	(claudicant* or claudication).tw. or claudication/	14731
7	((arter* or peripher*) adj3 (occlu* or reocclu* or re-occlu* or steno* or resteno* or obstruct* or lesio* or block* or harden* or stiffen* or obliter*)).tw.	143781
8	critical limb ischaemia.tw. or critical limb ischemia/	4023
9	Arterial Occlusive Diseases/ or exp artery occlusion/	123389
10	or/6-9	226396
11	5 and 10	14059
12	(peripher* adj2 arter* adj2 disease*).tw. or peripheral arterial disease/ or peripheral occlusive artery disease/	40669
13	11 or 12	50586
14	(percutaneous transluminal angioplasty or pta).tw.	14256
15	exp angioplasty/	80941
16	plain old balloon angioplast*.tw.	273
17	plain balloon*.tw.	227
18	POBA.tw.	515
19	(balloon* adj3 angioplast*).tw.	12640
20	or/14-19	91139
21	target lesion revasculari?ation*.tw.	6686

22	TLR.tw.	29270
23	or/21-22	32473
24	13 and 20 and 23	357
25	limit 24 to yr="2008-Current"	343
26	animals/ not (animals/ and humans/)	1327028
27	25 not 26	343
28	(case report or editorial or letter).pt.	1560651
29	27 not 28	343

- Cochrane Libraries (CDSR, CENTRAL, DARE, Cochrane Methodology Register, HTA Database and NHSEED)
- Search date: 5th March 2018

ID	Search	Hits
#1	popliteal or [mh ^"popliteal artery"]	1205
#2	Femoropopliteal	522
#3	femoral near/3 arter*	1970
#4	[mh ^"femoral artery"] or [mh ^"superficial femoral artery"]	976
#5	[mh "lower limb"] or [mh "lower extremity"]	6715
#6	{or #1-#5}	9213
#7	claudication or [mh ^claudication]	1997
#8	claudicant*	128
#9	critical limb ischaemia or [mh ^"critical limb ischaemia"]	248
#10	[mh ^"Arterial Occlusive Diseases"] or (arter* or peripher*) near/3 (occlu* or reocclu* or re-occlu* or steno* or resteno* or obstruct* or lesio* or block* or harden* or stiffen* or obliter*)	9488
#11	((stenot* near/3 arter*) or "arterial stenosis") or [mh "artery occlusion"]	210
#12	(Rocha-Singh et al. -#11)	10956
#13	#6 and #12	1421
#14	(peripher* near/2 arter* near/2 disease*) or [mh ^"peripheral arterial disease"] or [mh ^"peripheral occlusive artery disease"]	2631
#15	#13 or #14	3593
#16	percutaneous transluminal angioplasty	845
#17	[mh Angioplasty]	4878
#18	pta	848
#19	plain old balloon angioplast*	31
#20	plain balloon*	52
#21	POBA	67
#22	balloon* near/3 angioplast*	5023

#23	{or #14-#22}	9352
#24	target lesion revasculari?ation*	1365
#25	TLR	905
#26	(Cordeiro et al. -#25)	1751
#27	#15 and #23 and #26 Publication Year from 2008	144

- PubMed
- Search date: 5th March 2018

Search	Query	Items found
#26	Search (#12 and #20 and #23) Filters: published in the last 10 years; Humans Sort by: PublicationDate	191
#25	Search (#12 and #20 and #23) Filters: published in the last 10 years Sort by: PublicationDate	210
#24	Search (#12 and #20 and #23)	228
#23	Search (#21 or #22)	20033
#22	Search "TLR"[tiab]	18329
#21	Search target lesion revascularization[tiab]	2858
#20	Search (#13 or #14 or #15 or #16 or #17 or #18 or #19)	78771
#19	Search balloon angioplasty	55107
#18	Search POBA[tiab]	167
#17	Search plain balloon[tiab]	95
#16	Search plain old balloon angioplasty[tiab]	122
#15	Search "plain old balloon angioplast*"[tiab]	0
#14	Search "pta"[tiab]	7678
#13	Search angioplasty	73460
#12	Search (#10 or #11)	33746
#11	Search (peripheral arterial disease OR peripheral occlusive artery disease)	21705
#10	Search (#4 and #9)	14496
#9	Search (#5 or #6 or #7 or #8)	251376
#8	Search arterial stenosis	51450
#7	Search Arterial Occlusive Diseases	214978
#6	Search critical limb ischaemia	5132
#5	Search claudication	12558
#4	Search (#1 or #2 or #3)	45997
#3	Search femoral artery	40689
#2	Search Femoropopliteal	3122
#1	Search popliteal artery	11031

- Web of Science
- Search date: 27th February 2018

# 18	178	#17 AND #14 AND #8 Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI Timespan=2008-2018
# 17	17,024	#16 OR #15 Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI Timespan=2008-2018
# 16	15,721	TS=("TLR") Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI Timespan=2008-2018
# 15	2,268	TS=("target lesion revascularization*" OR "target lesion revascularisation*") Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI Timespan=2008-2018
# 14	10,807	#13 OR #12 OR #11 OR #10 OR #9 Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI Timespan=2008-2018
# 13	5,004	TS=(balloon* NEAR/3 angioplast*) Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI Timespan=2008-2018
# 12	100	TS=(POBA) Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI Timespan=2008-2018
# 11	81	TS=("plain balloon*") Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI Timespan=2008-2018
# 10	80	TS=("plain old balloon angioplast*") Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI Timespan=2008-2018
# 9	6,399	TS=("percutaneous transluminal angioplast*" or pta) Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI Timespan=2008-2018
# 8	14,209	#7 OR #6

		Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI Timespan=2008-2018
# 7	12,078	TS=(peripher* NEAR/2 arter* NEAR/2 disease*) Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI Timespan=2008-2018
# 6	2,980	#5 AND #1 Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI Timespan=2008-2018
# 5	54,870	#4 OR #3 OR #2 Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI Timespan=2008-2018
# 4	16,049	TS=(((stenot* NEAR/3 arter*) or "arterial stenosis") or ("artery occlusion")) Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI Timespan=2008-2018
# 3	49,928	TS=((arter* or peripher*) NEAR/3 (occlu* or reocclu* or re-occlu* or steno* or resteno* or obstruct* or lesio* or block* or harden* or stiffen* or obliter*)) Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI Timespan=2008-2018
# 2	7,435	TS=(claudication OR claudicant* OR critical limb ischaemia OR Arterial Occlusive Disease*) Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI Timespan=2008-2018
# 1	12,274	TS=(popliteal artery OR Femoropopliteal OR femoral artery) Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI Timespan=2008-2018