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# BMJ Open Economic analysis of endovascular drug-eluting treatments for femoropopliteal artery disease in the UK

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## ABSTRACT

**Objectives:** To estimate the clinical and economic impact of drug-eluting endovascular treatment strategies for femoropopliteal artery disease compared with current standard of care.

**Design:** Systematic literature search to pool target lesion revascularisations (TLR). Model-based per-patient cost impact and quasi-cost-effectiveness projection over 24 months based on pooled TLRs and current reimbursement.

**Setting:** The UK's National Health Service (NHS).

**Participants:** Patients presenting with symptomatic femoropopliteal disease eligible for endovascular treatment.

**Interventions:** Current National Institute for Health and Care Excellence (NICE) guideline-recommended treatment with percutaneous transluminal balloon angioplasty (PTA) and bailout bare metal stenting (BMS) versus primary BMS placement, or drug-coated balloon (DCB), or drug-eluting stent (DES) treatment.

**Primary and secondary outcome measures:** 24-month per-patient cost impact to NHS (primary outcome). Secondary outcomes: pooled 24-month TLR rates; numbers needed to treat (NNTs); cost per TLR avoided and estimated incremental cost-effectiveness ratio (ICER) in £ per quality-adjusted life year (QALY).

**Results:** N=28 studies were identified, reporting on 5167 femoropopliteal lesions. Over 24 months, DCB, DES and BMS reduced TLRs of de novo lesions from 36.2% to 17.6%, 19.4% and 26.9%, respectively, at an increased cost of £43, £44 and £112. NNTs to avoid 1 TLR in 24 months were 5.4, 6.0 and 10.8, resulting in cost per TLR avoided of £231, £264 and £1204. DCB was estimated to add 0.011 QALYs, DES 0.010 QALYs and BMS 0.005 QALYs, resulting in estimated ICERs of £3983, £4534 and £20 719 per QALY gained. A subset analysis revealed more favourable clinical and economic outcomes for a 3.5 µg/mm<sup>2</sup> DCB with urea excipient, compared with the rest of DCBs. A modest reduction of 10% in DCB and DES prices made drug-eluting treatments dominant.

**Conclusions:** Widespread adoption of drug-eluting endovascular therapies for femoropopliteal disease would add meaningful clinical benefit at reasonable additional costs to the NHS. Based on currently

## Strengths and limitations of this study

- To the best of our knowledge, this is the largest systematic literature review of different endovascular options for the femoropopliteal artery conducted to date (28 clinical studies were pooled reporting on more than 5000 femoropopliteal artery lesions) to inform a health economic analysis comparing percutaneous transluminal balloon angioplasty (PTA) and bailout bare metal stenting (BMS), or primary BMS placement, or drug-coated balloon application, or drug-eluting stent placement.
- The primary strength of the present study was the development of a robust decision-analytic per-patient cost impact model for the UK National Health Service (NHS) on the basis of the pooled probabilities of future target lesion revascularisation, whose results question the National Institute for Health and Care Excellence-guideline recommended standard of care (PTA and bailout BMS) and support a paradigm shift towards drug-eluting therapies.
- We explored several outcome measures, including the per-patient cost impact of drug-eluting therapies, the numbers needed to treat and the estimated incremental cost-effectiveness ratio of competing treatment strategies as measures of clinical effectiveness and cost-effectiveness, along with extensive subset and sensitivity analyses.
- The main limitation of the present health economic analysis is that it has been developed according to the current practice pattern, the market forces and tariff system applicable to the NHS in the UK.
- Our economic analysis is also limited by a 24-month time horizon in the absence of longer term data, and also by the potential under-representation of critical limb ischaemia cases.

available data, DCBs offer the highest clinical and economic value.

## INTRODUCTION

Peripheral artery disease causes significant morbidity and reduced quality of life for patients, with vascular restenosis and vessel failure leading to frequent revascularisation in some patients or even amputations, representing a significant economic burden on the UK National Health Service (NHS).<sup>1 2</sup> Current guidance from the National Institute for Health and Care Excellence (NICE) recommends offering percutaneous transluminal balloon angioplasty (PTA) only after advice on risk factor modification has been reinforced, a supervised exercise programme has been tried and imaging has confirmed a lesion suitable for intervention.<sup>3 4</sup> Stenting is currently not recommended as a primary treatment for femoropopliteal disease. If stenting is needed or offered, the NICE guidance specifies that bare metal stents (BMS) should be used. Both drug-eluting stents (DESs) and drug-coated balloons (DCBs) have shown promising results in the femoropopliteal segment by reducing vascular restenosis and consequently the need for target lesion revascularisation (TLR).<sup>5</sup> DCB in particular, as a relatively novel and effective treatment approach that does not require any long-term device implant, has not yet been considered in the current NICE guidance.

