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

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Declared interests of the authors

Description of any pecuniary relationship with the company, both personal and of the EAC. Please refer to NICE's Code of Practice for declaring and dealing with conflicts of interests.
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Rider on responsibility for report

The views expressed in this report are those of the authors and not those of NICE. Any errors are the responsibility of the authors.

Contents

ABBREVIATIONS

Term	Definition
ABI	Ankle–Brachial Index
BMS	Bare Metal Stent
BTK	Below -The-Knee (Lesion)
CAD	Cad: Coronary Artery Disease
CD-TLR	Clinically Driven Target Lesion Revascularization
CI	Confidence interval
CLI	Critical Limb Ischemia
CTO	Chronic Total Occlusion
DCB	Drug-Coated Balloon Angioplasty
DEB	Drug-Eluting Balloon
DES	Drug-Eluting Stent
DM	Diabetes Mellitus
DUS	Duplex Ultrasound
EAC	External Assessment Centre
EQ-5D	5-Dimension Health-Related Quality of Life Questionnaire
HTA	Health Technology Assessment
ISR	In-Stent Restenosis
IQR	Interquartile range
LLL	Late Lumen Loss
MAE	Major Adverse Events
MAUDE	Manufacturer and User Facility Device Experience
MHRA	Medicines & Healthcare products Regulatory Agency
MTEP	Medical Technologies Evaluation Programme
MIB	Medtech Innovation Briefing
NR	Not reported
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NICE CG	NICE clinical guideline
NICE MTG	NICE medical technology guidance
NICE QS	NICE quality standard
PAD	Peripheral Arterial Disease
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PTA	Percutaneous Transluminal Angioplasty
QOL	Quality of Life
QUORUM	Quality of Reporting of Meta-analyses
RCT	Randomized Clinical Trial
SD	Standard Deviation
SFA	Superficial Femoral Artery
TLR	Target Lesion Revascularization

TVR	Target Vascular Revascularization
Vs.	Versus

1 Executive Summary

The sponsor identified 12 clinical studies reported in 16 peer-reviewed papers and 7 conference abstracts. Some of the studies included a patient population that did not fit the scope so only evidence from 5 peer-reviewed publications and 2 abstracts were included. The EAC identified 2 more relevant peer-reviewed publications and 2 conference abstracts providing updates on 3 of the previously included trials and 1 new study (IN.PACT SFA, PACIFIER, IN.PACT Global and ISAR PEBIS).

The pivotal study was the superiority multi-centre international IN.PACT SFA (n = 331) RCT, which compared IN.PACT admiral DCB with standard PTA with a 2-year follow up (Laird et al., 2015; Krishan et al., 2016). The results reported a statistically significant reduction in CD-TLR, in primary restenoses, and in target limb major amputation with IN.PACT compared with standard PTA. The two groups performed equally in terms of functional outcomes. People treated with IN.PACT SFA had a statistically significant higher mortality at 2 year, however, based on the independent committee that assessed this outcome and the views of the clinical experts, this was not attributed to the intervention.

The EAC considered that although this RCT, which was fully funded by the sponsor, was subject to some potential sources of bias - mainly unclear risk of attrition bias and unclear risk of performance bias - the largest comparative benefit was attributable to IN.PACT DCB.

The level of benefit in terms of target lesion revascularization and safety was also broadly supported by evidence from single-armed observational data. Although none of the included studies was conducted in the UK, the results should be generalisable to the UK setting.

The sponsor's systematic search of economic evidence included 8 papers. The EAC confirmed that the search strategy was appropriate and had identified all the relevant literature. The EAC however included only 2 papers which specified the IN.PACT technology and excluded the others, which were included various DCBs. The 2 papers showed that IN.PACT results in cost

saving in the long term due to reduced TLR rates. The sponsor submitted a cost model which compared IN.PACT DCB compared to PTA for a time horizon of 3 years. The results showed that IN.PACT was nearly cost neutral at 3 years and cost saving at 4 years. The EAC reviewed the cost model and in general found the model structure and parameters to be reasonable. The sponsor used TLR rates from its own meta-analysis which was not agreeable to the EAC, since the EAC excluded many studies included by the sponsor. The EAC estimated a relative risk for TLR with IN.PACT based on its own included papers. The EAC then applied this relative risk to the sponsor's estimate of TLR rates with PTA to estimate TLR rates for IN.PACT. The results showed that IN.PACT DCB realised cost savings from approximately between 3-4 years after the index procedure.

2 Background

2.1 Overview and critique of company's description of clinical context

The sponsor provided a brief overview of peripheral arterial disease (PAD) and a brief description of the CG147 guideline, focusing mainly on the 2-year surveillance update and the fit of drug-eluting technologies in the pathway. The clinical context is appropriate it doesn't however, focuses specifically to patient with intermittent claudication that is defined by the scope.

Relevant guidance

Peripheral arterial disease (PAD) is associated with progressive narrowing of one or more arteries in the lower extremities resulting in decreased blood flow and oxygen to the affected tissues and muscles. It is usually associated with coronary artery disease and currently there is no cure for it. Initial management of PAD focuses on lifestyle changes and treatments that aim to reduce symptoms and the risk of developing other types of cardiovascular disease such as a stroke or heart attack.

The NICE guideline on peripheral arterial disease recommends educating all patients about their condition and providing them with information on lifestyle changes such as smoking cessation, diet, body weight and exercises. In addition, to provide information on how to manage pain and treatment options including management of comorbidities such as high blood pressure, diabetes and hyperlipidaemia.

For patients with intermittent claudication specifically, the guideline recommends a supervised exercise programme which involves 2 hours of supervised exercise a week for a 3‑month period and encouraging people to exercise to the point of maximal pain. When supervised exercise fails to provide satisfactory clinical improvement, and the person does not prefer to undergo angioplasty or bypass surgery then naftidrofuryl oxalate can be used, reviewed every 3-6 months according to symptomatic progress.

People with intermittent claudication may be offered angioplasty or surgical procedures such as bypass grafts. Angioplasty (with or without stenting) can be offered after advice on lifestyle modifications have been reinforced, supervised exercise has failed to improve symptoms and imaging has confirmed that angioplasty is suitable. After balloon angioplasty the vessel may open satisfactorily, or the stenosis in the vessel may immediately recoil back, or the vessel may dissect in which case the guideline advices the use of a bare metal stent. People with intermittent claudication caused by femoro‑popliteal disease should not be offered primary stent placement.

Bypass surgery may be offered to people with intermittent claudication when angioplasty has been unsuccessful or is unsuitable, and where imaging has confirmed that it is appropriate. The guideline recommends that an autologous vein should be used whenever possible for people with intermittent claudication having infra-inguinal bypass surgery.

The 2-year surveillance evidence update for CG147 suggests that supervised exercise appears to be more cost effective than either angioplasty alone or supervised exercise plus angioplasty in people with intermittent claudication due to femoro-popliteal occlusion. The 4-year surveillance impact statement from CG147 refers specifically to the use of bare metal stents vs. drug-coated stents and the ongoing BASIL-3 trial that includes DCB in Group 2, however, no changes to CG147 were recommended.

NICE has also issued guidance on percutaneous laser atherectomy as an adjunct to balloon angioplasty (with or without stenting) for peripheral arterial disease. Percutaneous laser atherectomy as an adjunct to balloon angioplasty (with or without stenting) for peripheral arterial disease aims to achieve recanalisation when balloon angioplasty and/or stenting alone are considered not to be technically feasible or sufficiently safe. However, the guidance does not specify the relevance of laser atherectomy in patients with intermittent claudication specifically.

NICE has also published a Lutonix drug-coated balloon for peripheral arterial disease (MIB72) for a drug-coated balloon.

2.2 Critique of company's definition of the decision problem

Table 1 below outlines the main issues with the company's definition of the decision problem based on the original scope.

Table 1 Critique of decision problem

Decision problem	Company submission	Matches decision problem? (Y/N/partially)	EAC comment
Population	Scope: “People with femoro-popliteal peripheral arterial disease undergoing revascularization for intermittent claudication.” Submission: All submitted evidence involved patients with peripheral arterial disease. No evidence was specific to UK but the IN.PACT SFA trial and the IN.PACT Global study involved European sites.	Partially	Some of the evidence submitted meets the final scope for the population. All populations in the submitted evidence were patients with femoro-popliteal peripheral arterial disease, however, some also included patients with critical limb ischaemia and few with below the knee disease. All sponsor submitted studies were from secondary care settings.
Intervention	Scope: ‘’Percutaneous transluminal angioplasty (PTA) with IN.PACT drug coated balloon (Pacific or Admiral	Yes	Although the majority of the submitted evidence were on Admiral the sponsor claimed that ‘’the clinical evidence generated with IN.PACT Admiral can be convincingly used to demonstrate the safety and effectiveness of

	versions) (with or without bailout stenting)'' Submission: 3 studies (PACIFIER trial, Real world registry and the Belgian diabetic IN.PACT Trial) included the Pacific version. The rest tested only the Admiral DCB.		IN.PACT Pacific to deliver paclitaxel to the target lesion in the peripheral artery.'' The EAC requested further clarification on this statement which the sponsor provided. The EAC also requested feedback from the specialist commentators regarding this issue. Responses were unanimously supporting the sponsor's statement. Regulatory requirements are complied with.
Comparator(s)	Scope: ''Percutaneous transluminal angioplasty (PTA) with a non-drug coated balloon (with or without bailout stenting)'' Submission: The sponsor submitted both comparative and non-comparative evidence. All the comparative evidence submitted by the sponsor compared the intervention with PTA with or without stenting. Comparative data were available from 6 RCTs IN.PACT SFA Trial	Partially	Comparative evidence from 4 trials were included in the final report (IN.PACT SFA, FAIR, ISAR-PEBIS and PACIFIER trials). The rest were excluded because the population did not fit the scope. The EAC retrieved 1 additional RCT the ISAR-PEBIS trial (Ott et al., 2017) that compared the intervention against PTA.

	FAIR trial PACIFIER trial DEBATE-SFA study Belgian diabetic IN.PACT Trial DEBELLUM trial		
Outcomes	Scope: “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	Yes	In the sponsor submission outcomes are tabulated by study (table B9 and B10). Outcomes from 6 RCTs and 6 non-comparative studies are presented in 23 references (7 abstracts and 16 full texts). Some of the references provided outcomes from overlapping populations from the following non-comparative studies: – Multicentre Italian registry – SFA long study – Real World registry – IN.PACT Global

	– Rates of vessel thrombosis – Angiographically determined late lumen loss – Device-related adverse events'' Details on outcomes are given by study submitted in tables B9 (published) and B10 (unpublished).		And from 1 RCT, the IN.PACT SFA. Most outcomes in the evidence submitted relates to primary patency rates and target lesion revascularisation. No evidence where identified with regards to rate of hospitalisation Fifteen sponsor-submitted references (4 unpublished and 11 published) were excluded from the EAC report due to overlapping populations.
Cost analysis	Scope: Comparator(s): 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	Yes	The technology, comparator, model structure, time horizon and sensitivity analysis are in line with the scope.

	numbers and combinations of devices are needed.		
Subgroups	People presenting with in-stent restenosis People with restenosis or recurrence. The sponsor submitted 1 RCT (FIAR trial, Krankenberg et al. 2015) and 3 non-comparative (PLAISIR study, DEBATE-ISR study, IN.PACT Global) studies on patients with in-stent restenosis.	Yes	The EAC identified I extra RCT ISAR-PEBIS (Ott et al. 2017) on patients with in-stent restenosis. The EAC asked the clinical experts whether it was appropriate to combine results from studies with patients with in-stent restenosis vs. de novo lesions. They unanimously responded that results from de novo and in-stent restenosis lesions should not be combined due to the differences in pathophysiology and outcomes between the 2 populations.

Special considerations, including issues related to equality

No equality issues were identified in the sponsor submission (see section 6.1.1). The sponsor states that 'there are no equality issues related to the use of the IN.PACT DCB in any appropriately selected, clinically qualified patient.'

The EAC notes that a number of population groups are identified by the scope as having potential special considerations for equality. The scope identifies the following groups: "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."

The EAC has not identified equality issues other than those highlighted in the scope.

All studies included patients with diabetes, 2 of the submitted studies the DEBATE ISR study (Grotti et al. 2016) and the Belgian diabetic IN.PACT trial (Debing et al. 2016) investigated the effectiveness of the intervention in a purely diabetic population.

3 Clinical evidence

3.1 Critique of and revisions to the company's search strategy

The sponsor provided details of their search strategy in the original submission and further details were sent subsequently following a request for information from the EAC. The sponsor stated they searched PubMed, Embase and the Cochrane Library although no results were retrieved from the latter. The sponsor also hand-searched reference lists of systematic reviews (but did not specify which ones). For unpublished material, the sponsor hand-searched conference proceedings for data on the IN.PACT SFA and IN.PACT GLOBAL trials (also not specified).

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.

The sponsor's search was neither clear nor reproducible and therefore the EAC conducted their own search run in Embase, Ovid MEDLINE(R) Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily, Ovid MEDLINE(R), Global Health, HMIC, Cochrane, PubMed and Web of Science. A search of Clinicaltrials.gov and the WHO ICTRP was performed

using a modified search strategy. The EAC also searched for grey literature using a simpler set of search terms (see Appendix A for details of all search strategies and PRISMA flow diagram).

3.2 Critique of the company's study selection

The sponsor's inclusion/exclusion criteria are listed in *Table 2* below.

Table 2 sponsor's inclusion/exclusion criteria for study selection

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

The EAC requested further clarification on 2 of the sponsor's exclusion criteria:

- Patients with below-the-knee lesion (BTK)
- Mixed population

The sponsor clarified that with regards to the mixed population they have excluded studies where more than 1 device model has been used (i.e. publications where both IN.PACT Admiral and another DCB has been used). For the patient with BTK lesions population they have excluded studies that were treated for BTK lesions rather than femoropopliteal lesions.

Of the 25 full text peer-reviewed publications retrieved by their search strategy considered for inclusion, the sponsor excluded 9. As a result, 16 full text

publications were included in qualitative synthesis. From these 16, the sponsor included 11 in quantitative synthesis of evidence consisting of 12 months follow-up, while further 6 were used for evidence synthesis providing outcomes at 24 months follow-up. Seven conference presentations that reported on follow-up data from the IN.PACT SFA RCT (3 year follow-up) and the IN.PACT Global registry (1 year follow-up) were also included by the sponsor.

The EAC considered these inclusion/exclusion criteria to be appropriate. However, 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.

3.3 Included and excluded studies

The sponsor submitted multiple peer-review publications and conference abstracts reporting results from the same study. For clarity when in the document the word reference is used it refers to a single publication. Whenever the word study or trial is used it refers to a single study (for example the IN.PACT SFA trial) but may include several peer publications arising from this trial. The sponsor's submission included 16 full text references (Bague et al. 2017, Debing et al. 2017, Fanelli et al. 2012, Grotti et al. 2016, Krankenberg et al. 2015, Laird et al 2015, Liistro et al. 2013, Micari et al. 2012, Micari et al 2013, Micari et al 2016, Micari et al 2017, Tepe et al 2015, Schmidt et al 2012, Stabile et al. 2012, Virga et al. 2014, Werk et al. 2012). The sponsor also submitted 7 conference abstracts (Ansel et al. 2017, Brodmann et al. 2015, Fanelli et al. 2017, Jaff et al. 2016, Krishan et al. 2016, Scheinert et al. 2015, Tepe et al. 2014).

The EAC reviewed all evidence identified by the sponsor. All studies that did not fit the EAC's inclusion criteria were excluded from further review. The EAC included 5 (Krankenberg et al. 2015, Laird et al 2015, Micari et al 2013, Micari et al 2017, Werk et al. 2012) of the 16 full text published references submitted by the sponsor. The EAC included 2 conference abstracts from the sponsor's submission (Ansel et al. 2017, Krishan et al. 2016). Four further references, 2 full text peer-reviewed publications (Brodmann et al. 2017, Ott et al. 2017) and 2 conference abstracts (Krishan et al. 2017, Werk et al. 2014) were identified and included by the EAC. Table 3 below lists all studies, whether or not they were included by the sponsor or the EAC and reasons for disagreement.

Table 3 List of included studies identified by the sponsor and the EAC

Primary study number	Primary study reference	Study name	Sponsor inclusion	EAC inclusion	Reason for disagreement
1.	Tepe et al 2015	IN.PACT SFA Trial	Yes	No	Excluded by the EAC = overlap with Laird 2015
2.	Laird et al 2015	IN.PACT SFA Trial	Yes	Yes	NA
3.	Krishan et al. 2016 (abstract)	IN.PACT SFA Trial	Yes	Yes	NA
4.	Krankenberg et al. 2015	FAIR trial	Yes	Yes	NA
5.	Werk et al. 2012	PACIFIER trial	Yes	Yes	NA
6.	Micari et al. 2012	Multicentre Italian Registry	Yes	No	Excluded by the EAC overlap with Micari 2013
7.	Micari et al 2013	Multicentre Italian Registry	Yes	Yes	NA
8.	Micari et al 2016	SFA-Long study	Yes	No	Excluded by the EAC = overlap with Micari 2017
9.	Micari et al 2017	SFA-Long study	Yes	Yes	NA
10.	Bague et al. 2017	PLAISIR study	Yes	No	Excluded by the EAC = included >10% patients with CLI

11.	Liistro et al. 2013	DEBATE-SFA study	Yes	No	Excluded by the EAC = included >10% patients with CLI
12.	Grotti et al. 2016	DEBATE-ISR Study	Yes	No	Excluded by the EAC = included >10% patients with CLI
13.	Schmidt et al 2012	Real-world Registry	Yes	No	Excluded by the EAC = included >10% patients with CLI
14.	Stabile et al. 2012	Real-world Registry	Yes	No	Excluded by the EAC = overlap with Virga et al. 2014 and because included >10% patients with CLI
15.	Virga et al. 2014	Real-world Registry	Yes	No	Excluded by the EAC = included >10% patients with CLI
16.	Debing et al. 2017	Belgian diabetic IN.PACT Trial	Yes	No	Excluded by the EAC = included >10% patients with CLI, BTK lesions, Intervention

17.	Fanelli et al. 2012	DEBELLUM trial	Yes	No	Excluded by the EAC = BTK lesions and because included >10% patients with CLI
18.	Jaff et al. 2016	IN.PACT Global	Yes	No	Excluded by the EAC = included >10% patients with CLI
19.	Scheinert et al. 2015	IN.PACT Global	Yes	No	Excluded by the EAC = included >10% patients with CLI
20.	Brodmann et al. 2015	IN.PACT Global	Yes	No	Excluded by the EAC = of overlapping population with full-text publication of Brodmann et al. 2017 (please see below)
21.	Tepe et al. 2014	IN.PACT Global	Yes	No	Excluded by the EAC = included >10% patients with CLI
22.	Fanelli et al. 2017	IN.PACT Global	Yes	No	Excluded by the EAC = included >10% patients with CLI

23.	Ansel et al. 2017	IN.PACT Global (standard use)	Yes	Yes	NA
24.	Brodmann et al. 2017	IN.PACT Global	No	Yes	Not identified by the sponsor (published October 2017)
25.	Ott et al. 2017	ISAR-PEBIS	No	Yes	Not identified by the sponsor
26.	Krishan et al. 2017 (abstract)	IN.PACT SFA	No	Yes	Not identified by the sponsor
27.	Werk et al. 2014	PACIFIER	No	Yes	Not identified by the sponsor

Included studies

The EAC included the following studies (comprising of 7 full text peer review publications and 4 conference abstracts):

RCTs

Full text publications

IN.PACT SFA: Laird et al. (2015)

Laird et al. (2015) reported the 24-month follow-up data from the IN.PACT SFA international RCT. The trial was prospectively designed to be conducted in 2 phases: IN.PACT SFA I (conducted in Europe) and IN.PACT SFA II (conducted in the United States), which are jointly referred to as IN.PACT SFA. The efficacy and safety of IN.PACT Admiral was compared to standard PTA with or without stenting in 331 patients (n=220 vs. 111, respectively) with symptomatic (Rutherford 2 to 4) femoropopliteal lesions up to 18 cm in length. Patients were randomly assigned in a 2:1 ratio to treatment with DCB or PTA after successful dilatation was achieved. Independent core laboratories and a clinical events committee evaluated the outcomes. Follow-up was 60-months. Patients received aspirin and clopidogrel before and after the procedure. Post-dilatation with a standard PTA balloon was allowed at the discretion of the operator. At 24 months, patients treated with DCB showed significantly higher primary patency when compared with PTA (78.9% vs. 50.1%; p<0.001). The rates of CD-TLR were 9.1% and 28.3% (p < 0.001) for the DCB and PTA groups, respectively. The overall mortality rate in the DCB group was 8.1% versus 0.9% in the PTA group (p=0.008). There were no device- or procedure-related deaths and no major amputations in either group through 24-month follow-up. The rate of vessel thrombosis was 1.5% for the DCB vs. 3.8% for PTA (p=0.243), with no new events reported between 1 and 2 years of follow-up. Both groups showed similar functional improvement at 2 years, although DCB patients achieved this level of function with 58% fewer reinterventions.

Critical appraisal

An independent clinical events committee adjudicated all major adverse events. Independent core laboratories analyzed all images, including duplex ultrasonography and angiography. Although the patient, study sponsor, and independent angiographic and ultrasound laboratories were blinded to the treatment received, the clinicians responsible for the procedure and follow-up

were not. The study population is representative of other SFA trials, however the study included a 5% proportion of patients with CLI that is outside the scope. The difference in number of pre-dilation procedures in the interventional and control cohorts was statistically significant, pre-dilation procedures were more prevalent in the intervention cohort. The study was funded by the sponsor. The trial was powered for the primary efficacy endpoint in both the intention-to-treat and non-stented cohorts to address concerns about the effect of provisional stenting on the results.

PACIFIER: Werk et al. 2012

Werk et al. (2012) reported the results of the PACIFIER trial, a multicentre RCT conducted in Germany. The efficacy and safety of IN.PACT Pacific was compared to standard PTA with or without stenting in 85 patients (n=41 vs. 44, respectively) with symptomatic (Rutherford 2 to 5) femoropopliteal lesions between 3 and 30 cm in length. Patients were randomly assigned in a 1:1 ratio to treatment with DCB or PTA pre-dilation. Independent core laboratory evaluated the outcomes. Follow-up was 12-months. Patients received aspirin and thienopyridine l before and after the procedure. Pre-dilation with a standard PTA balloon was allowed at the discretion of the operator. At 12 months, patients treated with DCB showed significantly lower recurrent restenosis (binary outcome) when compared with PTA (29.5% versus 62.5% p=0.004).There was no difference in the residual stenosis rate between both groups. The rates of CD-TLR were 9.2% and 47.4% ($p < 0.0001$) for the DCB and PTA groups, respectively. The overall mortality rate in the DCB group was 4.3% versus 6.8% in the PTA group (p=0.51). There were no device- or procedure-related deaths and no major amputations in either group through 12-month follow-up. The MACE events were similar between the 2 groups (4.5% DCB vs. 4.5% PTA; $p>0.05$). Werk et al. 2014 reported the 2-year follow-up results of the PACIFIER trial, the TLR and major adverse events rates for DCB versus PTA were 16.7% vs. 28.9% (p=0.2) and 21.4% vs. 37.8% (p=0.1), respectively.

Critical appraisal

This randomized trial was powered on a 6-month angiographic primary end point (LLL), therefore results pertaining to secondary clinical end points (such as TLR) should be taken with caution. The 2 groups were imbalanced with regards to the total number of balloons used for the procedure in favour of the intervention. Similar to other studies the operators could not be blinded to the assigned treatment because of the different appearance of coated and uncoated balloons. The trial had a short follow-up duration of 12 months.

FAIR: Krankenberg et al. 2015

Krankenberg et al. (2015) reported the results of the FAIR trial - a multicentre RCT conducted in Germany. The efficacy and safety of the IN.PACT Admiral DCB was compared to standard PTA, with or without stenting, in 119 patients (n = 62 vs. 57, respectively) with symptomatic in-stent restenosis involving femoropopliteal lesions up to 20 cm in length. Patients were randomly assigned in a 1:1 ratio to treatment with DCB or PTA pre-dilation. Follow-up was 12-months. Patients received 100 mg per day of acetylsalicylic acid and 75 mg per day of clopidogrel. Patients not on this premedication regimen were given an intravenous bolus of 500mg of aspirin and a pre-loading dose of 600mg of clopidogrel. Pre-dilation with a standard PTA balloon was performed in the DCB group. Freedom from TLR was significantly higher in the DCB than the PTA group at both 6 and 12 months, respectively (96.4% vs. 81.0%, p = 0.0117; 90.8% vs. 52.6%, p < 0.0001). No major amputations were required, however 2 patients in the DCB group and 3 in the PTA group died; none of the deaths were procedure-related.

Critical appraisal

This was a randomized, multi-center study that included a power calculation. The study was powered based on an estimated binary recurrent restenosis rate of 6 months, so 12 month outcomes carry less weight. The 12 month follow up is also fairly short. Randomization was performed using a 1:1 ratio in blocks of 10. No subgroup analysis was performed and there were significant differences in pre-dilation between the treatment groups. Similarly to other studies the operators could not be blinded to the assigned treatment because of the different appearance of coated and uncoated balloons. Rutherford classes 2 to 4 were included.

ISAR-PEBIS: Ott et al. 2017

Ott et al. (2017) reported the results of the ISAR-PEBIS trial - a multicentre RCT conducted in Germany. The efficacy and safety of the IN.PACT Admiral DCB was compared to standard PTA, with or without stenting, in 70 patients (n = 36 vs. 34, respectively) with symptomatic in-stent restenosis involving femoropopliteal lesions. Patients were randomly assigned in a 1:1 ratio to treatment with DCB or PTA. Follow-up was 24-months. Patients received 100 mg per day of acetylsalicylic acid and 75 mg per day of clopidogrel. Patients were given an intra-arterial bolus of 500mg of aspirin and of 5000U of heparin. Pre-dilation with a standard PTA balloon was performed in both groups, the intervention received addionally the DCB. At control angiography (6-8 months follow-up), the primary endpoint percentage diameter stenosis (44±33% versus 65±33%, p=0.01) and binary restenosis were significantly reduced with

DCB versus PTA (30% versus 59%, p=0.03). At 24-month follow-up, DCB was associated with a reduction of TLR in comparison to PTA (19% versus 50%, p=0.007). No major amputations were required, 3 patients in the DCB and 0 in the PTA group died (p=0.24), although none were procedure-related.

Critical appraisal

This was a randomized, multi-center study that included a power calculation. The study was powered only for the primary angiographic end point (stenosis rate) at 6 months, therefore long term follow-up outcomes including clinical outcomes results should be interpreted with caution. Randomization was performed using a 1:1 ratio. Similarly to other studies the operators could not be blinded to the assigned treatment because of the different appearance of coated and uncoated balloons. Rutherford classes 2 to 5 were included. There were statistically significant differences in the rates of bailout stenting between the two groups (higher in the PTA group).

Conference abstracts

Krishnan et al. 2016

The 36-month follow-up data of the IN.PACT SFA trial were reported by Krishnan et al. (2016) as a conference abstract. At 36 months, patients treated with DCB showed significantly higher primary patency when compared with PTA (69.5% vs. 45.1%; p<0.001). The rates of CD-TLR were 15.2% and 31.1% (p = 0.002) for the DCB and PTA groups, respectively. The overall mortality rate in the DCB group was 10.7% versus 1.9% in the PTA group (p=0.006). There were no device- or procedure-related deaths and no major amputations in either group through 36-month follow-up. The rate of vessel thrombosis was low (2% DCB vs. 4.9% PTA; p>0.05). Both groups showed similar functional improvement at 3 years, although DCB patients achieved this level of function with 48% fewer reinterventions.

Critical appraisal

This is a conference abstract, therefore, there is limited information to perform a methodological quality assessment. However, since these are updated results of the IN.PACT SFA trial the same methodological quality as in Laird et al. 2015 is assumed.

Krishnan et al. 2017

Krishnan et al. 2017 reported a subgroup analysis of the IN.PACT SFA trial. Of the 331 patients enrolled, 143 had diabetes (89 DCB and 54 PTA) and 188 were non-diabetic (131 DCB vs. 57 PTA). There were no differences between the two groups in terms of baseline demographics, clinical, and lesion

characteristics status. DCB treatment was effective in both groups at 24 months with significantly higher primary patency (diabetic 73.3% vs. 45.8%, p=0.0025 and Non-diabetic 82.5% vs. 54.5%, p<0.0002) when compared to PTA. Likewise, the rates of CD-TLR were significantly lower for diabetic patients treated with DCB when compared to those treated with PTA (p=0.0030). There were no major amputations and no device- or procedure-related deaths reported in either group.

Critical appraisal

This is a conference abstract, therefore, there is limited information to perform a methodological quality assessment. However, since these are updated results of the IN.PACT SFA trial the same methodological quality as in Laird et al. 2015 is assumed.

Werk et al. 2014

Werk et al. 2014 reported the 2-year follow-up results of the PACIFIER trial, the TLR and major adverse events rates for DCB versus PTA were 16.7% vs. 28.9% (p=0.2) and 21.4% vs. 37.8% (p=0.1), respectively.

Critical appraisal

This is a conference abstract, therefore, there is limited information to perform a methodological quality assessment. However, since these are updated results of the PACIFIER trial the same methodological quality as in Werk et al. 2012 is assumed.

Non-comparative studies

Full-text publications

Brodmann et al. 2017

Brodmann et al. (2017) reported the results of 131 patients enrolled in the IN.PACT Global study. The study was a prospective, multi-centre single-arm trial, at 64 sites around the world. The authors aimed to assess the efficacy and safety of the IN.PACT Admiral DCB in patients with in-stent restenosis. The primary effectiveness endpoint was 12-month primary patency, defined as freedom from CD TLR and freedom from restenosis. The primary safety composite endpoint was freedom from device- and procedure-related mortality through 30 days, and freedom from major target limb amputation and target lesion revascularization. The 12-month CD-TLR rate was found to be 7.3% and the primary patency rate was 88.7%. The primary safety outcome at 12 months, was 92.7%. There were no major target limb amputations, no deaths, and a low thrombosis rate (0.8%) was observed.

Critical appraisal

This was a non-comparative study that did not report a sample size calculation. The study also did not report CIs. All analyses were based on the intention-to-treat principle. Adjudication was independently performed by a Clinical Events Committee but no information on blinding was reported. Rutherford classes 2-5 were included. The study had a short follow-up of only 12 months.

Micari et al. 2013

Micari et al. (2013) presents the 2-year results of a prospective multicentre registry of DCB for femoropopliteal PTA in Italy. A total of 105 people were enrolled. They had symptomatic SFA and/or proximal popliteal artery disease (Rutherford 2-4) and were treated with IN.PACT Admiral DCB and provisional stenting. Follow-up after a mean of 27 months was obtained in 93.3% of people. Primary patency was 83.7% and 72.4% at 1 and 2 years, respectively. Major adverse events had occurred in 17 people (17.5%), and 2 deaths were reported (2.2%). There were persistently significant benefits in Rutherford classification, ankle-brachial index, absolute claudication distance, and quality of life ($p<0.001$). Secondary patency rate was achieved in 89 cases (84.7%).

Critical appraisal

This was a non-comparative study with no reported power calculation or CIs. Patients were followed up at 12 and 24 months, which is a longer follow up period than the majority of the studies. Results on subgroups (stented vs. not stented, calcified vs. not calcified, popliteal involvement vs. no involvement, occlusion vs. stenosis) are not included due the small numbers in the groups making them underpowered.

Micari et al. (2017)

Micari et al. (2017) reported the results of the SFA-Long study – a prospective, multicenter, single-arm study conducted in Italy. The efficacy, safety and functionality of the IN.PACT Admiral DCB were assessed in 105 patients with symptomatic SFA and/or proximal popliteal artery disease. All lesions were predilated for 2 minutes with an undersized (0.5 to 1.0mm smaller than reference vessel), uncoated balloon. The primary patency rate after 24 months was 70.4% and the rate of clinically driven TLR was 15.3% (95% CI: 9.2% to 22.4%). The secondary patency rate was 79.6% (95% CI: 71.4% to 87.8%). Vessel thrombosis was reported in 2% of patients. 51% of patients were asymptomatic after 24 months.

Critical appraisal

This was a non-comparative study with no reported power calculation. However, the study did report CIs. Furthermore, the study focused on a single treatment strategy, so there can be no conclusions drawn about the IN.PACT Admiral in comparison to other interventions. Three of the 6 sites contributed the majority of the 105 cases and this imbalance may have had an effect on the results. Subgroups (i.e. hypertension, diabetic) were small, so no conclusions can be drawn on these high risk patients. Rutherford classes 2-4 were included. Follow up was reasonably long at 24 months.

Conference abstracts

Ansel et al. 2017

Ansel et al. (2017) reported the results of 281 standard use patients from the IN.PACT Global study. The study was a prospective, multi-centre cohort trial, at 64 sites around the world, aiming to assess the efficacy and safety of the IN.PACT Admiral DCB. Standard use patients were defined as IDE-like patients with simple de novo lesions, lesion lengths ≤18cm, single lesions, total occlusions ≤ 10cm, calcium levels of none to mild and excluding in-stent restenosis. It was found that the IN.PACT Admiral had a CD-TLR rate of 3.4%. Major limb amputation was 0% in the standard patients and 0.3% in the complex set.

Critical appraisal

This is a conference abstract, therefore, there is limited information to perform a methodological quality assessment. This was a non-comparative study that did not report a sample size calculation. The study also did not report CIs. Adjudication was independently performed by a Clinical Events Committee. In the standard use group, Rutherford classes 2-4 were included.

Excluded studies

The EAC excluded 11 full text peer-reviewed publications and 5 conference abstracts. For a detailed summary of these studies please see appendix D.

Table 4: Table of included studies

Included reference	Design and intervention(s)	Participants and setting	Outcomes	Results	Withdrawals	EAC Comments
Laird et al. (2015)	IN.PACT SFA Trial RCT prospective, international, multicentre, single-blinded, randomized 2 year follow-up IN.PACT Admiral with or without stenting ● PTA with or without stenting ●	331 patients (2:1 ratio assigned to the intervention) with symptomatic SFA and/or proximal popliteal artery disease Mean age = 67.5 ± 9.5 Men = 65% Hypertension = 91.4% Hyperlipidemia = 84.5% Diabetic = 40.5% Current smoking = 38.6% Coronary Artery Disease = 57.0% ABI = 0.769 ± 0.228 Rutherford 2–4 = 100% Patent run-off vessels: 0 = 3.3%, 1 = 13.7%, 2 = 41.5%, 3 = 41.5% (p=0.04 between groups) Stenosis >70% Lesion lengths between 4-18 cm and occlusion with lengths 10 cm involving the superficial femoral and proximal popliteal arteries.	Primary patency CD-TLR Major amputations Functional improvement Device related deaths Mortality at 2 years follow-up ●	Significantly favours treatment with IN.PACT Admiral at 2 years follow-up, however mortality was higher in this group <u>Primary patency</u> DCB 42 (78.9%) vs. PTA 54 (50.1%) (p<0.001) <u>CD-TLR</u> DCB 18, 9.1% vs. PTA 30, 28.3% (p<0.001) <u>MAE</u> DCB 38, 19.2% vs. PTA 33, 31.1% (p=0.023) <u>Functional improvement</u> DCB 133, 76.9% vs. PTA 61, 59.2% (p=0.003)	11 w/d (10 intervention and 1 comparator) 6 lost to follow-up (3 in each group)	Good methodological quality Powered to detect clinically significant TLR at 1 year follow-up, however results presented for follow-up up to 3 years (see Krishan et al 2016 below) Higher mortality in intervention group not related to the technology according to the authors and the clinical experts The intervention

Included reference	Design and intervention(s)	Participants and setting	Outcomes	Results	Withdrawals	EAC Comments
		Stat. significant differences in pre-dilation % and Number of treatment balloons per subject.		Device related deaths None Mortality DCB 16, 8.1% vs. PTA 1, 0.9% (p=0.008)		cohort had a higher number of pre-dilation procedures performed (statistically significant). Directly company funded
Krishan et al. 2016 (abstract)	Same as above 3-year follow-up	Same as above	Primary patency and CD-TLR at 3 years	Primary patency DCB 42 (69.5%) vs. PTA 54 (45.1%) (p<0.001) CD-TLR DCB 15.2% vs. PTA 31.1% (p=0.002)	NR	Same as above
Krishan et al. 2017 (abstract)	Same as above Sungroup analysis patients with diabetes, follow-up 2 years	Same as above	Primary patency and device-related death	Primary patency DM DCB 73.3% vs. PTA 45.8%, p=0.0025 Non-DM DCB 82.5% vs. PTA 54.5%, p<0.0002)	NR	Same as above

Included reference	Design and intervention(s)	Participants and setting	Outcomes	Results	Withdrawals	EAC Comments
Werk et al. 2012	PACIFIER trial Prospective, multicentre randomized trial, Germany, 6 and 12 month follow up IN.PACT Pacific with or without stenting PTA with or without stenting	85 patients with symptomatic SFA and/or proximal popliteal artery disease (randomised to 1:1) Mean age = 71 ± 7 Men = 59% Hypertension = 65.9% Hypercholesterolemia = 50% Diabetic = 43.2% Current or prior smoking = 48.8% Coronary Artery Disease = 31.8% ABI = 0.73 ± 0.30 Infrapopliteal patent vessels: 1 = 27%, 2 = 36%, 3 = 36% Rutherford 2-5 Stenosis >70% Lesion length 3-30cm Stat. significant difference in balloons per lesion between groups	LLL Binary restenosis CD-TLR MAE Device related deaths Mortality at 1 years follow-up	Significantly favours treatment with IN.PACT Pacific at 1 year follow-up <u>LLL</u> DCB -0.01mm (-0.29-0.26) vs. PTA 0.65mm (-0.37-0.93) (p=0.001) <u>Binary restenosis</u> <u>CD-TLR</u> DCB 3 (7.1%) vs. PTA 12 (27.9%), p=0.02 <u>MAE</u> DCB 3 (7.1%) PTA 15 (34.9%) (p=0.01)	6 lost to follow-up (2 in the intervention and 4 in the comparator group)	Good methodological quality. Powered to detect an geographicic endpoint at 6 months follow-up, however results presented for follow-up up to 2 years (see Werk et al 2014 below)

Included reference	Design and intervention(s)	Participants and setting	Outcomes	Results	Withdrawals	EAC Comments
Werk et al. 2014 (abstract)	Same as above 2 year follow-up	Same as above	Same as above	Differences between IN.PACT Pacific and PTA at 2 year follow-up are not statistically significant CD-TLR DCB 16.7% vs. PTA 28.9%, p=0.2 MAE DCB 21.4% vs. PTA 37.8% p=0.1	NR	Same as above

Included reference	Design and intervention(s)	Participants and setting	Outcomes	Results	Withdrawals	EAC Comments
Krankenberg et al. 2015	FAIR trial RCT (Germany), 5 centres, block randomised 1:1, non-blinded. 12-month follow-up. IN.PACT Admiral with or without stenting PTA with or without stenting	119 patients with superficial femoral artery in-stent restenosis (randomised to 1:1) Proximal popliteal artery had to be patent Mean age = 69 ± 8 Men = 53.2% Hypertension = 83.9% Hyperlipidemia = 77.4% Diabetic = 45.2% Current smoking = 29% Coronary artery disease = 41.9% ABI = 0.63 ± 0.27 Rutherford 2–5 Patent run-off vessels: all = 54.8%, ≥ 1 occluded = 43.5% Stenosis >70% Lesion lengths up to 20 cm Stat. significant difference in pre-dilation between groups.	Binary restenosis CD-TLR Major amputations Functional improvement Device related deaths Mortality at 1 years follow-up	Significantly favours treatment with IN.PACT Admiral at 1 years follow-up <u>Binary restenosis</u> DCB 29.5% vs. PTA 62.5% (p=0.004) <u>CD-TLR</u> DCB 8.2% vs. PTA 52.6% (p<0.0001) <u>MAE</u> DCB 2.1% vs. PTA 33, 4.5% <u>Functional improvement</u> DCB 133, 77.8% vs. PTA 52.3% (p=0.015) <u>Device related deaths</u> None <u>Mortality</u> DCB 2, 4.3% vs. PTA 3, 6.8% (p=0.591)	NR	The study was powered based on an estimated binary recurrent restenosis rate of 6 months, so 12 month outcomes and clinical outcomes are not powered. The 12 month follow up is not adequate. There were significant differences in pre-dilation between the treatment groups.