The objectives of the present study were (1) to systematically search for and synthesise the clinical efficacy of different endovascular treatment approaches taking into account the most recent published evidence on PTA, BMS, DCB and DES; (2) to estimate the per-patient cost impact on the NHS of these competing endovascular treatment strategies and (3) to study related secondary outcome measures of cost-effectiveness.

## MATERIALS AND METHODS

We conducted a systematic literature search for clinical trials and registries reporting TLR rates in de novo superficial femoral artery (SFA) and/or popliteal artery disease (see online supplementary appendix). Treatment-specific probabilities of TLR were pooled and used in the budget impact decision-analytic model in order to estimate treatment-specific total reimbursement related to index procedure and applicable revascularisation over a 24-month time horizon. We pursued a primary analysis that assumed any repeat interventions to be treated according to the current guideline-recommended approach of PTA with bailout BMS, and a secondary analysis exploring variations in repeat revascularisation strategies.

The primary outcome was the 24-month per-patient cost impact to NHS. Secondary outcomes included pooled 24-month TLR rates; numbers needed to treat (NNTs); cost per TLR avoided and estimated incremental cost-effectiveness ratio (ICER) in £ per quality-adjusted life year (QALY).

### Systematic literature search and pooling

Our systematic literature search was carried out in June 2015, and was performed as an update of prior PubMed

and EMBASE searches completed in December 2012 for a budget impact analysis focused on the USA and Germany.<sup>6</sup> In short, our search identified all relevant studies of endovascular interventions for treatment of de novo SFA lesions, limiting the analysis to one of the following four therapies—PTA, BMS, DES or DCB. Only studies that reported TLR as an end point were included. In order to avoid potential confounders and to ensure an unbiased comparison, we excluded studies reporting mean lesion lengths >20 mm, more complex lesions and studies that primarily investigated interventions of restenotic lesions.

Applying the same approach as in the prior analysis, we extracted the probability of TLR reported for the longest follow-up (up to 24 months) for each of the identified studies.<sup>6</sup> Estimates of 24-month TLR probabilities of each of the four interventions were subsequently computed using a weighted pooling approach based on sample size. For studies only reporting shorter follow-up of 12 months, the 12-month TLR rates were pooled, and then extrapolated to the corresponding 24-month TLR probability, under the assumption of a constant hazard rate.

### Decision-analytic model structure and reintervention strategies

A decision-analytic model was developed to estimate, by index procedure strategy, the primary and secondary end points of this analysis. The model considered the index procedure and up to one reintervention, over a 24-month analysis horizon. This time horizon was chosen as it reflects the follow-up horizon available for most of the included studies. Reintervention rates were based on the pooled rates of the four modalities PTA, BMS, DCB and DES. For strategies that included bailout stenting (ie, stenting performed if index balloon intervention was technically not feasible or suboptimal), the 24-month TLR was computed considering the primary device's TLR estimate for the cases not requiring bailout stenting, and the BMS-specific TLR for the remainder. Mortality was not considered given the limited time horizon of the analysis, and because the included clinical studies do not suggest a mortality difference related to the study devices or procedures.

The primary analysis compared BMS, DCB and DES strategies to current guideline-recommended approach. For this analysis, we assumed that any necessary reintervention would be performed using the same guideline-recommended approach (PTA with bailout BMS stenting), with an assumed 20% bailout proportion, based on recent data<sup>7–11</sup> and our own clinical experience (coauthors KK, HZ, TC). Several additional treatment strategies, such as the use of drug-eluting therapies in case of a TLR, were considered in the secondary analysis to explore possible variations in reintervention approaches.

### Cost assumptions

Costs were assumed based on the current 2015/2016 NHS England Tariff (Enhanced Tariff Option), Hospital

Episodes Statistics (HES) data, and on market research data on current device prices of BMS, DCB and DES. The total 24-month costs calculated in this analysis included the reimbursement for the index procedure and applicable reintervention. Costs for each intervention were based on the complication-adjusted and market forces factor-adjusted inpatient tariff, as well as one outpatient specialist visit preintervention and postintervention, and the tariff for one colour duplex imaging (see table 1). For BMS, DCB and DES, the respective current selling price of the device was added, per current tariff rules which allow separate reimbursement as excluded devices.