Included reference	Design and intervention(s)	Participants and setting	Outcomes	Results	Withdrawals	EAC Comments
Ott et a. 2017	ISAR-PEBIS Prospective, randomised, controlled trial, Germany, 2 year follow up IN.PACT Admiral with or without stenting PTA with or without stenting	70 patients with symptomatic in-stent restenosis of SFA, randomised 1:1 (DCB, 36 patients, mean lesion length 132mm, mean age 70-yrs, 12 female, 33 hypertension, 35 dyslipidemia, 12 diabetes, 21 smokers, 17 CAD. PTA, 34 patients, mean lesion length 146mm, mean age 68-yrs, 10 female, 30 hypertension, 33 dyslipidemia, 12 diabetes, 24 smokers, 16 CAD).	Binary restenosis CD-TLR Mortality (all cause)	Binary restenosis DCB 30% vs. PTA 59% (p=0.03) CD-TLR DCB 19% vs. PTA 50% (p=0.007) Mortality DCB 3, 8.3% vs. PTA 0, 0.0% (p=0.24)	16 lost to follow-up (9 in the intervention and 7 in the comparator group)	Primary endpoint was angiographic not clinical. There were statistically significant differences in the rates of bailout stenting between the two groups (higher in the PTA group).

Included reference	Design and intervention(s)	Participants and setting	Outcomes	Results	Withdrawals	EAC Comments
Micari et al 2013	Multicentre Italian Registry, prospective, multicentre, 2 year follow-up IN.PACT Admiral with or without stenting No comparator	105 patients with symptomatic SFA and/or proximal popliteal artery disease Mean age = 68 Men = 81% Hypertension = 85.7% Hyperlipidemia = 74.3% Diabetic = 48.6% Current smoking = 62.8% Coronary Artery Disease = 42.9% ABI = 0.56 ± 0.15 Rutherford 2-4 (7.6%) Stenosis unknown Lesion length ≤15cm	CD-TLR Major amputations MAE Functional improvement Device related deaths Mortality at 1 years follow-up	CD-TLR DCB 14, 14.3% MAE DCB 17, 17.5% Major amputations DCB 1, 1% Functional improvement DCB 133, 76.9% vs. PTA 61, 59.2% (p=0.003) Device related deaths None Mortality DCB 2, 2.2%	NR	Non comparative study. Follow was adequate (12 and 24 months). Results on subgroups are not included due to the small numbers in the groups, making them underpowered.

Micari et al. 2017	SFA Long study, prospective, multicentre, Italy, 2 year follow-up IN.PACT Admiral with or without stenting  No comparator 	105 patients with symptomatic SFA and/or proximal popliteal artery disease Mean age = 68 Men = 81.9% Hypertension = 88.6% Diabetic = 57.2% Current smoking = 68.6% Rutherford 2-4 (7.6%) Stenosis unknown Lesion length >15cm 	Primary patency CD-TLR MAE Functional improvement Quality of life Device related deaths Mortality at 2 years follow-up 	<u>Primary patency</u> DCB 70.4% (95% CI: 60.2% to 79.6%) <u>CD-TLR</u> DCB 84.7% (95% CI: 77.6% to 90.8%) <u>MAE</u> DCB 10 (10.2%) <u>Functional improvement</u> DCB 51% <u>Device related deaths</u> None <u>Mortality</u> DCB 5	7 patients did not complete 24-month follow-up (1 withdrew consent, 6 were lost to follow-up)	Non comparative and non-powered study. CIs reported Adequate follow-up (24 months). Three of the 6 sites contributed the majority of the 105 cases and this imbalance may have had an effect on the results. Subgroups (i.e. hypertension, diabetic) were small, so no conclusions can be drawn on these high risk patients.

Included reference	Design and intervention(s)	Participants and setting	Outcomes	Results	Withdrawals	EAC Comments
Brodmann et al. 2017	IN.PACT Global study Prospective, multicentre, non-comparative, 1 year follow-up IN.PACT Admiral with or without stenting No comparator	131 Patients with 149 femoropopliteal and below the knee ISR lesions Mean age = 67.8 ± 10.1 Men = 69.5% Hypertension = 81.5% Hyperlipidemia = 72.1% Diabetic = 35.1% Current Smoking = 35.9% Coronary Heart Disease = 36.5% ABI = 0.667 ± 0.187 Rutherford 2-5 No runoff vessel data Stenosis = 84.8 ± 14.9 % Mean Lesion Length = 17.17 ± 10.47 cm	CD-TLR Thrombosis Major amputation Device related deaths	<u>CD-TLR</u> DCB 7.5% <u>Thrombosis</u> DCB 2.9% <u>Major amputation</u> DCB 0.2% <u>Device related deaths</u> None	6 patients	Non-comparative, non-powered, inadequate follow-up. Adjudication was independently performed.

Included reference	Design and intervention(s)	Participants and setting	Outcomes	Results	Withdrawals	EAC Comments
Ansel et al. 2017	IN.PACT Global study Prospective, multicentre, non-comparative, 1 year follow-up IN.PACT Admiral with or without stenting No comparator	281 Patients with femoropopliteal and below the knee lesions <u>Standard Use Patients:</u> Mean age = 67.2 ± 10.4 Men = 63.3% Hypertension = 76.7% Hyperlipidemia = 68.8% Diabetic = 36.6% Current smoking = 38.1% Coronary Heart Disease = 33.1% ABI = 0.695 ± 0.229 Rutherford 2-4 Stenosis = 89.1 ± 11.2% Mean Lesion Length = 7.86 ± 4.53 cm	CD-TLR Thrombosis Major Amputation Device Related Death	<u>CD-TLR</u> DCB 3.4% <u>Thrombosis</u> DCB 1.1% <u>Major Amputation</u> DCB 0.0% <u>Device Related Death</u> DCB 0.4%		Non-comparative, non-powered, inadequate follow up. Adjudication was independently performed.

3.4 Overview of methodologies of all included studies

- All primary studies included by the sponsor and the EAC were prospective, interventional, 4 were RCTs (Laird et al. 2015, Krankenberg et al. 2015, Krishan et al. 2016, Krishan et al. 2017, Ott et al. 2017, Werk et al. 2012, Werk et al. 2014) and the rest were non-comparative studies (Micari et al. 2013, Micari et al. 2017, Ansel et al. 2017 and Brodmann et al. 2017). All studies evaluated the intervention specified in the scope. All comparative studies compared DCB with PTA with or without stenting.

- Seven of the included references were full text publications, and 4 were reported as conference abstracts.

- The prevalent population in the submitted studies were patients with Rutherford score 2-3 (moderate to severe claudication). However, most studies included patients with Rutherford score equal or above 4 which indicates patients with CLI. As per the EACs inclusion criteria all the included studies had ≥90% of patients with intermittent claudication.

- Baseline characteristics were provided in 9 of the included references. All published references included baseline characteristics. With the exception of references describing results from the IN.PACT Global study, the other unpublished references provide updated results of the IN.PACT SFA and PACIFIER trial, therefore, it is assumed that baseline characteristics are the same unless stated otherwise. The mean age varied from 67.5 (Laird et al. 2015) to 71 (Werk et al. 2012) and the proportion of males varied from 59% (Werk et al. 2012) to 81.9% (Micari et al. 2017).

- Pre-dilation was reported to have been carried out in 5 of the included references and post-dilatation was carried out in 2 (Laird et al. 2015 and Krishnan et al. (2016), both IN.PACT SFA trial).

- Follow up durations varied from 6 months (Werk et al. 2012) to 3 years (Krishnan et al. 2016).

- All of the included publications came from studies using a multi-centre approach. 7 of the included publications included a power calculation. Four reported that adjudication was performed by an independent Clinical Events Committee. The levels of blinding varied but due to the nature of the procedure, interventionists could not be blinded. Three out of the 7 comparative studies reported statistically significant imbalances in a baseline characteristic between the 2 groups.

- All studies reported CD-TLR as an outcome. Three studies reported CD-TLR at a 6 month follow up (Werk 2012, Ott 2017, Krankenberg 2016), 4 studies reported 1 year results (Ansel 2017, Brodmann 2017, Krankenberg 2016 and Werk 2012), 5 studies reported 2 year results (Laird 2015, Micari 2013, Micari 2017, Ott 2017 and Werk 2014) and only 1 reported 3 year results (Krishnan 2016).

- With regards to adverse events, 4 studies reported both procedure- or device-related mortalities and total mortalities, 2 reported only the total number of mortalities and 1 reported only procedure- or device-related mortalities. 5 studies reported amputations, 4 studies reported MAE and 3 studies reported thrombosis.

- Only 2 publications from the same trial produced significant results for a subgroup, Laird et al. (2015) and Krishnan et al. (2017) reported outcomes for a cohort of diabetic patients at 24 and 36 months respectively. Other papers reporting subgroup analyses (Micari 2013, Micari 2017 and Tepe 2015) failed to produce significant results due to small sample sizes. They reported subgroup analyses on patients with diabetes, hypertension, stented versus non-stented, calcified versus non-calcified, popliteal involvement versus no involvement and occlusion versus stenosis.

- A number of the outcomes reported were only present in a single study, such as EuroQOL EQ5D score, late lumen loss, CD-TVR and multiple relating to improvements in Rutherford class.

3.5 Overview and critique of the company's critical appraisal

The sponsor used the checklist proposed by NICE for the critical appraisal included into their submission. For RCTs, they followed the "CRD's guidance for undertaking reviews in health care" from the Centre for Reviews and Dissemination, University of York, 2008 (Chapter 1, section 1.3.4.). For the observational studies they used the CASP guidelines.

The EAC carried out a quality appraisal of the final 11 references selected for inclusion in the systematic review. The checklist proposed by NICE's guidelines manual (Appendix C) was adapted in accordance with a previous published assessment by Candy et al. 2017. For the non-comparative studies the CASP guidelines were used. A copy of the EACs methodological quality appraisal checklist is included in appendix B.

The EACs checklist assess the risk of bias in 4 domains categorised as selection bias, performance bias, attrition bias and detection bias. The detection bias domain was adapted to include questions about the definition

of TLR, and whether or not an independent laboratory or an events committee was involved with one extra general category was added to assess issues related to conflict of interest, sample size calculations and whether a clinical vs. an angiography endpoint was used. All domains are categorised as low (risk of bias or applicability), high, or unclear, and no attempt is made to formally grade the strength of evidence the study provides. The results of the assessment are illustrated in Table 5 and Table 6 below.

Table 5: Results of methodological assessment for RCTs

Study	**Werk 2012**	**Ott 2017**	**Laird 2015**	**Krankenberg 2016**
Selection Bias	Low risk of bias	Unclear/ unknown risk	Low risk of bias	Unclear/unknown risk
Performance Bias	Unclear/ unknown risk	Unclear/ unknown risk	Unclear/ unknown risk	**High risk of bias** – Comparison group did not receive the same care apart from the intervention and individuals were not blinded to their treatment
Attrition Bias	Low risk of bias	Low risk of bias	Low risk of bias	Unclear risk of bias
Detection Bias	Unclear/ unknown risk	Unclear/ unknown risk	Low risk of bias	**High risk of bias** – short study duration, investigators were not blinded and bias in selection for TLR
Other	Low risk of bias	Low risk of bias	Unclear/ unknown risk	Low risk of bias

Table 6: Results of methodological assessment for observational studies

Study	Ansel 2017	Brodmann 2017	Micari 2013	Micari 2017
Is the study based on a representative sample selected from a relevant population?	Yes	Yes	Yes	Yes
Are criteria for inclusion explicit?	Yes	Yes	Yes	Yes

Did all individuals enter the study at a similar point in their disease progression?	Unclear	Yes	Yes	Yes
Was follow up long enough for important events to occur?	No	No	Yes	Yes
Were outcomes assessed using objective criteria or was blinding used?	Yes	Yes	Yes	Yes
If comparisons of sub-series are being made, was there sufficient description of the series and the distribution of prognostic factors?	No	No	No	No

3.6 Results

The sponsor presented results from 16 full text published and 7 conference abstracts primary studies. After excluding Tepe et al 2015, Micari et al. 2012, Micari et al 2016, Bague et al. 2017, Liistro et al. 2013, Grotti et al. 2016, Schmidt et al 2012, Stabile et al. 2012, Virga et al. 2014, Debing et al. 2017, Fanelli et al. 2012, Jaff et al. 2016, Scheinert et al. 2015, Tepe et al. 2014, and Fanelli et al. (2017) the EAC accepted 5 full text publications and 2 conference abstracts. The results from these studies along with 2 full text publication (Brodmann et al. 2017, Ott et al. 2017) and 2 conference abstract (Krishan et al. 2017, Werk et al. 2014) identified by the EAC are included in Table 7 below.

Table 7: Included studies results

Study	Study Publications	Primary patency	Clinically driven TLR (CD-TLR)	MAE	Procedure or device-related death	Mortality
FAIR trial	Krankenberg 2016	At 6 months:DCB 84.6% vs. PTA 55.3% (p = 0.002) At one year: DCB 70.5% vs. PTA 37.5% (p= 0.004)	At 6 months: DCB 3.6 % vs. PTA 19.0% (p = 0.0117) At one year: DCB 8.2% vs. PTA 52.6% (p< 0.0001)	DCB 2.1% vs. PTA 33, 4.5%	None	DCB 2, 4.3% vs. PTA 3, 6.8% (p=0.591)
INPACT SFA trial	Laird 2015 and Krishnan 2016	At 2 years: DCB 42 (78.9%) vs. PTA 54 (50.1%) (p<0.001) At 3 years: DCB 42 (69.5%) vs. PTA 54 (45.1%) (p<0.001)	At 2 years: DCB 18, 9.1% vs. PTA 30, 28.3% (p<0.001) At 3 years: DCB 15.2% vs. PTA 31.1% (p=0.002)	At 2 years: DCB 38, 19.2% vs. PTA 33, 31.1% (p=0.023)	None	At 2 years: DCB 16, 8.1% vs. PTA 1, 0.9% (p=0.008)
INPACT SFA trial (subgroup analysis)	Krishnan 2017	At 2 years: DM DCB 73.3% vs. PTA 45.8%, p=0.0025 Non-DM DCB 82.5% vs. PTA 54.5%, p<0.0002)	NR	NR	None	NR

ISAR-PEBIS	Ott 2017	At 6 months: DCB 30% vs. PTA 59%, (p=0.03)	At 2 years: DCB 19% vs. PTA 50% (p=0.007)	At 2 years: DCB 3% vs. PTA 0% (p=0.33)	NR	At 2 years: DCB 3, 8.3% vs. PTA 0, 0.0% (p=0.24)
PACIFIER	Werk 2012 and Werk 2014	At 6 months: DCB 8.6% vs. PTA 32.4%, (p=0.01).	At 1 year: DCB 3 (7.1%) vs. PTA 12 (27.9%), p=0.02 At 2 years: DCB 16.7% vs. PTA 28.9%, p=0.2	At 1 year: DCB 3 (7.1%) PTA 15 (34.9%) (p<0.01) At 2 years: DCB 21.4% vs. PTA 37.8% p=0.1	NR	At 1 year: DCB 0% vs. PTA 7.5% (p=0.24)
IN.PACT Global	Ansel 2017	NR	At 1 year: DCB 3.4%	At 1 year: DCB 7.9%	At 1 year: DCB 0.4%	At 1 year: DCB 3.8%
IN.PACT Global	Brodmann 2017	At 1 year: DCB 88.7%	At 1 year: DCB 7.1%	At 1 year: DCB 8.9%	None	None
Multicentre Italian registry	Micari 2013	At 2 years: DCB 72.4%	At 2 years: DCB 14, 14.3%	At 2 years: DCB 17, 17.5%	None	At 2 years: DCB 2, 2.2%
SFA Long study	Micari 2017	At 2 years: DCB 70.4% (95% CI: 60.2% to 79.6%)	At 2 years: DCB 15.3% (95% CI: 22.4% to 9.2%)	At 2 years: DCB 10 (10.2%)	None	At 2 years: DCB 5.1%
NR= not reported						

3.7 Description of the adverse events

The manufacturer did not run a separate search for adverse events. The EAC searched the MHRA alerts database (searched 9th November 2017: "in.pact", 0 results) and FDA-MAUDE database (searched 9th November 2017: "in.pact admiral", 684 results; "in.pact pacific", 114 results). There have been no recalls of IN.PACT devices. The EAC limited the search of MAUDE to 'Event type: Death' and excluded events where the investigator ruled the event was not related to the device, or events taken from published studies. The results of the remaining events are summarised in appendix C.

With regards to adverse events reported in the literature, 4 studies reported both procedure- or device-related mortalities and total mortalities, 2 reported only the total number of mortalities and 1 reported only procedure- or device-related mortalities. Five studies reported amputations, 4 studies reported MAE and 3 studies reported thrombosis. With the exception of the IN.PACT SFA trial that reported a clinically and statistically significant difference in the overall mortality between the intervention and the comparator group, adverse events were either in favor of the DCB or equal between the 2 groups. However, none of the included studies was powered to detect a statistically significant difference between the two groups.

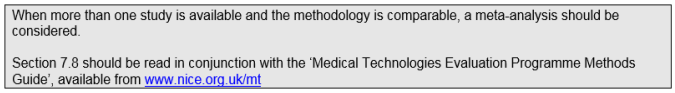
3.8 Description and critique of evidence synthesis and meta-analysis

The sponsor included in their submission an evidence synthesis labelled a 'meta-analysis'. This evidence synthesis consisted of publications identified through the search strategy used to identify published clinical evidence earlier in their submission. The EAC queried several aspects of the sponsors meta-analysis through the teleconference held on the 13th October 2017. The table below (Table 8) includes various areas of query and the EAC and sponsors questions/response along with the EAC conclusion.

Table 8: Sponsors meta-analysis evaluation based on selected queries to Sponsor

EAC question	Sponsor response	EAC conclusion
In section 7.6.6, the sponsor states that 'Fo*r the comparator arm it was not*	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	Suggests that Sponsor have applied different

EAC question	Sponsor response	EAC conclusion
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 their search strategy for retrieving evidence on the comparator if a different search strategy from the intervention was used?	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.	search strategies in identifying studies for inclusion in the Sponsors meta-analysis. This does not fit the scope.
'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.' *'Can the sponsor please explain why these studies (Katsanos et al 2014 etc.) 'would be appropriate for use for the comparator'?'*	*'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.'*	As above.