### Computation of study end points

The study end points were computed as follows: 24-month TLR was computed based on the pooled TLR rates, and where applicable, by considering the probability of bailout BMS stenting. Cost difference was computed considering the 24-month total cost of each strategy, versus the current guideline-recommended treatment strategy of PTA with bailout BMS stenting. NNTs were computed based on the absolute difference between estimated TLR rates. For each of the alternative strategies, cost difference and NNTs were multiplied to obtain cost per TLR avoided.

To obtain an estimate for incremental cost-effectiveness, we considered a decrement of 0.06 QALYs associated with each TLR on the basis of previously published health utilities.<sup>13</sup> This decrement was based on the observed differences in health-related quality of life (utility) between pretreatment baseline and post-treatment, and also based on the differences in health-related quality of life observed between patients requiring a TLR and patients not requiring a TLR.<sup>13</sup> Estimated QALY gain was computed by multiplying the difference in TLR rate by the QALY decrement, under the assumption of no mortality difference. The resulting ICER estimate is the ratio of incremental costs to incremental QALYs. For all computations, we opted to not discount costs or effects because of the short follow-up horizon of the analysis of only 24 months and the fact that most costs are incurred at time zero.

### Base cases, subset analyses and sensitivity analyses

The base cases of the primary and secondary analysis, as described earlier, reflect point estimates of the 24-month cost per patient to NHS by index procedure strategy, as well as secondary outcome measures including cost per TLR avoided, NNT to avoid one TLR in 24 months, estimated QALY gain and estimated ICER. A subset analysis was computed to estimate the differences

**Table 1** Input parameter assumptions used in the model

Variable	Definition	Source
<i>Clinical parameters</i>		
Mean 24-month proportion of TLRs		
PTA	38.5%	Weighted pooling of TLRs in identified trials (see online supplementary table)
BMS	26.9%	
DES	19.4%	
DCB	17.6%	
DCB (paclitaxel with urea excipient—In.Pact)	11.2%	
DCB (other)	21.9%	
Probability of bailout stenting in balloon procedures		
Probability of bailout stenting	0.20	Author estimate based on Schillinger <sup>12</sup> and Laird <i>et al</i> <sup>7</sup>
<i>Cost parameters</i>		
Costs associated with every intervention		
HRG best practice tariff, therapeutic endovascular interventions, CC-adjusted and MFF-adjusted	£1702	Based on HRG QZ15B, QZ15B, adjusted for frequency
Outpatient tariff for specialist visit preintervention and postintervention, including colour duplex imaging	£323	
WF01B (1xpre, 1xpost), HRG RA24Z		
Data used to compute HRG tariff		
Percentage of intermediate CC cases	59%	Based on 2014/2015 admissions data
Percentage of non-CC cases	41%	
MFF	1.0809	Average MFF for the NHS England
Device cost (added to respective procedure cost)		
BMS	£384	Average annual selling prices from Decision Resources Group Reports (US PV Pricetrack, EU PV Marketrack) through September 2015
DES	£474	
DCB	£512	
DCB (paclitaxel with urea excipient—In.Pact)	£636	

BMS, bare metal stents; CC, Complication and Comorbidity; DCB, drug-coated balloon; DES, drug-eluting stent; HRG, Healthcare Resource Group; MFF, market forces factor; NHS, National Health Service; PTA, percutaneous transluminal balloon angioplasty; TLR, target lesion revascularisation.



between 3.5 µg/mm<sup>2</sup> urea excipient-based DCB (IN.PACT Admiral, Medtronic) and other DCBs, as there is experimental evidence<sup>14 15</sup> which suggests different DCB coating formulations with different pharmacokinetic profiles may produce different vessel tissue bioavailability and ultimately result in significant differences of DCB clinical results.<sup>7 16</sup> Several sensitivity analyses were performed to study the effect of parameter uncertainty on the base case and subset analysis results. These included an assumed device use of 1.5 instead of 1 device per procedure for DCB and DES strategies to account for longer lesions, a decrease in assumed device costs for BMS, DES and DCB by 20%, an increase in device costs by 10%, and a scenario in which DCB and DES costs were reduced by 10%. In addition, we studied the effect of parameter uncertainty in each therapy's clinical effectiveness by considering lower and upper TLR bounds. To obtain realistic TLR ranges for sensitivity analysis, we pooled the subsets of higher and lower performing studies separately for each therapy (see online supplementary appendix), yielding 24-month TLR rate ranges of 30.8–47.0% for PTA, 21.9–33.1% for BMS, 11.8–23.8% for DCB and 17.5–36.0% for DES.

## RESULTS

### Systematic literature search

We identified a total of 32 publications representing 28 studies or registries published between 2006 and 2015 that fulfilled our criteria.<sup>4 7–9 11 17–43</sup> The Preferred Reporting Items for Systematic Reviews and Meta-Analyses diagram outlining the results of the systematic search process is included in the online supplementary appendix. The total number of lesions included was 5167 (n=886 for PTA, 2463 for BMS, 989 for DES and 829 for DCB, with lesion counts based on numbers reported at longest follow-up). Most patients suffered from intermittent claudication (Rutherford class 2 or 3), and 15–20% presented with critical limb ischaemia (CLI). Lesion location was primarily in the SFA.

### Clinical efficacy

The pooled 24-month TLR estimate for PTA was 38.5% (based on a total of 13 studies). For BMS, the TLR estimate was 26.9% (15 studies), and for DES 19.4% (4 studies). The pooled TLR estimate for DCB was 17.6% (nine studies). Subset analyses for DCB yielded TLR estimates of 11.2% for DCB with urea excipient (IN.PACT Admiral; three studies),<sup>7 23 40</sup> and 21.9% for all other DCB (six studies).<sup>17 18 24–26 41</sup> A detailed overview of the studies and the TLR rate computations from reported 12-month and 24-month follow-up are shown in [table 2](#).

### Economic analysis results

The average per-patient cost over a 24-month period, including the index procedure and applicable reintervention costs, was lowest for the current

guideline-recommended strategy, PTA with bailout BMS stenting, at £2863, followed by DCB (incremental £43), DES (incremental £44) and primary BMS (incremental £112). The projected cost increases of drug-eluting therapies of <2% were accompanied by marked reductions in TLRs, with DCB reducing the 24-month reintervention rate to 17.6%, and DES to 19.4% compared with 36.2% in case of the guideline-recommended strategy. Primary BMS placement, at increased cost of 3.9%, was projected to be associated with 26.9% TLRs at 24 months (see [figure 1](#)).

The NNT was lowest for DCB (5.4), followed by DES (6.0) and BMS (10.8). Resulting costs per TLR avoided were £231 and £264 for DCB and DES, respectively, and £1204 for BMS. Estimated QALY gains were 0.005 for BMS 0.010 for DES and 0.011 for DCB, resulting in the estimated ICERs of £3983 (DCB), £4534 (DES) and £20 719 (BMS) per QALY gained. See [table 3](#) for details.

### Subset and sensitivity analyses

The performed subset analyses comparing the study outcomes of 3.5 µg/mm<sup>2</sup> urea excipient-based DCBs (Medtronic IN.PACT) to those of the remainder of DCBs showed lower TLR rates for the urea-based devices (11.2%, compared with 21.9%), resulting in lower NNTs (4.0 instead of 7.0). Cost per TLR avoided and the estimated ICER were lower with the 3.5 µg/mm<sup>2</sup> urea excipient-based DCBs (£31 vs £947 and £2259 vs £16 290 per QALY gained, respectively).

The conducted sensitivity analyses of the primary, base case, analysis tested the effect of using more than one device, and of variations in device prices. Under the assumption of 1.5 devices per procedure used for the DCB and DES strategies, a higher cost difference of £299 and £281 was found, resulting in increased cost per TLR avoided of £1604 and £1675, and ICERs of £27 596 and £28 815 per QALY gained for DCB and DES, respectively. Urea excipient-based DCBs had more favourable results than the non-urea-based DCBs in these scenarios as well (see online supplementary appendix). For the multiple device use scenarios, DCB and DES were the economically less favourable strategies, as compared with BMS.

In case of variations in the prices of DES and DCB, a reduction in device prices by 10% would make DCB and DES economically dominant, providing improved clinical outcomes at overall cost savings for the NHS budget at 2 years follow-up (£8 saving for DCB, £3 saving for DES). See details in the online supplementary appendix.

Lower clinical effectiveness of PTA (24-month TLR of 47.0%) led to more favourable outcomes for BMS, DCB and DES, making all three strategies cost saving and thus dominant, while higher PTA performance (30.8%) increased added cost of BMS, DCB and DES to £242, £173 and £174, respectively. Lower BMS performance (TLR 33.1%) increased added cost of the BMS first strategy to £216, but decreased DCB and DES added cost to