EAC question	Sponsor response	EAC conclusion
'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?'	*'*  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 *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 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.'*	The EAC note that EAC question was with regards to meta-regression, and the Sponsors response relates to meta-analysis.
'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?'	Sponsor response was verbally given during TC, of which Sponsor confirmed that no formal evaluation on the quality of the studies was undertaken and offered to do so. NICE confirmed that this was not necessary now that the clinical section had been submitted. The Sponsor stated that considering the number of subjects, he suspects that a fixed-effects model was used, and not a random effects model for the Katsanos (2016) meta-analysis.	The EAC note that using sample size to determine whether a meta-analysis used a fixed or random effects model is not appropriate.
'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 sponsors meta-analyses? Ie. Katsanos et al 2014, Katsanos et al 2016, Herten et al 2016, Giacoppo et al 2016.'	The sponsor provided further detailed analysis from several of the 'comparator' studies.	The EAC note that the Sponsors meta-analysis provide proportions only, however, the 'comparator' studies provided different outcome measures such as relative risks, and

EAC question	Sponsor response	EAC conclusion
		number needed to treat.

Given the responses from the Sponsor, the EAC can conclude that the Sponsor has not performed a meta-analysis based on the scope. Indeed, what they have provided in their submission is various pooled results of the intervention only (ignoring any comparator information contained within the included studies), and then used these intervention-only pooled results to compare to the comparator only results from other studies (Katsanos et al., 2014, Katsanos et al., 2016, Herten et al., 2016, Giacoppo et al 2016).

The Sponsor's meta-analysis included RCT, retrospective and prospective cohort study results, which is not advisable (Higgins et al. 2011). Pooled outcomes (of the intervention arm only) were presented as proportions, not hazard ratios or relative risks, unlike the outcomes reported in the 'comparator' studies. The Sponsor also performed a meta-regression, however, as noted in Table 8, the EAC concludes that this was an inappropriate method to use. Furthermore, the Sponsor fails to provide a sufficient rationale for the choice of covariates in the meta-regression. The sponsor fails to consider the impact of notable heterogeneity of studies, and did not appraise the quality of each study included in the Sponsor's meta-analysis.

Given the various methodological concerns related to the Sponsor's meta-analysis, the EAC excludes all of the Sponsor's evidence synthesis/meta-analysis due to several major methodological flaws, inaccurate synthesis of various study types and that fact that it does not fit the scope. The EAC therefore, has considered all included studies in qualitative analysis for a meta-analysis. The considered studies were reviewed and population outcome data were extracted. Results presented included values for TLR at 6, 12 and 24 months, restenosis, thrombosis, amputation, deaths, other AEs and primary patency.

After careful review of papers, 4 RCT studies were considered by the EAC for inclusion in a potential meta-analysis (*Table 9*). The studies are split into de novo (PACIFIER and IN.PACT SFA) and restenosis (FAIR trial and the study by Ott et al.,

2017) patient groups. Two of the included studies also had later updates available (Werk et al., 2012 and Laird et al., 2015). Following on from Werk et al., 2012, an abstract was published, Werk et al., 2014, which provides 3-year results of the PACIFIER trial. However, the EAC have excluded this abstract as the information provided within is not of sufficient quality to include in the meta-analysis: no denominator values and has not adhered to CONSORT. A PowerPoint presentation updating on Laird et al., 2015 was produced by Krishnan et al. 2016 and the sponsor. This provides 3-year results of the In.Pact SFA trial. However, the EAC have excluded this evidence from the meta-analysis as it is not peer-reviewed, provides insufficient information to include in the meta-analysis and furthermore, does not adhere to CONSORT.

Table 9: Studies included in meta-analysis

References, trial name & patient group.	Target lesion revascularization (TLR) at 6 months	Target lesion revascularization (TLR) at 12 months	Target lesion revascularization (TLR) at 24 months	Restenosis	Thrombosis	Amputations	Deaths	AEs	Primary Patency
Werk et al 2012 PACIFIER trial De novo	3/39 for DCB and 8/39 for PTA. The EAC note that the denominator values at 6 months is not the same as the denominator values given at baseline. There is a loss of 2 patients in DCB and 3 patients in PTA group.	3/39 for DCB and 10/40 for PTA. The EAC note that for PTA group, there is a gain on n=1 patient compared to 6 months.		N=3 in DCB and n=9 in PTA. Denominator value not given.	No reported thrombosis in either group.	No reported amputations in either group.	No deaths in DCB group and n=2 deaths in PTA group at 6 months (cardiovascular failure and pneumonia and septic shock). At 12 months, a total of 3 deaths in PTA group (two from 6 month period and additional death from cardiovascular failure) and	No other reported AEs.	

References, trial name & patient group.	Target lesion revascularization (TLR) at 6 months	Target lesion revascularization (TLR) at 12 months	Target lesion revascularization (TLR) at 24 months	Restenosis	Thrombosis	Amputations	Deaths	AEs	Primary Patency
							none in DCB group.		
Laird et al 2015 In.PACT SFA trial De novo			Study reports 20/198 for DCB, and 31/106 for PTA.	Unclear.	Thrombosis reported in 3/198 for DCB group and 4/106 for PTA group. The EAC were not able to determine the accuracy of the denominator values. See notes below.	No reported amputations at 24 months for either group.	N=16 deaths in DCB and 1 death in PTA group. Study gives causes, and stated unrelated to study intervention. See notes below.	No other reported AEs.	At 24 months, primary patency of n=42 (78.9%) in DCB group and n=54 (50.1%) in PTA group. However, the EAC note that the various denominator values given were not able to

References, trial name & patient group.	Target lesion revascularization (TLR) at 6 months	Target lesion revascularization (TLR) at 12 months	Target lesion revascularization (TLR) at 24 months	Restenosis	Thrombosis	Amputations	Deaths	AEs	Primary Patency
									reproduce the % figures given. See notes below.
Krackenberg et al 2016 FAIR trial Restenosis	2/62 – DCB (EAC - determined values) Difficulty calculating TLR for PTA group based on KM graph.				One late stent thrombosis in DCB group and 'one subacute stent thrombosis after TLF with DCB in a PTA group patient.	No reported amputations .	Two deaths in DCB group and three deaths in PTA group within 12 months. Cause stated as not procedure related.	In PTA group, one tibioperoneal trunk occlusion at 294 days. Two DCB patients had transient cerebral ischemic attack (not related to procedure). Two DCB	

References, trial name & patient group.	Target lesion revascularization (TLR) at 6 months	Target lesion revascularization (TLR) at 12 months	Target lesion revascularization (TLR) at 24 months	Restenosis	Thrombosis	Amputations	Deaths	AEs	Primary Patency
								patients had distal embolization which required no further intervention. No reported myocardial infarctions, or major bleeding.	
Ott et al 2017 ISAR-PEBIS trial Restenosis	Ott's reported values state 0/36, however the EAC note that the denominator value does not consider loss to		Ott's reported values state 7/36, however, EAC note that the denominator missed out the 3 deaths later	Binary restenosis given as 8/27 for DCB and 16/37 for PTA. The	Reports n=1 thrombosis at 382 days in DCB group. None are mentioned in	No reported amputations for either group.	Three reported deaths in DBC group and none in PTA group. One death is listed as unknown,	Reports one occurrence of *'acute thrombotic occlusion after bailout stenting was*	

References, trial name & patient group.	Target lesion revascularization (TLR) at 6 months	Target lesion revascularization (TLR) at 12 months	Target lesion revascularization (TLR) at 24 months	Restenosis	Thrombosis	Amputations	Deaths	AEs	Primary Patency
	follow-up at 6 months. Taking into account the deaths recorded before 6 months, EAC determine that the denominator value is 0/34 for DCB. For the PTA group it is 7/34, which the EAC determine is accurate as no reported deaths and no reported loos to follow-up in PTA group at 6 months.		reported in the article. Furthermore, the KM graph suggests multiple censoring. However, the EAC have only the information to determine loss to follow for deaths. Therefore, determines that the denominator value is 7/33. For PTA, the reported TLR is 0/34 as no reported deaths. Similarly the EAC were unable to account for	denominator value is based on angiogram performed at 6 to 8 months.	the PTA group.		which concerns the EAC. One death was cardiac related and one was multi-organ failure and sepsis.	*successfully treated with thrombotic aspiration'*. Patient was in the PTA group.	

References, trial name & patient group.	Target lesion revascularization (TLR) at 6 months	Target lesion revascularization (TLR) at 12 months	Target lesion revascularization (TLR) at 24 months	Restenosis	Thrombosis	Amputations	Deaths	AEs	Primary Patency
			censoring, so used the reported TLR of 0/34.						

The EAC notes the following:

- Werk et al (2012): Study provides outcome variables for per-lesion (which includes the n=6 patients who were treated twice) and per-patient. The EAC has considered the per-patient outcomes.

- Laird et al (2015): The EAC note that the outcome of TLR at 24 months are based on available case analysis which is of concern with this study as loss to follow-up is not adequately described. For example, 17 patients withdrew from DCB group and 6 patients withdrew from PTA group, and no clear reasons for withdrawal were given. Furthermore, there is a large number of deaths, with 16 deaths occurring in DCB group, and one death in PTA group. The study states that no deaths were related in the study intervention as determined by an '*independent DMC'*, concluding that the mortality rate in DCB of 8.1% was expected, although the low rate in the PTA group of 0.9% was unexpected. The EAC sought clarification from the Sponsor about the '*independent DMC'* and received the following response:

'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'.

  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.

- Krackenberg et al (2016): EAC notes the large difference in baseline figures for predilation with 90.3% (n=56) for DCB and 12.3% (n=7) for PTA groups and inflation times (seconds) of 131.1 ± 46 for DCB and

153 ± 63 for PTA groups. The EAC note that the denominator value for primary angiograph success for the DCB group is n=61, but the denominator value for DCB group for TLR at 6 months is n=62. No clear information is given about loss to follow up reasons (drop-out rates at 6 months of 16.1% for DCB and 17.5% for PTA and at 12 months of 29.0% for DCB and 29.8% for PTA, which are notably large), and variable denominators are provided through the study which makes the denominator values unreliable. The EAC also note the following statement *''one subacute stent thrombosis after TLF with DCB in a PTA group patient'.* This suggests that there is patient cross-over between the two arms of the study. The EAC concludes that this study is not suitable for inclusion in a meta-analysis.

- Ott et al (2017): EAC notes that one patient in each trial arm was classed as '*Class 5'* on the Rutherford classification. All others were Class 3 or below.

Table 10 documents the EACs calculated relative risk (RR) and 95% confidence intervals were applicable/possible for target lesion revascularization at 6, 12 and 24 months. Synthesis of the other outcome variables of interest where either not appropriate or possible.

Table 10: EAC calculated relative risk for TLR at 6, 12 and 24 months

Reference	Target lesion revascularization (TLR) at 6 months	Target lesion revascularization (TLR) at 12 months	Target lesion revascularization (TLR) at 24 months
De novo			
Werk et al 2012	RR: 0.38 (95% CI: 0.11 to 1.31)	RR: 0.31 (95%CI: 0.09 to 1.03)	
Laird et al 2015			RR: 0.35 (95% CI: 0.21 to 0.58)*

Reference	Target lesion revascularization (TLR) at 6 months	Target lesion revascularization (TLR) at 12 months	Target lesion revascularization (TLR) at 24 months
Restenosis			
Krackenberg et al 2016	Not applicable		
Ott et al 2017	RR 0.07 (95% CI: 0.00 to 1.12)		RR 0.43 (95% CI: 0.20 to 0.89)

*available case analysis rather than intention-to-treat analysis.

Due to the lack of comparable data for the same time points across the studies (and study populations) considered for the EACs meta-analysis, no meta-analysis was able to be performed on the currently available studies with acceptable quality/validity.

3.9 Ongoing studies

The manufacturer included 4 unpublished studies which were not found by the EAC's search (it is not clear whether or not they were found by the sponsor's search). The EAC searched ClinicalTrials.gov, the WHO ICTRP and PROSPERO and found 374 ongoing studies (283 following de-duplication). 2 of the ongoing studies have results available, both of which are funded by the sponsor (INPACT SFA I - NCT01175850 and INPACT SFA II - NCT01566461).

4 Economic evidence

4.1 Published economic evidence

Critique of the company's search strategy

The sponsor conducted an economic evidence search on Embase, Ovid MEDLINE (R) Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) for articles published from 2004 to current. The economic evidence related to drug-coated balloons, rather than a search specific to IN.PACT DCB. A total of 85 records were screened and 7 studies were included. From these only 2 described IN.PACT DCB, with the others describing general DCB.

The EAC reviewed the search strategy (Appendix 3 of manufacturer's submission) and found it be appropriate. In order to confirm that all relevant evidence has been included, the EAC conducted its own search (see Appendix A). Following application of cost and economic filters, the searches retrieved 496 abstracts related to economic evidence. After reviewing these abstracts, the EAC confirmed that no economic evidence, additional to that included by the sponsor was available for the technology.

Critique of the company's study selection

The sponsor selected studies based on the scope: population included patients with peripheral arterial disease as an indication for invasive treatment; intervention included DCB compared to PTA; outcomes included any health economics outcomes (all types of economic evaluation, cost studies, cost analyses, cost – effectiveness and budget-impact analyses). The exclusion criteria applied were: population included patients without peripheral artery disease; population included patients with below-the-knee lesion only; and population did not include patients treated with DCB. Non-English and pre 2004 studies were excluded. The EAC reviewed the inclusion and exclusion criteria and determined that they were appropriate. The EAC also used the same inclusion and exclusion criteria except for the span of search which was limited to studies after 2007.

Included and excluded studies

Though the sponsor's PRISMA diagram and stated submissions of full texts lists 8 studies, the sponsor had only included 7 studies (Diehm and Schnieder 2013; Salisbury et al 2016, Poder and Fisette 2016; Kearns and Thomas 2017, Pietzsch 2014; Katsanos et al 2016; Simpson 2014) in their submission. One paper (Kearns et al 2013) was not included in the submission. The EAC is unclear about the reason for this. Out of the 7 studies, 5 of them were related to general DCB and only 2 (Salisbury et al 2016; Katsanos et al 2016) were related to IN.PACT. As set by the scope, this assessment pertains to only IN.PACT technology and inclusion of general DCB was deemed not relevant for this assessment. The EAC included only those 2 relevant studies.

Overview of methodologies of all included economic studies

Of the listed studies, 4 were decision analytic models, 2 were Markov models, and 2 were discrete event simulations. Five studies were cost-utility analysis, 2 were cost-effectiveness analysis and 1 was a budget impact analysis. Four studies reported data from the UK, 2 from Germany, 1 from US, 1 from Canada and 1 from Switzerland. Two studies reported results from 2 countries in the same paper.

The two relevant studies (Salisbury et al 2016; Katsanos et al 2016) were modelling studies, one being a Markov model alongside an RCT conducted in the US (Salisbury et al 2016) and the other was a decision analytic model for a UK setting (Katsanos et al 2016).

Salibury et al 2016 performed a cost-effectiveness analysis using a state transition Markov model to estimate 2-year QALYs and costs for treatment with DCB (IN.PACT) angioplasty or standard PTA for a typical patient in the US. Though based on the IN.PACT SFA II trial, due to the significant imbalance in 2-year mortality observed between the treatment and standard arm, a modelling approach was used to estimate cost-effectiveness. The observed mortality difference would have led to lower costs and QALYs in the DCB group, but may be a chance finding, and was ignored in the model. Index procedural costs were approximately $1300 per patient higher for the DCB angioplasty group compared with standard PTA, driven by the cost of DCB itself. Index hospitalization costs (ICU, nonprocedural hospitalization

including room, nursing and ancillary costs) were $1129 higher for patients treated with DCB angioplasty. At 2 years' follow-up, target limb revascularization was less frequent in patients treated with DCB angioplasty, yielding savings in TLR costs of $1200 per patient. QALYs were higher among patients treated with DCBs compared to standard PTA (1.53 vs 1.47). The probability that DCB angioplasty is cost-effective compared with standard PTA was 70% using a threshold of $50,000 per QALY gained. The only limitation of this study is that the population included both claudication and ischemic rest pain (Rutherford classes II to IV).

Katsanos et al 2016 implemented a model based per patient cost impact and cost-effectiveness analysis over a 24 month period on pooled TLRs from a UK NHS setting. The strategies evaluated included endovascular drug-eluting treatments for femoropopliteal artery disease compared to with standard care (PTA). Four specific strategies were compared: PTA and bailout bare metal stenting (BMS); primary BMS; drug-coated balloon (DCB) and bailout BMS; and drug-eluting stent (DES) treatment. Estimated from a systematic review of literature, the pooled 24 month TLR estimate was 38.5% (PTA), 26.9% (BMS), 17.6% (DCB) and 19.4% (DES). In a sub-analysis, DCB was separated out as DCB (3.5 microgram with urea-based excipient – IN.PACT) which had a pooled TLR of 11.2%, and other DCB which had a pooled TLR rate of 21.9%. The 24-month cost were £2863 (PTA), £2975 (BMS), £2906 (DCB) and £2907 (DES). QALY gains were 0.005 for BMS, 0.010 for DES and 0.011 for DCB compared to PTA, resulting in the estimated ICERs of £3983 (DCB), £4534 (DES) and £20,719 (BMS) per QALY gained compared to PTA. The study concluded that drug-eluting endovascular therapies for femoropopliteal disease would add meaningful clinical benefit at reasonable additional costs to NHS, with DCBs offering the highest clinical and economic value. The sub-analyses which differentiated the TLR rate for IN.PACT compared to the remainder of DCBs reported an ICER of £2259 per QALY for IN.PACT DCB and £16290 per QALY gained for other DCB. As with the previous paper, the limitation of mixing IC and CLI is applicable to this paper too.

Overview and critique of the company's critical appraisal for each study

The sponsor used the suggested tables to summarise each study's location, model and comparators, patient population, costs, patient outcomes, and results for 7 studies. Further, the sponsor also completed quality assessment for each health economic study included. The EAC thinks, the critical appraisal for each of the included studies have been appropriately performed.

Does the company's review of economic evidence draw conclusions from the data available?

Though the sponsor has included a critical appraisal of the studies, no specific conclusions were draw from the available data. The sponsor felt that the previous economic evaluations for IN.PACT DCB were insufficient as they were not conducted with current UK costs or tariffs, or they did not include latest evidence. In addition, the majority of economic analyses were not specific to IN.PACT DCB and instead looked at DCBs as a class effect. From the two included studies, the EAC draws the conclusion that IN.PACT has higher index procedural costs. However, at 2 years follow-up, TLR is less frequent in patients treated with DCB angioplasty and might result in cost savings or reasonable additional costs. If combined with QALYS, the IN.PACT DCB is cost-effective over a time horizon of 2 years.

4.2 Company de novo cost analysis

The sponsor submitted a de novo cost model since the published economic evidence did not include current UK costs or tariffs, or did not include latest evidence. Further, most of the sponsor's included studies looked at DCBs generally. The EAC agrees with the justification provided. In line with the scope, the sponsor's cost model compares index and TLR costs (with bailout stenting using BMS) compared to PTA with a non-drug coated balloon (withbailout stenting using BMS). The resultant cost and QALYs are estimated for a time horizon of 36 months as a base case.

Patients

The patient population included in the cost analysis are those with femoro-popliteal peripheral arterial disease undergoing revascularization for

intermittent claudication either due to a *de novo* lesion (base case analysis) or an in-stent restenosis (sub-group analysis) of a previously treated lesion. This is in line with the scope.

Technology & Comparator(s)

The technology used as the intervention is IN.PACT DCB and is aligned with the scope. This is compared against PTA with a non-DCB as specified by the scope. When angioplasty is indicated, NICE guidance recommends the use of stenting only as a bail-out undertaking which has also been incorporated with the intervention and comparator.

Model structure

The sponsor has submitted a cost model which applies an NHS and personal social services perspective to estimate the cost-effectiveness of the technology against PTA. The model patient cohort are patients eligible for PTA treatment as per NICE Guidance. To reflect current clinical practice, a certain proportion of ballooned lesions show either an inadequate post-treatment flow or a significant dissection is present – the model captures the cost of stenting with a bare metal stent ("bail out stenting") in such a case, and allows separate consideration of the TLR risk for patients receiving bailout stenting. The probability of TLR is modelled over 3 years in the base case, and total costs for the initial procedure and any TLR are estimated. The schematic representation of the model is shown in Fig 1.

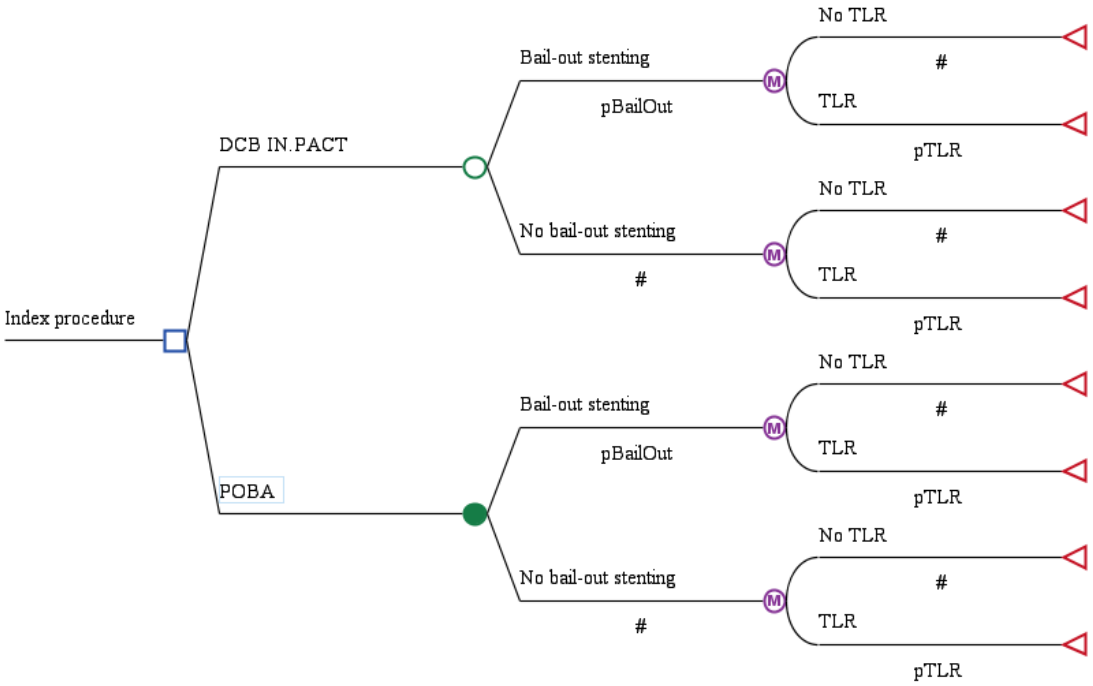


Figure 1: Schematic representation of the model

The EAC thinks that the model structure is adequate to capture the cost and consequences (primarily TLR rates). 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.

The chosen time horizon of 36 months reflects the maximum follow-up horizon available among published studies. A cycle length of 3 months was used in the model, with the justification that TLR proportions of 7 to 21% per year necessitate a cycle length shorter than a year. The EAC does not think these proportions necessitate a shorter cycle length. A short cycle length would have been more appropriate if the TLR rate changed rapidly over time (Sonnenberg and Beck, 1993). As the sponsor assumes the rate of TLR is constant over time, the EAC believes that a cycle length of a year would have captured the cost-consequences adequately and would have allowed a simpler model. However, a shorter cycle length used by the sponsor does not present any issues.

The cost of bailout stenting with BMS is captured in the model for both the index procedure and any repeat revascularisations. The model includes an option to apply a different TLR rate for patients receiving bailout stenting compared to those for whom the angioplasty is successful. The sponsor's submission applies the a single TLR rate according to the primary procedure (PTA or IN.PACT DCB) regardless of whether the patient requires bailout stenting. This parameterization would be appropriate where data on TLR rates for the index procedures includes patients who receive bailout stenting. Where data used to estimate TLR rates for the index revascularisations excludes patients who receive bailout stenting it would be appropriate to select the option to apply a different TLR rate for those patients.

Overall, the EAC thinks that the model structure and time horizon are adequate for this assessment.

Summary of the base case

The sponsor's model reports the ICER after valuing utilities accrued and combining with costs. Since a cost-consequences analysis is usually sufficient for MTEP, the EAC considered only the estimated costs for the technology and comparators, and the resultant cost savings (Table 11). The base case costs are generated after selecting the model parameterization which assumes that the TLR rates for patients undergoing bailout stenting are already captured by the TLR rate estimated for POBA and DCB patients.

Table 11: Sponsor's base case results

	Expected cost (£)	Cost difference (£) per patient
IN.PACT DCB with BMS bailout TLR (Technology)	3,947	-
PTA with BMS bailout TLR (Comparator)	3,936	11

The base case results are for a 36-month period and show that PTA has a slight cost advantage. Higher index costs for IN.PACT than (£3504 vs £2694,

respectively) are not completely offset by lower TLR costs (£443 vs £1,242, respectively) at 36 months. The sponsor also provided results for a 48-month time horizon where a saving of £95 per patient was realised for IN.PACT DCB. Over a 36 month time horizon the sponsor reports an Incremental Cost-Effectiveness Ratio (ICER) of £665 per QALY. Over 48 months IN.PACT DCB dominates (lower cost and better outcomes).

In a subgroup analysis of in-stent restenosis, there was a cost saving of £49 for the IN.PACT DCB at 36 months.

Under the alternative parameterization of the model in which a separate TLR rate is applied to all patients receiving bail-out stenting, the difference in costs is slightly higher. In this scenario the ICER rises to £5,754 per QALY.

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.

	Expected cost (£)	Cost difference (£) per patient
IN.PACT DCB with BMS bailout TLR (Technology)	3,981	-
PTA with BMS bailout TLR (Comparator)	3,894	87

Clinical parameters and variables

There are a number of assumptions around the clinical parameters and variables used in the model, which are described and critiqued below. The sponsor consulted 3 clinical advisers for their advice on the model inputs and parameters. Where model assumptions were not available in the literature, the advisers also provided expert consensus.

- No mortality difference is assumed between the intervention and comparator cohorts. The sponsor cites evidence from the IN.PACT

SFA and PACIFIER studies, which did not show a statistically significant difference in all-cause mortality(Tepe et al 2015; Werk et al 2015). These studies present results at 12 months. Since the time horizon of the model is 36 months, a more appropriate reference would have been Laird et al 2015. However, Laird reports all-cause mortality was higher for patients treated with DCB compared with PTA (8.1% vs. 0.9%;p value 0.008) at 24 months. The causes of death were adjudicated by a blinded, independent clinical events committee and no relationship was found between any death and either the study device or index revascularization procedure. Whilst the findings in Laird et al. 2015 are concerning, the EAC accepts the assumption of no additional mortality risk attributable to DCB on the grounds that this assumption has a high degree of biological plausibility. The model has also used lifetables multiplied with PAD specific hazard ratio of 3.1 to estimate survival of the model cohort, which the EAC believes to be a reasonable value.

- Random effects models were used to pool TLR rates by follow-up time horizon (12, 24 and 36 months). Proportions obtained from the sponsor's meta-analysis for 36 months were converted to 3 month probabilities to parameterize TLR rates in the sponsor's model. The 36 month TLR estimates are 49.4% for PTA and 17.8% for IN.PACT DCB. The sponsor's meta-analysis included a number of observational studies which have been excluded by the EAC. Newer relative risks have been estimated by the EAC in its own analysis. The EAC has applied these updated estimates in the sponsor's cost model.

- For the subgroup analysis (in-stent restenosis), the same methods for estimating proportions were used. The TLR rates were 34.1% (IN.PACT DCB) and 67.5% (PTA).

- The proportion of PTA and IN.PACT procedures that require bailout stenting has been sourced from the IN.PACT SFA trial (Laird et al

2015). These estimates are 12.6% for PTA and 7.3% for IN.PACT. The EAC agrees that these might be used in the base case analysis. However, NICE experts have opined that such a difference might not be clinically plausible. This might warrant a sensitivity analysis where the rates are as assumed the same. In the sensitivity analysis provided by the sponsor, only one of the rates is varied at a time.

- An assumption that 31.5% in all re-interventions require bailout stenting has been used in the cost model. This has been sourced from literature (Rocha-Singh et al 2015) and is reasonable to the EAC.

- 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. The sponsor has assumed the use of 1.4 DCB and 1.5 BMS devices taken from Tepe et al 2015 and Krankenberg et al 2015, respectively. This is agreeable to the EAC as a base case. Any uncertainty surrounding these estimates have been explored by the sponsor in their sensitivity analysis.

Resource identification, measurement and valuation

A number of assumptions on resource identification, measurement and valuation have been applied to estimate costs used in the model, which are described and critiqued below:

- The cost of PTA was estimated as £2,214 (2015/16 Elective Inpatient Reference Costs codes YR11, weighted average). To this was added the device costs (IN.PACT DCB or BMS) according to the procedure performed. The EAC thinks these costs are appropriate to be used in the model. The sponsor did not use HRG codes YR14 and YR15 for the stent bailout procedure costs, on the basis that their cost estimates were more conservative with respect to IN.PACT DCB. The EAC agrees with this justification.

- The cost of any pre-operative work up for any procedure was estimated as outpatient costs of £367. This was based on an estimated 2 vascular surgery outpatients visits (pre and post) plus a vascular ultrasound scan, which is a reasonable estimate according to the EAC. Katsanos et al 2016 has also used such estimates in their UK based economic analysis.

- To reduce the risk of thrombus formation, patients receive a dual antiplatelet (DAPT) regimen for four weeks in PTA and DCB index procedures, and for three months if bailout stenting is performed, which is a common clinical practice. The sponsor sourced the cost of Aspirin (75/330mg) and Clopidogrel 75mg daily for 4 weeks (no bailout) and for 3 months (with bailout) from British National Formulary 2017. The cost of DAPT is £32 (no bailout) and £103 (bailout), which the EAC thinks is reasonable.

Table 12 below lists the parameters and relevant sources used in the sponsor's model, and any changes made by the EAC

Table 12: Model parameters in the sponsor's submission and amendments by the EAC

Parameter	Sponsor's value	Source	EAC value
Probabilities			
36 month TLR risk after DCB (primary)	17.8%	Sponsor's meta-analysis	18.6%
36 month TLR risk after PTA (primary)	49.4%	Sponsor's meta-analysis	No change
36 month TLR after bailout BMS*	36.3%	Sponsor's meta-analysis	No change (base case)

36 month TLR risk after DCB (restenosis)	34.1%	Sponsor's meta-analysis	36.3%
36 month TLR risk after PTA (restenosis)	67.5%	Sponsor's meta-analysis	No change
Bailout rate for DCB	7.3%	Laird et al. 2015	No change (base case)
Bailout rate for PTA	12.6%	Laird et al. 2015	No change
Bailout rate for TLR	31.5%	Rocha-Singh et al. 2015	No change
General population mortality	varies by age	ONS data, England 2014-16	No change
Increased mortality risk for patients, HR	3.1	Criqui et al. 1992	No change
Proportion of male patients	66%	Laird et al. 2015	No change
Resource Use			
Number of DCB	1.4	Tepe et al. 2015	No change (base case)

Number of BMS	1.5	Krankenberg et al. 2015	No change
Outpatient visits	1.0	Assumption	No change
Thromboprophylaxis after PTA	50% 75mg Aspirin, 75mg Clopidogrel/ 50% 300mg Aspirin, 75mg Clopidogrel for 4 weeks	Assumption	No change
Thromboprophylaxis after bailout stenting	50% 75mg Aspirin, 75mg Clopidogrel/ 50% 300mg Aspirin, 75mg Clopidogrel for 3 months	Assumption	No change
Unit Costs			
IN.PACT DCB (balloon only)	£603.00	Sales data, Medtronic	No change (base case)
BMS (stent only)	£384.00	Katsanos et al 2016	No change
Angioplasty procedure	£2,213.82	2015/16 NHS Ref. costs	No change

Outpatient visit	£366.90	2015/16 NHS Ref. costs	No change
Daily cost 75mg Aspirin	£0.04	BNF< Mar-Sep 2017	No change
Daily cost 300mg Aspirin	£0.10	BNF< Mar-Sep 2017	No change
Daily cost 75mg Clopidogrel	£1.08	BNF< Mar-Sep 2017	No change

ONS – Office for National Statistics; HR – hazard ratio; NHS – National Health Service; Ref. – Reference; BNF – British National Formulary

*TLR rate for patients receiving bailout stenting was not applied in the sponsor's submission; this parameter was applied in the EAC model

Technology and comparators' costs

The UK list price for all Medtronic DCB (Pacific and Admiral) is £910. The sponsor has however used the average selling price of £603, calculated from rolling 12 month sales data for all IN.PACT DCB sales in the UK. The EAC accepts this technology cost. As for the comparator costs, the PTA procedure cost of £2,214 (as detailed in the previous section) was used. The only additional costs were those for BMS, an outpatient visit and thromboprophylaxis. The cost of BMS was £384 and was sourced from literature (Katsanos et al 2016), which the EAC thinks is reasonable. The costs for an outpatient visit and the drug costs for thromboprophylaxis aere drawn from appropriate sources and acceptable to the EAC.

Sensitivity analysis

The sponsor has performed deterministic sensitivity analysis on all clinical and cost parameters. These include: PAD specific mortality hazard ratio; 36 month TLR for PTA and IN.PACT; proportion of PTA and IN.PACT index procedures that receive bailout stenting; proportion of TLR procedures that receive bailout stenting; number and cost of IN.PACT and BMS device used; cost of PTA/DCB procedure (with and without BMS bailout); time horizon of 48 months and discount rates. Sensitivity analysis revealed that the key drivers of the cost results are the cost of the technology, clinical performance in terms of TLR between IN.PACT and PTA and the number of devices used. For a 48-month time horizon, a saving of £95 per patient was realized for IN.PACT DCB. For the subgroup analysis (in-stent restenosis), there was a cost saving of £49 for the IN.PACT DCB. The EAC thinks that all the parameter ranges are valid and the sensitivity analysis have been appropriately performed.

4.3 Interpretation of economic evidence

The sponsor interprets their results of the cost model to be consistent with the findings of published economic studies. The EAC agrees with this interpretation because the evidence review concluded that IN.PACT has a higher index procedural costs but at 2 years follow-up, TLR was less frequent in patients treated with DCB angioplasty and might result in cost savings or reasonable additional costs. The sponsor's results are consistent with the literature; IN.PACT has a slight increased cost at 36 months and cost savings at 48 months.

4.4 Results of EAC analysis

The EAC updated the sponsor's model using alternative TLR estimates for IN.PACT DCB derived from the relative risks of TLR with IN.PACT compared to PTA calculated by the EAC. The EAC assumed that bailout stenting TLR was considered where clinically indicated, consistent with current medical practice. The EAC accepted the sponsor's value for the 36 month TLR probability for PTA. The EAC elected to apply the relative risk for TLR at 24 months for IN.PACT DCB compared with PTA determined from Laird et al. 2015. The EAC notes this value is similar to the RR determined at 6 and 12 months from Werk et al. 2012. The EAC converted the 36 month probability of

TLR with PTA to a 24 month probability and applied the RR of 0.35 to estimate a 24 month probability of TLR with IN.PACT DCB. The 24 month TLR probability for IN.PACT DCB was then converted to a 36 month probability. The resulting probability was very slightly higher than the value used in the sponsor's original model. (Note: the sponsor's model which the EAC adapted converts the 36 month probability of TLR to a 3 month probability to estimate the cost of TLR).

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 trentment or control after successful dilatation.

Base-case analysis results

The base case, which assumes TLR of 18.6% for DCB and 49.4% for PTA at 36 months, is given in Table 13. IN.PACT DCB was cost incurring (£106) compared to PTA. Over 48 months, IN.PACT has a slightly higher cost of £13 (Table 14).

Table 13: Expected cost of technology and comparator (36 months)

	Index cost	TLR cost	Total cost
PTA with BMS bailout	£2,694	£1,200	£3,894
IN.PACT DCB with BMS bailout	£3,504	£496	£4,000
Difference			£106

Table 14: Expected cost of technology and comparator (48 months)

	Index cost	TLR cost	Total cost
PTA with BMS bailout	£2,694	£1,410	£4,105

IN.PACT DCB with BMS bailout	£3,504	£613	£4,118
Difference			£13

Sensitivity analysis results

The EAC performed a number of sensitivity analyses (Table 4-10) to test the robustness of the results to uncertainty in key parameters and model assumptions. The following changes to model assumptions were made:

- the same rate of bail-out stenting (12.6%) during the index procedure with DEB or PTA was assumed and it was assumed that no DCB would be applied when bailout stenting was required
- the TLR rate after bailout stenting was assumed to be the same as for PTA
- the same rate of bail-out stenting for DEB and PTA was applied (with no use of DCB prior to stenting) and the TLR rate following bailout stenting was assumed to be the same as for PTA

The following key parameters were varied in sensitivity analysis: the number of DCB devices used; the cost of IN.PACT DCB; and the RR of TLR with IN.PACT DCB. The model results were generally robust to structural assumptions (tables 15-17) although in each case IN.PACT DCB was cost saving at four years. Model results were more sensitive to uncertainty in key parameter values (tables 18-23).

Table 15: Sensitivity analysis with same rate of bail-out stenting (12.6%) and no DCB used where stenting is indicated.

36 months	Index cost	TLR cost	Total cost
PTA with BMS bailout	£2,694	£1,200	£3,894
IN.PACT DCB with BMS bailout	£3,432	£519	£3,952
Difference			£57

48 months	Index cost	TLR cost	Total cost
PTA with BMS bailout	£2,694	£1,410	£4,105
IN.PACT DCB with BMS bailout	£3,432	£641	£4,073
Difference			-£32

Table 16: Sensitivity analysis assuming TLR rate after bail-out stenting is the same as rate with POBA (49.4% at 3 years instead of 36.3%)

36 months	Index cost	TLR cost	Total cost
PTA with BMS bailout	£2,694	£1,242	£3,936
IN.PACT DCB with BMS bailout	£3,504	£520	£4,024
Difference			£88

48 months	Index cost	TLR cost	Total cost
PTA with BMS bailout	£2,694	£1,456	£4,150
IN.PACT DCB with BMS bailout	£3,504	£640	£4,144
Difference			-£6

Table 17: Sensitivity analysis assuming TLR rate after bailout stenting is the same as rate with POBA (49.4% at 3 years instead of 36.3%) and no difference in rates of bailout stenting between DEB and POBA

36 months	Index cost	TLR cost	Total cost
PTA with BMS bailout	£2,694	£1,242	£3,936
IN.PACT DCB with BMS bailout	£3,432	£561	£3,994
Difference			£57

48 months	Index cost	TLR cost	Total cost
PTA with BMS bailout	£2,694	£1,456	£4,150
IN.PACT DCB with BMS bailout	£3,432	£686	£4,119
Difference			-£32

Table 18: Sensitivity analysis with 1.2 DCBs

36 months	Index cost	TLR cost	Total cost
PTA with BMS bailout	£2,694	£1,200	£3,894
IN.PACT DCB with BMS bailout	£3,384	£496	£3,879
Difference			-£14

48 months	Index cost	TLR cost	Total cost
PTA with BMS bailout	£2,694	£1,410	£4,105
IN.PACT DCB with BMS bailout	£3,384	£613	£3,997
Difference			-£108

Table 19: Sensitivity analysis with 1.7 DCBs

36 months	Index cost	TLR cost	Total cost
PTA with BMS bailout	£2,694	£1,200	£3,894
IN.PACT DCB with BMS bailout	£3,685	£496	£4,181
Difference			£287

48 months	Index cost	TLR cost	Total cost
PTA with BMS bailout	£2,694	£1,410	£4,105
IN.PACT DCB with BMS bailout	£3,685	£613	£4,298
Difference			£194

Table 20: Sensitivity analysis with DCB cost £500

36 months	Index cost	TLR cost	Total cost
PTA with BMS bailout	£2,694	£1,200	£3,894
IN.PACT DCB with BMS bailout	£3,360	£496	£3,856
Difference			-£39

48 months	Index cost	TLR cost	Total cost
PTA with BMS bailout	£2,694	£1,410	£4,105

IN.PACT DCB with BMS bailout	£3,360	£613	£3,973
Difference			-£131

Table 21: Sensitivity analysis with DCB cost £750

36 months	Index cost	TLR cost	Total cost
PTA with BMS bailout	£2,694	£1,200	£3,894
IN.PACT DCB with BMS bailout	£3,710	£496	£4,206
Difference			£311

48 months	Index cost	TLR cost	Total cost
PTA with BMS bailout	£2,694	£1,410	£4,105
IN.PACT DCB with BMS bailout	£3,710	£613	£4,323
Difference			£219

Table 22: Sensitivity analysis assuming RR of TLR with IN.PACT of 0.21 (lower 95% confidence interval) (TLR risk 11.3% at 36 months)

36 months	Index cost	TLR cost	Total cost
PTA with BMS bailout	£2,694	£1,200	£3,894
IN.PACT DCB with BMS bailout	£3,504	£327	£3,831
Difference			-£63

48 months	Index cost	TLR cost	Total cost
PTA with BMS bailout	£2,694	£1,410	£4,105
IN.PACT DCB with BMS bailout	£3,504	£407	£3,912
Difference			-£193

Table 23: Sensitivity analysis assuming RR of TLR with IN.PACT of 0.58 (upper 95% confidence interval) (TLR risk 30.0% at 36 months)

36 months	Index cost	TLR cost	Total cost
PTA with BMS bailout	£2,694	£1,200	£3,894

IN.PACT DCB with BMS bailout	£3,504	£761	£4,265
Difference			£371

48 months	Index cost	TLR cost	Total cost
PTA with BMS bailout	£2,694	£1,410	£4,105
IN.PACT DCB with BMS bailout	£3,504	£926	£4,430
Difference			£325

Subgroup analysis

For the restenosis subgroup with 36 month TLR of 32.0% for DCB and 67.5% for PTA, the results showed that IN.PACT was almost cost neutral at 36 months (Table 24) and cost saving at 48 months (Table 25).

Table 24: Expected cost of technology and comparator (36 months)

	Index cost	TLR cost	Total cost
PTA with BMS bailout	£2,694	£1,610	£4,305
IN.PACT DCB with BMS bailout	£3,504	£808	£4,312
Difference			£7

Table 25: Expected cost of technology and comparator (48 months)

	Index cost	TLR cost	Total cost
PTA with BMS bailout	£2,694	£1,819	£4,513
IN.PACT DCB with BMS bailout	£3,504	£979	£4,484
Difference			-£29

Model validation

The EAC did not make any change to the sponsor's model. So no validation was required. The EAC however did check the model and it did not have any errors. The EAC only updated the TLR rates in the sponsor's model.

4.5 EAC Interpretation of economic evidence

The EAC accepted the cost model submitted by sponsor. All the parameters, except TLR rates were reasonable. Based on the TLR rates derived from the EAC's estimate of the relative risk of TLR with IN.PACT, the EAC re-estimated the cost savings; results indicate cost savings which offset initial costs around four years after the procedure. This is in line with literature since the cost savings come from the reduced TLR rates for the IN.PACT DCB.

Impact on the cost difference between the technology and comparator of additional clinical and economic analyses undertaken by the External Assessment Centre

The EAC changed the TLR rates in the sponsor's model and applied a separate TLR rate for patients receiving bailout stenting. This has resulted in an increase in cost for IN.PACT at 36 months (base case). The difference between the sponsor's estimate and EAC's estimate is £93 (Table 26)

Table 26: Cost difference between Sponsor and EAC estimates

	Sponsor*	EAC*	Difference
PTA with BMS bailout	£3,947	£3,894	£47
IN.PACT DCB with BMS bailout	£3,936	£4,000	£64
Cost savings	-£11	-£106	

*Both the sponsor's model and the EAC's modified model estimate costs of £3,894 for PTA with the option selected to parameterize TLR after bailout stenting independently of treatment, and at £3,947 for PTA when the option is selected to parameterize TLR according to treatment arm regardless of bailout stenting.

5 Conclusions

5.1 Conclusions on the clinical evidence

The sponsor provided a submission that included the majority of the available clinical evidence on the technology. Due to some of the studies including a patient population that did not fit the scope, and others providing the same results in overlapping populations, the majority of the evidence submitted by the sponsor were excluded by the EAC. The final list of evidence included by the EAC consisted of 4 RCTs (IN.PACT SFA, PACIFIER, FAIR and ISAR-PEBIS) and 3 observational studies (Multicentre Italian Registry, SFA-Long study and IN.PACT Global).

The pivotal study was the superiority multi-centre international IN.PACT SFA (n = 331) RCT, which compared IN.PACT admiral DCB with standard PTA with a 2-year follow up (Laird et al., 2015; Krishan et al., 2016). The results reported a statistically significant reduction in CD-TLR, in primary restenoses, and in target limb major amputation with IN.PACT compared with standard PTA. The two groups performed equally in terms of functional outcomes. 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.

The EAC considered that this RCT, which was fully funded by the sponsor, was subject to some potential sources of bias - mainly unclear risk of attrition bias and unclear risk of performance bias. 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. This finding was also observed in the FAIR trial whilst the PACIFIER trial also reported a higher number of balloons used per lesion for the intervention group. Despite these limitations the EAC considered that the largest comparative benefit from this trial was attributable to IN.PACT DCB.

The level of benefit in terms of target lesion revascularization was also broadly supported by evidence from single-armed observational data. Although none of the included studies were conducted in the UK, the results should be generalisable to the UK setting.

5.2 Conclusions on the economic evidence

In line with literature, the EAC estimation of the sponsor's cost model with updated TLR rates indicates cost savings which offset initial costs around four years after the procedure.

Results were robust to structural assumptions but sensitive to the value of key parameters: the cost of the IN.PACT DCB; the mean number of balloons used per procedure; and the RR of TLR with IN.PACT DCB. Higher purchase costs or increased numbers of balloons per procedure raises the initial cost of angioplasty with IN.PACT DCB; at £750 per DCB or if usage averages 1.7 DCB per procedure costs including TLRs are higher with IN.PACT at four years. Conversely, if the price of IN.PACT falls to £500 or mean balloon usage is 1.2 per procedure IN.PACT is cost saving at three years. INPACT.DCB is cost neutral at three years at a unit cost of £527, and is cost neutral at four years at a unit cost of £593.

Unsurprisingly, results are sensitive to the RR of TLR with IN.PACT DCB. Uncertainty in the EAC's estimate of the RR spans values which generate cost savings at three years and are not cost saving at four years from the index procedure. The RR for TLR with IN.PACT DCB in patients undergoing a first procedure would have to fall from the EAC's estimate of 0.35 to 0.26 for savings in avoided TLR to offset increased initial costs for IN.PACT DCB at 3 years. A RR of 0.34 would represent the break even point at 4 years.

The EAC notes that further cost savings are likely beyond four years due to a reduction in TLR rates from IN.PACT DCB. Costs arising from a reduction in amputations are also likely from a reduction in TLR rates. Quantifying these additional cost savings would require more complex modelling and additional longer term outcome data. The EAC considers the cost estimates at 4 years to represent conservative estimates of the cost impact of IN.PACT DCB.

6 Summary of the combined clinical and economic sections

The effectiveness of IN.PACT DCB is supported by evidence provided by randomised comparative studies, mainly the IN.PACT SFA, and broadly supported by evidence from single-armed observational data. Although none of the included studies were conducted in the UK, the results should be generalisable to the UK setting. With the exeption of IN.PACT survival rates the technology IN.PACT DCB as described in the scope seems to be of equal safety to standard PTA, however, none of the studies was adequately powered to detect such difference. Cost savings for the technology from reduced TLR, realised around four years after the procedure, are sufficient to offset the additional cost of the DCB.

7 Implications for research

Although comparative evidence on the effectiveness and safety of IN.PACT DCB exist, the majority (with the exeption of the IN.PACT SFA trial) have limited follow-up (up to 1 year). In addition, some notable differences in the pre-dilation rates between the intervention and the comparator groups are observed. Given the high number of non-comparative studies for this technology, future research should focus on producing comparative evidence with more than 2 years follow-up and adequately powered to detect statistically significant differences with CD-TLR at that point. Finally, there is a lack of evidence with regards to functional outcomes for this population which future research can address.

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Appendices

Appendix A: Search strategies

Appendix B: Methodological quality template

Appendix C: Adverse events data

Appendix D: Excluded studies

Appendix A

In order to create a reference set the EAC searched for the references provided by manufacturer in their clinical submission. The following databases were searched using the title field in Ovid:

- Embase 1974 to 2017 Week 41
- Ovid MEDLINE(R) Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) 1946 to Present
- Global Health 1973 to 2017 Week 40
- HMIC Health Management Information Consortium 1979 to July 2017

20 studies were found in the databases and 4 more were found manually (7 are unpublished and not locatable). The titles and abstracts of the 24 studies were run through an online text analysis tool (http://textalyser.net) and the results were used to inform the keywords for the EAC's search strategy.

Clinical evidence

Total records retrieved: 10191
Total following de-duplication: 5943

- 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: 16th October 2017

1	popliteal.tw. or popliteal artery/	18563
2	Femoropopliteal.tw.	3237
3	(femoral adj3 arter*).tw.	23910
4	femoral artery/ or superficial femoral artery/	28224
5	or/1-4	53931
6	(claudicant* or claudication).tw. or claudication/	13365
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.	110977
8	critical limb ischaemia.tw. or critical limb ischemia/	596
9	Arterial Occlusive Diseases/ or exp artery occlusion/	27986

10	or/6-9	137067
11	5 and 10	11705
12	(peripher* adj2 arter* adj2 disease*).tw. or peripheral arterial disease/ or peripheral occlusive artery disease/	16312
13	11 or 12	26789
14	(percutaneous transluminal angioplasty or pta).tw.	10761
15	exp angioplasty/	62179
16	paclitaxel.tw. or paclitaxel/	33918
17	((paclitaxel elut* or drug elut* or drug coat* or paclitaxel coat*) adj3 balloon*).tw.	1003
18	dcb.tw.	1078
19	or/14-18	102523
20	13 and 19	3800
21	("in.pact*" or in pact* or inpact*).tw.	169
22	medtronic.af. and 12	25
23	or/20-22	3954
24	animals/ or (rat or rats or mouse or mice or hamster or hamsters or animal or animals or dog or dogs or cat or cats or bovine or sheep or ovine).ti,ab,sh.	6940787
25	24 not (24 and exp humans/)	4926479
26	23 not 25	3866
27	(case report or editorial or letter).pt.	1487164
28	26 not 27	3711
29	limit 28 to yr="2007 -Current"	1859

- Embase 1974 to 2017 Week 41
- Search date: 16th October 2017

1	popliteal.tw. or popliteal artery/	20139
2	Femoropopliteal.tw.	4051
3	(femoral adj3 arter*).tw.	31462
4	femoral artery/ or superficial femoral artery/	31751
5	or/1-4	61673
6	(claudicant* or claudication).tw. or claudication/	14513
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.	141697
8	critical limb ischaemia.tw. or critical limb ischemia/	3907
9	Arterial Occlusive Diseases/ or exp artery occlusion/	122478
10	or/6-9	223637
11	5 and 10	13896

12	(peripher* adj2 arter* adj2 disease*).tw. or peripheral arterial disease/ or peripheral occlusive artery disease/	39986
13	11 or 12	49766
14	(percutaneous transluminal angioplasty or pta).tw.	14022
15	exp angioplasty/	80096
16	paclitaxel.tw. or paclitaxel/	92280
17	((paclitaxel elut* or drug elut* or drug coat* or paclitaxel coat*) adj3 balloon*).tw.	1904
18	dcb.tw.	1408
19	or/14-18	179600
20	13 and 19	6626
21	("in.pact*" or in pact* or inpact*).tw.	322
22	medtronic.af. and 12	309
23	or/20-22	7052
24	animals/ or animal experiment/ or (rat or rats or mouse or mice or hamster or hamsters or animal or animals or dog or dogs or cat or cats or bovine or sheep or ovine).ti,ab,sh.	6034326
25	24 not (24 and (exp humans/ or human experiment/))	4734122
26	23 not 25	6894
27	(case report or editorial or letter).pt.	1542205
28	26 not 27	6666
29	limit 28 to yr="2007 -Current"	4127

- Cochrane Libraries
- Search date: 16th October 2017

ID	Search	Hits
#1	popliteal or [mh ^"popliteal artery"]	1163
#2	Femoropopliteal	496
#3	femoral near/3 arter*	1915
#4	[mh ^"femoral artery"] or [mh ^"superficial femoral artery"]	952
#5	[mh "lower limb"] or [mh "lower extremity"]	6532
#6	{or #1-#5}	8951
#7	claudication or [mh ^claudication]	1959
#8	claudicant*	126
#9	critical limb ischaemia or [mh ^"critical limb ischaemia"]	246
#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*)	9185
#11	((stenot* near/3 arter*) or "arterial stenosis") or [mh "artery occlusion"]	206
#12	{or #7-#11}	10626
#13	#6 and #12	1380

#14	(peripher* near/2 arter* near/2 disease*) or [mh ^"peripheral arterial disease"] or [mh ^"peripheral occlusive artery disease"]	2518
#15	#13 or #14	3465
#16	percutaneous transluminal angioplasty	836
#17	[mh Angioplasty]	4836
#18	pta	815
#19	paclitaxel or [mh paclitaxel]	5847
#20	(paclitaxel elut* or drug elut* or drug coat* or paclitaxel coat*) near/3 balloon*	375
#21	dcb	112
#22	revasculari?ation*	8847
#23	{or #16-#22}	17995
#24	#15 and #23	910
#25	in.pact* or "in pact*" or inpact*	66
#26	#15 and medtronic	29
#27	{or #24-#26} Publication Year from 2007	722

- PubMed
- Search date 16th October 2017

Search	Query	Items found
#25	Search (#19 or #22) Filters: published in the last 10 years; Humans	2116
#24	Search (#19 or #22) Filters: Humans	4822
#23	Search (#19 or #22)	5187
#22	Search (#20 or #21)	147
#21	Search (medtronic) AND #17	72
#20	Search ("in.pact*" or "in pact*" or inpact*)	84
#19	Search (#17 and #18)	5075
#18	Search (#9 or #10 or #11 or #12 or #13)	109143
l#17	Search (#8 or #16)	33128
#16	Search (#14 and #15)	14321
#15	Search (#4 or #5 or #6 or #7)	247745
#14	Search (#1 or #2 or #3)	45421
#13	Search "dcb"[tiab]	1031
#12	Search (drug coated balloon) OR drug eluting balloon	5909
#11	Search paclitaxel	31466
#10	Search "pta"[tiab]	7517
#9	Search angioplasty	72835
#8	Search (peripheral arterial disease) OR peripheral occlusive artery disease	21168
#7	Search arterial stenosis	50761
#6	Search Arterial Occlusive Diseases	211797
#5	Search critical limb ischaemia	4974
#4	Search claudication	12400
#3	Search femoral artery	40195

#2	Search Femoropopliteal	3067
#1	Search popliteal artery	10906

- Web of Science
- Search date: 16th October 2017

# 17	1,368	#16 OR #14 OR #13 Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI Timespan=**2007-2017**
# 16	27	#15 AND #8 Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI Timespan=1900-2017
# 15	3,934	TS=(medtronic) Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI Timespan=1900-2017
# 14	241	TS=("in.pact*" or "in pact*" or inpact*) Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI Timespan=1900-2017
# 13	1,800	#12 AND #8 Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI Timespan=1900-2017
# 12	59,700	#11 OR #10 OR #9 Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI Timespan=1900-2017
# 11	3,384	TS=(dcb) Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI Timespan=1900-2017
# 10	44,681	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=1900-2017
# 9	12,119	TS=("percutaneous transluminal angioplast*" or pta) Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI Timespan=1900-2017
# 8	22,300	#7 OR #6 Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI Timespan=1900-2017
# 7	17,311	TS=(peripher* NEAR/2 arter* NEAR/2 disease*) Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI Timespan=1900-2017
# 6	6,113	#5 AND #1 Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI Timespan=1900-2017
# 5	121,585	#4 OR #3 OR #2 Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI Timespan=1900-2017
# 4	32,986	TS=(((stenot* NEAR/3 arter*) or "arterial stenosis") or ("artery occlusion")) Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI Timespan=1900-2017

# 3	111,724	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=1900-2017
# 2	16,998	TS=(claudication OR claudicant* OR critical limb ischaemia OR Arterial Occlusive Disease*) Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI Timespan=1900-2017
# 1	26,760	TS=(popliteal artery OR Femoropopliteal OR femoral artery) Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI Timespan=1900-2017

- Global Health 1973 to 2017 Week 42, HMIC Health Management Information Consortium 1979 to July 2017
- Search date: 2nd November 2017

1	popliteal.tw. or popliteal artery/	453
2	Femoropopliteal.tw.	23
3	(femoral adj3 arter*).tw.	733
4	femoral artery/ or superficial femoral artery/	0
5	or/1-4	1193
6	(claudicant* or claudication).tw. or claudication/	284
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.	3247
8	critical limb ischaemia.tw. or critical limb ischemia/	17
9	Arterial Occlusive Diseases/ or exp artery occlusion/	0
10	or/6-9	3524
11	5 and 10	79
12	(peripher* adj2 arter* adj2 disease*).tw. or peripheral arterial disease/ or peripheral occlusive artery disease/	913
13	11 or 12	980
14	(percutaneous transluminal angioplasty or pta).tw.	571
15	exp angioplasty/	0
16	paclitaxel.tw. or paclitaxel/	1373
17	((paclitaxel elut* or drug elut* or drug coat* or paclitaxel coat*) adj3 balloon*).tw.	3
18	dcb.tw.	88
19	or/14-18	2033
20	13 and 19	3
21	("in.pact*" or in pact* or inpact*).tw.	27
22	medtronic.af. and 12	1
23	or/20-22	31

	Re-run in HMIC	16

- Other grey literature sources
- Search date: 31st October 2017

Searched “In.pact” in all

www.greylit.org/	0
www.opengrey.eu/	0
http://oaister.worldcat.org/	0
ntrl.ntis.gov/NTRL/	0
http://webarchive.nationalarchives.gov.uk/adv_search/	7

Ongoing studies

Total records retrieved: 374
Total following de-duplication: 283

- ClinicalTrials.gov
- Search date 1st November 2017

("drug coated balloon" OR "drug coated balloons" OR (paclitaxel AND peripheral vascular disease [DISEASE])) OR "in.pact"	with results	10
("drug coated balloon" OR "drug coated balloons" OR (paclitaxel AND peripheral vascular disease [DISEASE])) OR "in.pact"	without results	156

- WHO ICTRP
- Search date 1st November 2017

paclitaxel AND peripheral vascular disease OR drug coated balloon* OR in.pact	197

- PROSPERO
- Search date: 1st November 2017

#1	in.pact	0
#2	drug coated balloon*	9
#3	MeSH DESCRIPTOR Arterial Occlusive Diseases EXPLODE ALL TREES	189
#4	paclitaxel	35
#5	#1 or #2 or (#3 and #4)	11

Economics searches

- 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: 30th October 2017

1	popliteal.tw. or popliteal artery/	18581
2	Femoropopliteal.tw.	3245
3	(femoral adj3 arter*).tw.	23938
4	femoral artery/ or superficial femoral artery/	28250
5	or/1-4	53992
6	(claudicant* or claudication).tw. or claudication/	13373
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.	111161
8	critical limb ischaemia.tw. or critical limb ischemia/	598
9	Arterial Occlusive Diseases/ or exp artery occlusion/	27999
10	or/6-9	137266
11	5 and 10	11711
12	(peripher* adj2 arter* adj2 disease*).tw. or peripheral arterial disease/ or peripheral occlusive artery disease/	16365
13	11 or 12	26847
14	(percutaneous transluminal angioplasty or pta).tw.	10777
15	exp angioplasty/	62217
16	paclitaxel.tw. or paclitaxel/	33991
17	((paclitaxel elut* or drug elut* or drug coat* or paclitaxel coat*) adj3 balloon*).tw.	1011
18	dcb.tw.	1082
19	or/14-18	102645
20	13 and 19	3806
21	("in.pact*" or in pact* or inpact*).tw.	170
22	medtronic.af. and 12	25
23	or/20-22	3961
24	animals/ or (rat or rats or mouse or mice or hamster or hamsters or animal or animals or dog or dogs or cat or cats or bovine or sheep or ovine).ti,ab,sh.	6950334
25	24 not (24 and exp humans/)	4932234
26	23 not 25	3873
27	(case report or editorial or letter).pt.	1490737
28	26 not 27	3718
29	limit 28 to yr="2007 -Current"	1866
30	(cost$ or econ$).mp.	842708

31	29 and 30	101

- Embase 1974 to 2017 Week 41
- Search date: 30th October 2017

1	popliteal.tw. or popliteal artery/	20210
2	Femoropopliteal.tw.	4074
3	(femoral adj3 arter*).tw.	31588
4	femoral artery/ or superficial femoral artery/	31887
5	exp lower limb/ or exp lower extremity/	302777
6	or/1-5	356019
7	claudication.tw. or claudication/	14340
8	claudicant*.tw.	769
9	critical limb ischaemia.tw. or critical limb ischemia/	3946
10	Arterial Occlusive Diseases/	13779
11	((stenot* adj3 arter*) and arterial stenosis).tw. or exp artery occlusion/	110250
12	or/7-11	137756
13	6 and 12	14776
14	peripheral arterial disease*.tw. or peripheral arterial disease/ or peripheral occlusive artery disease/	37336
15	13 or 14	46315
16	percutaneous transluminal angioplasty.tw.	5400
17	exp angioplasty/	80393
18	pta.tw.	11086
19	paclitaxel.tw. or exp paclitaxel/	92968
20	((paclitaxel elut* or drug elut* or drug coat* or paclitaxel coat*) adj3 balloon*).tw.	1935
21	dcb.tw.	1424
22	revasculari?ation*.tw.	74548
23	or/16-22	240750
24	13 and 23	4736
25	("in.pact*" or in pact* or inpact*).tw.	328
26	medtronic.af. and 13	276
27	or/25-26	573
28	24 or 27	5121
29	animal/ or animal experiment/	3969172
30	(rat or rats or mouse or mice or hamster or hamsters or animal or animals or dog or dogs or cat or cats or bovine or sheep).ti,ab,sh.	5689725
31	or/29-30	6057532

32	exp human/ or human experiment/	19122268
33	31 not (31 and 32)	4752267
34	28 not 33	4983
35	limit 34 to yr="2007 -Current"	3186
36	(cost$ or econ$).mp.	1300673
37	35 and 36	169

- Cochrane Libraries
- Search date: 30th October 2017

ID	Search	Hits
#1	popliteal or [mh ^"popliteal artery"]	1163
#2	Femoropopliteal	496
#3	femoral near/3 arter*	1915
#4	[mh ^"femoral artery"] or [mh ^"superficial femoral artery"]	952
#5	[mh "lower limb"] or [mh "lower extremity"]	6532
#6	{or #1-#5}	8951
#7	claudication or [mh ^claudication]	1959
#8	claudicant*	126
#9	critical limb ischaemia or [mh ^"critical limb ischaemia"]	246
#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*)	9187
#11	((stenot* near/3 arter*) or "arterial stenosis") or [mh "artery occlusion"]	206
#12	{or #7-#11}	10628
#13	#6 and #12	1381
#14	(peripher* near/2 arter* near/2 disease*) or [mh ^"peripheral arterial disease"] or [mh ^"peripheral occlusive artery disease"]	2519
#15	#13 or #14	3466
#16	percutaneous transluminal angioplasty	836
#17	[mh Angioplasty]	4836
#18	pta	815
#19	paclitaxel or [mh paclitaxel]	5846
#20	(paclitaxel elut* or drug elut* or drug coat* or paclitaxel coat*) near/3 balloon*	375
#21	dcb	112
#22	revasculari?ation*	8846
#23	{or #16-#22}	17993
#24	#15 and #23	911
#25	in.pact* or "in pact*" or inpact*	66
#26	#15 and medtronic	29
#27	{or #24-#26} Publication Year from 2007	722
#28	cost* or econ*	87107
#29	#27 and #28	190

- PubMed

- Search date 30th October 2017

Search	Query	Items found
#28	Search (#26 and #27) Filters: published in the last 10 years; Humans	103
#27	Search (cost* or econ*) Filters: published in the last 10 years; Humans	274956
#26	Search ((#19 or #22)) Filters: published in the last 10 years; Humans	2108
#25	Search ((#19 or #22)) Filters: published in the last 10 years	2331
#23	Search ((#19 or #22))	5193
#22	Search ((#20 or #21))	149
#21	Search ((medtronic) AND #17)	72
#20	Search ("in.pact*" or "in pact*" or inpact*)	86
#19	Search (#17 and #18)	5079
#18	Search (#9 or #10 or #11 or #12 or #13)	109308
#17	Search (#8 or #16)	33185
#16	Search (#14 and #15)	14331
#15	Search (#4 or #5 or #6 or #7)	248104
#14	Search (#1 or #2 or #3)	45478
#13	Search "dcb"[tiab]	1036
#12	Search ((drug coated balloon) OR drug eluting balloon)	5925
#11	Search paclitaxel	31551
#10	Search "pta"[tiab]	7533
#9	Search angioplasty	72911
#8	Search ((peripheral arterial disease) OR peripheral occlusive artery disease)	21219
#7	Search arterial stenosis	50837
#6	Search Arterial Occlusive Diseases	212096
#5	Search critical limb ischaemia	4987
#4	Search claudication	12409
#3	Search femoral artery	40241
#2	Search Femoropopliteal	3074
#1	Search popliteal artery	10919

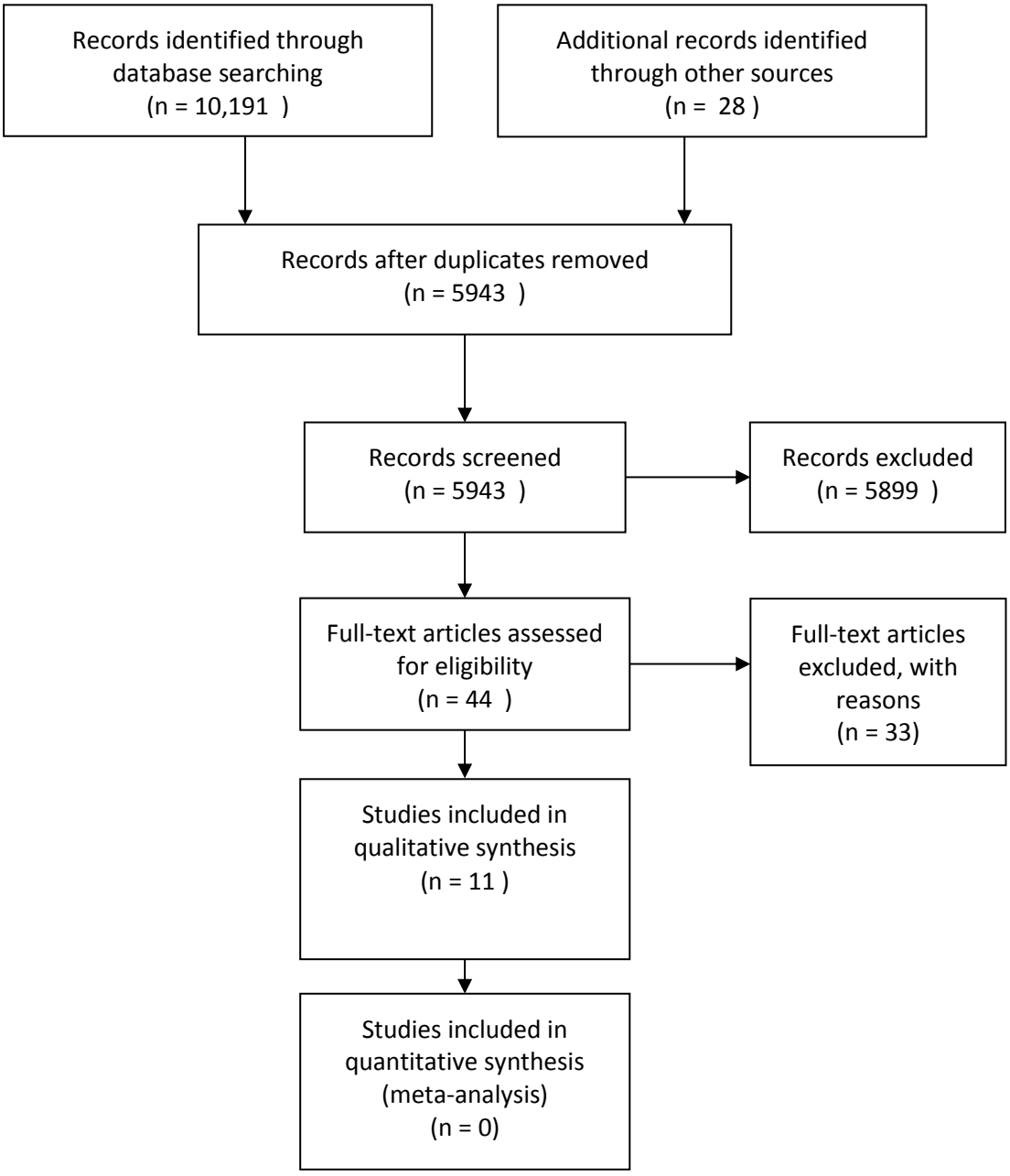
- Web of Science
- Search date: 30th October 2017

# 19	115	#18 AND #17 Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI Timespan=2007-2017
# 18	1,389,123	TS=(cost* or econ*) Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI Timespan=2007-2017
# 17	1,381	#16 OR #14 OR #13 Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI Timespan=2007-2017

# 16	26	#15 AND #8 Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI Timespan=2007-2017
# 15	2,506	TS=(medtronic) Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI Timespan=2007-2017
# 14	151	TS=("in.pact*" or "in pact*" or inpact*) Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI Timespan=2007-2017
# 13	1,227	#12 AND #8 Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI Timespan=2007-2017
# 12	43,120	#11 OR #10 OR #9 Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI Timespan=2007-2017
# 11	1,845	TS=(dcb) Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI Timespan=2007-2017
# 10	35,123	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=2007-2017
# 9	6,616	TS=("percutaneous transluminal angioplast*" or pta) Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI Timespan=2007-2017
# 8	14,485	#7 OR #6 Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI Timespan=2007-2017
# 7	12,267	TS=(peripher* NEAR/2 arter* NEAR/2 disease*) Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI Timespan=2007-2017
# 6	3,065	#5 AND #1 Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI Timespan=2007-2017
# 5	57,028	#4 OR #3 OR #2 Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI Timespan=2007-2017
# 4	16,590	TS=(((stenot* NEAR/3 arter*) or "arterial stenosis") or ("artery occlusion")) Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI Timespan=2007-2017
# 3	51,875	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=2007-2017
# 2	7,775	TS=(claudication OR claudicant* OR critical limb ischaemia OR Arterial Occlusive Disease*) Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI Timespan=2007-2017

# 1	12,676	TS=(popliteal artery OR Femoropopliteal OR femoral artery) Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI Timespan=2007-2017

EAC PRISMA 2009 Flow Diagram



Appendix B: Methodological quality template

Study identification Include author, title, reference, year of publication					
Guideline topic:	**Review question no:**				
Checklist completed by:					
		Circle or highlight one option for each question			
A. Selection bias (systematic differences between the comparison groups)					
A1	An appropriate method of randomisation was used to allocate participants to treatment groups (which would have balanced any confounding factors equally across groups)	Yes	No	Unclear	N/A
A2	There was adequate concealment of allocation (such that investigators, clinicians and participants cannot influence enrolment or treatment allocation)	Yes	No	Unclear	N/A
A3	The groups were comparable at baseline, including all major confounding and prognostic factors (patient and lesion characteristics)	Yes	No	Unclear	N/A
A4	Are the patient inclusion/exclusion criteria clearly defined?	Yes	No	Unclear	N/A
Based on your answers to the above, in your opinion was selection bias present? If so, what is the likely direction of its effect?					
Low risk of bias	Unclear/unknown risk	High risk of bias			
Likely direction of effect:					

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B. Performance bias (systematic differences between groups in the care provided, apart from the intervention under investigation)					
B1	The comparison groups received the same care apart from the intervention(s) studied	Yes	No	Unclear	N/A
B2	Participants receiving care were kept 'blind' to treatment allocation	Yes	No	Unclear	N/A
B3	Individuals administering care were kept 'blind' to treatment allocation	Yes	No	Unclear	N/A

Based on your answers to the above, in your opinion was performance bias present? If so, what is the likely direction of its effect?

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Low risk of bias	Unclear/unknown risk	High risk of bias

Likely direction of effect: Unclear

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C. Attrition bias (systematic differences between the comparison groups with respect to loss of participants)					
C1	All groups were followed up for an equal length of time (or analysis was adjusted to allow for differences in length of follow-up)	Yes	No	Unclear	N/A
C2	a. How many participants did not complete treatment in each group?				
	b. The groups were comparable for treatment completion (that is, there were no important or systematic differences between groups in terms of those who did not complete treatment)	Yes	No	Unclear	N/A
C3	a. For how many participants in each group were no outcome data available?				

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	b. The groups were comparable with respect to the availability of outcome data (that is, there were no important or systematic differences between groups in terms of those for whom outcome data were not available).	Yes	No	Unclear	N/A

Based on your answers to the above, in your opinion was attrition bias present? If so, what is the likely direction of its effect?

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Low risk of bias	Unclear/unknown risk	High risk of bias

Likely direction of effect:

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D. Detection bias (bias in how outcomes are ascertained, diagnosed or verified)

D1	The study had an appropriate length of follow-up	Yes	No	Unclear	N/A
D2	The study used a precise definition of outcome	Yes	No	Unclear	N/A
D3	A valid and reliable method was used to determine the outcome	Yes	No	Unclear	N/A
D4	Investigators were kept 'blind' to participants' exposure to the intervention	Yes	No	Unclear	N/A
D5	Investigators were kept 'blind' to other important confounding and prognostic factors	Yes	No	Unclear	N/A

D6	Are there defined criteria for how patients are selected for TLR?	Yes	No	Unclear	N/A
D7	Is quantitative angiographic follow-up data determined by an independent laboratory blinded to individual patient treatments?	Yes	No	Unclear	N/A
D8	Is an independent clinical events committee involved with selecting patients for TLR?	Yes	No	Unclear	N/A

Based on your answers to the above, in your opinion was detection bias present? If so, what is the likely direction of its effect?

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Low risk of bias	Unclear/unknown risk	High risk of bias

Likely direction of effect:

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Appendix C: Adverse events data

Brand Name: in.pact admiral Event Type: Death Report Date From: 01/01/2013 Report Date To: 10/31/2017
Brand Name: in.pact pacific Event Type: Death Report Date From: 01/01/2013 Report Date To: 10/31/2017

19/01/2017	Event Description: THE PATIENT HAD A TARGET VESSEL REVASCULARISATION OF L-1 (POPLITEAL ARTERY) WITH A INPACT ADMIRAL DEB AND A NON MDT PTA. APPROXIMATELY 15 MONTHS POST TVR THE PATIENT SUFFERED NSTEMI MYOCARDIAL INFARCTION. THIS WAS TREATED WITH A PCI OF THE MID LAD. THE PATIENT DIED. Manufacturer Narrative: .

2015/12/06	Event Description: AN IN.PACT ADMIRAL PACLITAXEL-ELUTING PTA BALLOON CATHETER WAS USED TO TREAT LESION RESTENOSIS. SIX MONTHS POST USE OF THE IN.PACT ADMIRAL THE PATIENT EXPIRED, CAUSE OF DEATH IS CURRENTLY UNKNOWN. Manufacturer Narrative: UPDATE TO CLARIFY DATE OF DEATH : (B)(6) 2015 . Manufacturer Narrative: CORRECTION TO OUTCOMES ATTRIBUTED TO ADVERSE EVENTS DATE OF DEATH IS (B)(6) 2015. A GOOD FAITH EFFORT WILL BE MADE TO OBTAIN THE APPLICABLE INFORMATION RELEVANT TO THE REPORT. IF INFORMATION IS PROVIDED IN THE FUTURE, A SUPPLEMENTAL REPORT WILL BE ISSUED. Manufacturer Narrative: .
2015/12/25	Event Description: DURING INDEX PROCEDURE ONE IN.PACT ADMIRAL PACLITAXEL-ELUTING PTA BALLOON CATHETER WAS USED TO TREAT A LESION LOCATED IN THE DISTAL SFA OF THE RIGHT LEG. APPROXIMATELY 10 MONTHS POST INDEX PROCEDURE THE PATIENT EXPIRED. Manufacturer Narrative: (B)(4).
2015/12/04	Event Description: DURING A REVASCULARIZATION TO THE LEFT SFA THREE IN.PACT ADMIRAL PACLITAXEL-ELUTING PTA BALLOON CATHETERS WERE USED. APPROXIMATELY 9 WEEKS LATER PATIENT DEATH OCCURRED. Manufacturer Narrative: THE PREVIOUSLY REPORTED DEATH OCCURRED FOLLOWING SEPSIS. MEDICATION WAS GIVEN AS TREATMENT FOR THE SEPSIS. (B)(4). Manufacturer Narrative: (B)(4).
2015/12/04	Event Description: DURING A REVASCULARIZATION TO THE LEFT SFA THREE IN.PACT ADMIRAL PACLITAXEL-ELUTING PTA BALLOON CATHETERS WERE USED. APPROXIMATELY 9 WEEKS LATER PATIENT DEATH OCCURRED. Manufacturer Narrative: (B)(4). Manufacturer Narrative: THE PREVIOUSLY REPORTED DEATH OCCURRED FOLLOWING SEPSIS. MEDICATION WAS GIVEN AS TREATMENT FOR THE SEPSIS. (B)(4).
2015/12/04	Event Description: DURING A REVASCULARIZATION TO THE LEFT SFA THREE IN.PACT ADMIRAL PACLITAXEL-ELUTING PTA BALLOON CATHETERS WERE USED. APPROXIMATELY 9 WEEKS LATER PATIENT DEATH OCCURRED. Manufacturer Narrative: (B)(4). Manufacturer Narrative: THE PREVIOUSLY REPORTED DEATH OCCURRED FOLLOWING SEPSIS. MEDICATION WAS GIVEN AS TREATMENT FOR THE SEPSIS. (B)(4).
2014/08/28	Event Description: DURING INDEX PROCEDURE THE PHYSICIAN USED ONE IN.PACT ADMIRAL PACLITAXEL-ELUTING PTA BALLOON CATHETER TO TREAT A LESION LOCATED IN THE SFA OF THE LEFT LEG. DEVICE WAS SUCCESSFUL. PATIENT EXPIRED APPROXIMATELY 11.5 MONTHS POST INDEX PROCEDURE. Manufacturer Narrative: (B)(4).
2015/07/02	Event Description: TWO IN.PACT ADMIRAL PACLITAXEL ELUTING BALLOON CATHETERS WERE USED DURING INDEX PROCEDURE , ONE IN THE PROX SFA (L-1) AND ONE IN THE DISTAL SFA - POP1 (L-2). APPROXIMATELY 23 MONTHS POST INDEX PROCEDURE PATIENT EXPIRED. Manufacturer Narrative: INVESTIGATOR ASSESSED THAT THE DEATH EVENT WAS NOT RELATED TO THE STUDY DRUG, DEVICE OR PROCEDURE. CAUSE OF DEATH IS UNKNOWN. Manufacturer Narrative: (B)(4).

2015/06/04	Event Description: AN IN.PACT ADMIRAL BALLOON WAS USED TO TREAT THE POPLITEAL ARTERY AND SFA (SAME IN.PACT ADMIRAL DEVICE WAS USED TO TREAT THE SFA AND POPLITEAL). APPROXIMATELY 4 MONTHS LATER THE PATIENT SUFFERED ANEMIA AND GENERAL DETORTATION, THE PATIENT WAS HOSPITALIZED AND EXPIRED APPROXIMATELY 2 MONTHS LATER. Manufacturer Narrative: (B)(4).

Appendix D: Excluded studies

RCTs

Full text publications

Debing et al. 2017

Debing et al. (2017) reported the results of the Belgian Diabetic IN.PACT trial, a prospective, multi-centre RCT. They aimed to demonstrate the efficacy of the DCB to inhibit restenosis of the infrainguinal arteries in 54 diabetic patients by comparing it to PTA in 52 patients. Patients were randomised at a ratio of 1:1 between PTA and an IN.PACT DCB. Randomisation only occurred after the most distal lesion was successfully crossed by a guide wire. Unfractionated heparin was recommended during the procedure. Pre-dilation was performed in all cases with a standard balloon. Inflation time for both groups was a minimum of 2 minutes. All patients received acetylsalicylic acid at a dose of 75 to 325mg per day or clopidogrel at 75mg per day. Patients were instructed to continue their medication for at least 6 months post-procedure. Follow up was performed at 1 and 6 months post-procedure. DUS was used to assess SFA and conventional angiography was used to assess popliteal and below the knee arteries. The primary patency was found to be significantly better in the DCB group (73% vs. 51%, p=0.03). The rate of TLR was higher in the PTA group but not significantly (29% vs. 19%, p=0.12).

Critical appraisal

This was a randomized, comparative, multicenter study, however no sample size calculation was reported. Randomization was 1:1 between IN.PACT balloons and PTAs, however the groups were unequal (52 vs. 54). None of the patient, investigator, independent angiographic nor ultrasound laboratories were blinded. The trial protocol did not provide guidelines for indication for amputation or wound care, meaning that these may have varied at the discretion of the interventionist. Rutherford classes 3 to 5 were included. The follow up period was notably short at only 6 months.

Fanelli et al. 2012

Fanelli et al. (2012) reported the results of the DEBELLUM trial, a prospective, RCT that aimed to compare the efficacy of the IN.PACT Admiral and Amphirion to a standard PTA balloon. 50 consecutive patients presenting with peripheral artery disease were randomised to the interventions in a 1:1 ratio without stratification. DEBs and ABs were either used for dilation of a de novo lesion at any level or for postdilatation after primary stenting in SFA. Implantation of a nitinol stent was at the discretion of the interventionist. Patients were given 100mg of aspirin and 75mg of clopidogrel per day, from

at least 3 days before the procedure. If patients were not on an antiplatelet regime prior to the procedure, they were administered a 300mg loading dose of clopidogrel. Aspirin was continued indefinitely after the procedure and clopidogrel was continued for 4 weeks. An intra-arterial 5000-unit bolus of heparin was administered immediately after sheath insertion. Predilation was performed in all native lesions with a non-coated balloon (undersized by 1mm) but not in cases of primary stenting. The Admiral balloon was used for femoropopliteal lesions and the Amphirion was used for BTK lesions. If more than one balloon was required, a 1cm overlap was used. The mean LLL after 6 months was significantly lower in the DEB group (0.5 ± 1.4 vs. 1.6 ± 1.7 mm, p<0.01). Mean LLL was 0.41 ± 0.5 vs. 1.55 ± 1.3 mm in the SFA (p<0.05) and 0.62 ± 0.9 vs. 1.65 ± 1.5 mm in the BTK arteries (p<0.05). TLR at 6 months was 6.1% for DEB and 23.6% for AB (p=0.02).

Critical appraisal

This was a randomized, prospective, comparative study with a sample size calculation, giving a power or 90% for the detection of absolute difference in LLL. LLL is an angiography-based endpoint and therefore less relevant than clinical endpoints such as TLR to the pathway. The patients were blinded to the intervention but the interventionists were not. Outcomes were only assessed at 6 months post-procedure and no later follow up is reported. Included Rutherford classes were not reported.

Liistro et al. 2013

Liistro et al. (2013) reported the results of the DEBATE-SFA trial – a prospective, randomized, single center trial. The study aimed to compare the safety and efficacy of the IN.PACT Admiral DCB with bare metal stents (BMS) with standard PTA balloons with BMS. 104 patients presenting with intermittent claudication or critical limb ischemia (CLI) were enrolled prospectively (with 110 lesions in 110 limbs). CLI patients at risk of major amputation were excluded if recanalizing BTK arteries failed. All lesions underwent pre-dilation with an uncoated balloon, which was undersized with respect to the vessel diameter. In patients randomized to the PTA + BMS groups, a nitinol stent was implanted. In the PEB + BMS group, further dilatation of a minimum of 120s with IN.PACT Admiral was performed before nitinol stenting. In both groups, all stents were post-dilated with a conventional balloon, maintaining a vessel/balloon diameter ratio of 1:1. In lesions requiring more than 1 balloon, a 5mm overlap was used. All patients received dual-antiplatelet therapy of 100mg of aspirin and 75mg of clopidogrel per day. Aspirin was administered indefinitely while in the PTA + BMS group, clopidogrel was continued for 1 month and in the PEB + BMS group, aspirin was continued for 3 months. After 12 months of follow up, target lesions were evaluated by repeat angiography or duplex ultrasonography. After 1 year,

freedom from TLR was 66.7% in the PTA + BMS group vs. 83.0% in the PEB + BMS group (p=0.07). LLL was significantly lower in the PEB + BMS group (0.86mm (0.80/0.94) vs. 1.68mm (1.60/4.2), p<0.001; values expressed as a median and compared with a Mann-Whitney U test).

Critical appraisal

This was a randomized, comparative study and included a power calculation. The study was only performed at a single center, however and was only powered to detect differences in the primary endpoint, not in hard clinical endpoints. Angiograms and DUS scans were assessed by blinded independent operators but not all patients were imaged using the same methodology (73% angiography, 27% DUS). Systematic stenting was performed in both groups, limiting the generalisability of the results to other procedural methods. No external adjudication committee or central lab was available. Patients in Rutherford classes 3-6 were included. Follow up was short (12 months).

Tepe et al. 2015

Tepe et al. (2015) reported the results of the IN.PACT SFA trial, a global, multicentre, single-blinded, randomised controlled trial. They aimed to assess the safety and efficacy of the IN.PACT Admiral DCB in comparison to standard PTA balloons in symptomatic patients presenting with superficial femoral and/or proximal popliteal artery disease. The SFA trial had 2 phases (1 conducted in Europe and 1 in the US) which were carried out sequentially in time. An independent clinical events committee adjudicated all major adverse events. 331 patients (2:1 ratio assigned to the intervention) with symptomatic SFA and/or proximal popliteal artery disease were enrolled. Patients were randomised after successful crossing of the lesion in phase I and after successful crossing and pre-dilation with a standard PTA balloon (1mm smaller than reference vessel diameter) in phase II. Follow up was 12 months. Patients randomised to the experimental arm were treated with the IN.PACT DCB, the length of which was 10mm longer than the target lesion length at the proximal and distal ends. Where treatment required multiple DCBs, an overlap of 10mm was applied. A loading dose of 300-325mg of aspirin and 300mg of clopidogrel was administered within 24 hours of the index procedure or 2 hours post procedure. Post-dilatation was allowed at the discretion of the operator and was performed using a standard PTA balloon. Provisional stenting was only allowed in cases of PTA failure after repeated and prolonged PTA inflations. It was found that the DCB resulted in significantly higher primary patency (82.2% vs. 52.4%; p<0.001). The CD-TLR rate was 2.4% in the DCB group and 20.6% in the standard PTA group (p<0.001). Rates of vessel thrombosis were low in both groups (1.4% after DCB and 3.7% after PTA (p=0.10)) and there were no procedure related

deaths or major amputations. After 12 months, there was no significant difference in baseline quality of life using the EQ-5D assessment (0.1059 vs. 0.0703 in the DCB and PTA groups, respectively, p=0.10).

Critical appraisal

This was a prospective, multicenter, randomized controlled trial with a calculated power of 80%. The trial was deliberately conducted in 2 phases, with phase I blinded until the completion of the second phase. Rutherford classes 2 to 4 were included. Follow up was short (12 months). Due to this and the specific nature of the subgroups, the results cannot be generalized. Quality of life assessments were subjective as they were partly evaluated using patient questionnaires and comorbidities further complicate the appraisal of these outcomes.

Non-comparative studies

Full-text publications

Bague et al. 2015

Bague et al. (2015) reported the results of the PLAISIR study - a prospective, multicenter, French cohort study. The safety and feasibility of the IN.PACT Admiral DCB for treating ISR FP lesions was investigated in 53 symptomatic patients, from 10 centers, according to symptoms of Rutherford classes 1-5. Predilation was performed using a standard balloon or a high pressure balloon for a residual restenosis > 50%. Where two or more PEB's were used, a 1cm overlap was required. All procedures were performed after administration of a bolus of heparin at a dose of 50 IU/kg. Patients were prescribed aspirin and clopidogrel for 6 months after treatment, followed by 1 antiplatelet agent. Quality of life was evaluated before the intervention, after the intervention and followed up after 1 year. Major adverse cardiac events (MACEs) were also collected in the follow up period (median length 17 months). Concomitant lesions were treated in 12 limbs (21%). After 1 year, freedom from TLR was 90.2 ± 4.2% and the primary patency rate was 83.7 ± 5.0%.

Critical appraisal

This is a prospective, non-comparative study without a sample size calculation. Furthermore, the study focused on a single treatment strategy, so there can be no conclusions drawn about the IN.PACT Admiral in comparison to other interventions. Inclusion and exclusion criteria were not strictly observed. Follow up times varied significantly - the median time was 17 months, with a range of 1-19 months. The study included patients with

Rutherford score 4 and 5 (>10%). In addition, 21% of the cases had concomitant lesions treated.

Grotti et al. 2016

Grotti et al. (2016) reported the results of the DEBATE-ISR study. They aimed to report the 3 year safety and effectiveness of the IN.PACT Admiral DCB in 44 consecutive diabetic patients with claudication or CLI and in-stent restenosis in comparison to conventional balloon angioplasty. Patients not already taking clopidogrel or aspirin were given a 300-mg dose of each 24 hours before the procedure. Seventy to 100U/kg of unfractionated heparin were injected intra-arterially to help maintain an activated clotting time of >200 seconds. Lesion predilation with an uncoated balloon was performed on all patients. A 5mm overlap was used where more than one balloon was required. All patients were given a dual-antiplatelet therapy of 100mg of aspirin per day and 75mg of clopidogrel per day. Aspirin was continued indefinitely and clopidogrel was continued for one month. Target lesion revascularisation (TLR) was only performed if clinically indicated and when a ≥50% target lesion stenosis was present. The 3 year incidence of TLR was the primary endpoint of the study and it was found that there were no significant differences between DEB and BA. It was also observed that the treatment of more complex ISR lesions was associated with an increased rate of TLR, regardless of whether DEB or BA was used. The authors concluded that the clinical benefit of DEBs, in terms of prevention of recurrent restenosis within 12 months, is lost between 1 and 3 years of follow up.

Critical appraisal

This was a non-randomised, retrospective, single-center study with no propensity score matching limit and no sample size calculation. This may limit the applicability and generalisability of the results. Angiograms and duplex scans were reviewed in a random order by 2 blinded independent investigators. No information on Rutherford class was reported. Outpatients were followed up at 1, 6, 12, 24 and 36 months, a reasonably long period. No external adjudication committee or central lab were used.

Micari et al. 2012

Excluded due to this paper presenting the same results as Micari et al. 2013.

Micari et al. 2016

Excluded due to this paper presenting the same results as Micari et al. 2017.

Schmidt et al. 2016

Schmidt et al. (2016) reported the results of 260 patients undergoing treatment of complex femoropopliteal lesions using DCBs from a Real-World Registry. The authors aimed to investigate the efficacy of the IN.PACT Pacific and IN.PACT Admiral in 288 of these complex lesions. No formal inclusion criteria were applied to the registry but all included patients were treated for symptomatic peripheral arterial disease of Rutherford class ≥ 1. Before the use of each DCB, either an uncoated balloon or an atherectomy/thrombectomy device was used for pre-treatment, at the discretion of the interventionist. The DCB diameter was 1.0mm larger than the uncoated balloon. If more than 1 DCB was used per lesion, then overlap was a minimum of 5mm. Minimum inflation time was 1 minute, with a recommended time of 3 minutes. All patients were taking 100mg of aspirin daily. Dual anti-platelet therapy with a daily dose of 100mg aspirin and 75mg clopidogrel was given for a minimum of 4 weeks and a single agent was used thereafter. Follow up was performed at 6, 12 and 24 months. Primary patency for in-stent restenosis treatment was 76.6% and 48.6%, at 1 and 2 years, respectively. Freedom from TLR was 83.0% and 58.7% for the same periods.

Critical appraisal

This was a single-center, retrospective analysis of a single treatment with no sample size calculation reported. Physicians performing interventions and scans were not blinded to the treatment strategy and some ultrasound scans were performed at other centers and so may not be to the same standard. Rutherford classes 1 to 6 were included. Follow up was for a period up to 24 months; however, it was noted that a number of patients did not attend all scheduled sessions.

Stabile et al. 2012 and Virga et al. (2014)

Stabile et al, (2012) and Virga et al. (2014) reported the results of 39 consecutive patients undergoing treatment of complex femoropopliteal lesions using DCBs from a real-world registry. They aimed to assess the efficacy and safety of the IN.PACT Pacific and the IN.PACT Admiral, 1 year (Stabile) and 2 years (Virga) after treatment for SFA in-stent restenosis. All patients received a dose of aspirin (75 to 160mg per day) and should have been receiving a 250mg dose of ticlopidine twice per day. If they were not receiving ticlopidine, then patients received a 300mg preloading dose of clopidogrel, 24 hours before the procedure. The thyenopiridines were continued for 30 days after the procedure, while the aspirin was continued indefinitely. Seventy to

100U/kg of unfractionated heparin was administered with an intended clotting time of >250s. All patients underwent PTA for at least 1 minute with a balloon 0.8 times the size of the reference vessel. At the interventionist's discretion, laser mediated lesion debulking was used as a substitute to PTA pre-dilation. Post-dilation was performed for at least 3 minutes. A 5mm overlap was allowed when more than 1 balloon was required. Patients were evaluated at 30 days, 3, 6 and 12 months after the procedure. Primary patency was obtained in 92.1% of patients and secondary patency was 100% at 1 year. The primary patency rate at 2 years was 70.3%.

Critical appraisal

This was a non-randomised, non-comparative, single centre study without a sample size calculation. As a prospective registry, the conclusions should be not be generalized and should be considered as hypothesis generating. The procedure was not consistent, as some patients were receiving ticlopidine and some were given clopidogrel. Additionally, laser mediated lesion debulking was used in some cases rather than PTA pre-dilation. This may impart some performance bias. No information on blinding was reported. Included Rutherford classes are unclear (a mean and standard deviation were reported). In the initial paper, the follow-up period is short (1 year), however with the addition of the latter paper, the follow up period is acceptable (2 years).

Conference abstracts

Jaff et al. 2016

Jaff et al. (2016) reported the results of 1406 patients enrolled in the IN.PACT Global study. The study was a prospective, multi-centre cohort trial, at 64 sites around the world. The authors aimed to assess the safety and efficacy of the IN.PACT Admiral DCB in patients with de novo or restenotic lesions in SFA or popliteal arteries. CD-TLR was found to be 7.5% after 12 months.

Critical appraisal

This was a non-comparative study that did not report a sample size calculation. However, a large cohort was included from multiple centers. Adjudication was independently performed by a Clinical Events Committee. Rutherford classes 2 to 5 were included.

Scheinert et al. 2015

Scheinert et al. (2015) presented the results of 157 patients enrolled in the ≥ 150mm Long Lesion Imaging cohort of the IN.PACT Global study. The study was a prospective, multi-centre cohort trial, at 64 sites around the world. The

authors aimed to assess the safety and efficacy of the IN.PACT Admiral DCB in the long lesion cohort. The 12-month CD-TLR rate was found to be 6.0% and the primary patency was 91.1%.

Critical appraisal

This was a non-comparative study that did not report a sample size calculation. Adjudication was independently performed by a Clinical Events Committee but no information on blinding was reported. Rutherford classes 2-5 were included.

Brodmann et al. 2015

Brodmann et al. (2015) reported the results of 131 patients enrolled in the IN.PACT Global study. The study was a prospective, multi-centre cohort trial, at 64 sites around the world. The authors aimed to assess the efficacy and safety of the IN.PACT Admiral DCB in patients with de novo In-stent Restenosis with pure ISR lesions. The 12-month CD-TLR rate was found to be 7.3% and the primary patency rate was 88.7%.

Critical appraisal

This was a non-comparative study that did not report a sample size calculation. Adjudication was independently performed by a Clinical Events Committee but no information on blinding was reported. Rutherford classes 2-5 were included.

Tepe et al. 2014

Tepe et al. (2014) reported the results of 126 patients with pure CTO lesions enrolled in the CTO imaging cohort of the IN.PACT Global study. The study was a prospective, multi-centre cohort trial, at 64 sites around the world. The authors aimed to assess the efficacy and safety of the IN.PACT Admiral DCB in patients with pure CTO lesions. The 12-month CD-TLR rate was found to be 11.3% and the primary patency rate was 82.7%.

Critical appraisal

This was a non-comparative study that did not report a sample size calculation. Adjudication was independently performed by a Clinical Events Committee. Rutherford classes 2-5 were included.

Fanelli et al. 2017

Fanelli et al. (2017) reported the results of 72 patients from the IN.PACT global study with complex lesions and severe calcium. The study was a

prospective, multi-centre cohort trial, at 64 sites around the world, aiming to assess the efficacy and safety of the IN.PACT Admiral DCB. It was found that the IN.PACT Admiral had a CD-TLR rate of 8.5% and a primary patency rate of 88.8%. Major adverse effects occurred in 11.9% of patients.

Critical appraisal

This was a non-comparative study that did not report a sample size calculation. Adjudication was independently performed by a Clinical Events Committee. Rutherford classes 2-5 were included.