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

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

Continued

Table 2 Continued

Therapy	Study	12-Month reported TLR	Reported lesions (n)	Pooled 12-month TLR	24-Month reported TLR	Reported lesions (n)	Pooled 24-month TLR	Total pooled 24-month TLR estimate (%)
DCB subanalyses								
DCB (3.5 microgram with urea-based excipient—Medtronic IN.PACT)	PACIFIER <sup>23</sup> IT Registry <sup>40</sup> IN.PACT SFA <sup>11 7</sup>	7.1%	42	11.9%	Estimation of 24-month TLR 14.3%	98	10.8%	11.2
DCB, other	BIOLUX-PI <sup>24</sup> LEVANT 2 <sup>26</sup> THUNDER <sup>17</sup> FEM-PAC <sup>18</sup> LEVANT 1 <sup>25</sup> ILLUMENATE FIH <sup>41</sup>	15.4% 12.3%	25 285	12.5%	Estimation of 24-month TLR 15.0% 13.0% 35.7% 14.9%	198 47 45 42 47		21.9

Where only 12-month data were reported, probabilities were converted to the corresponding 24-month TLR probability via rates, assuming a constant hazard rate. BMS, bare metal stent; DCB, drug-coated balloon; DES, drug-eluting stent; PTA, percutaneous transluminal balloon angioplasty (with uncoated balloon); TLR, target lesion revascularisation.

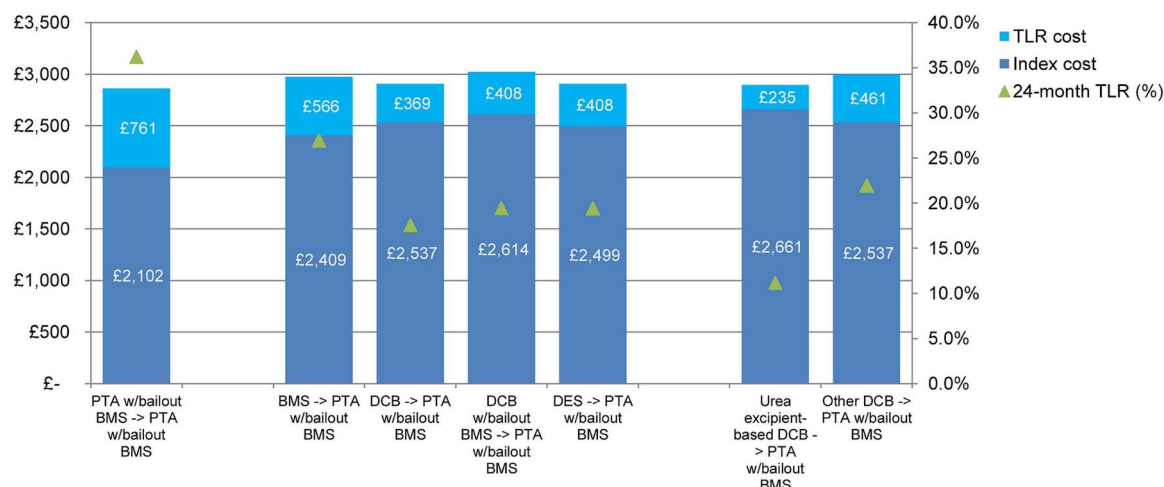
£17 and £18. Higher BMS performance (TLR 21.9%) reduced its added cost to £27, but left DCB and DES the clinically preferred options. An assumed higher TLR rate of 23.8% for DCB increased the added cost of DCB to £174 and the ICER to £24 148 per QALY gained, while a lower assumed TLR of 11.8% rendered DCB both cost saving and clinically superior. The low performance assumption of DES (TLR of 36.0%) increased added cost to £393, at minimally improved clinical outcome compared with standard of care. Reducing the 24-month TLR of DES to 17.5% reduced added cost to £4 and made DES preferable to DCB in terms of costs and TLR performance. See online supplementary appendix for further detail.

Assessing, in our secondary analysis, various alternative scenarios for repeat intervention device usage for each of the considered index procedure strategies led directionally to similar findings (see table 4 and see online supplementary appendix). The lowest overall cost increases were £29 for DES (DES as index procedure, followed by PTA intervention) and £30 for DCB (DCB as index procedure, followed by PTA intervention). The highest cost increase of £259 was found to be associated with a DCB with bailout BMS strategy pursued both for index and repeat intervention.

## DISCUSSION

Current guidelines recommend an endovascular-first approach for the majority of femoropopliteal stenoses or occlusions. Although vein bypass surgery still has a role in case of long or heavily calcified chronic total occlusions and in patients with a favourable life expectancy, it is associated with significant perioperative morbidity, which has led many centres to adopt an endovascular-first approach.<sup>3 44–47</sup> Although PTA and bailout stent placement has been long considered the endovascular standard of care, our results clearly indicate that drug-eluting endovascular therapies of femoropopliteal disease are associated with lower reintervention rates and marginally improved quality of life. We found DCB and DES to be associated with substantially lower TLR rates of around 18% and 19% over 24 months, compared with around 27% with a primary BMS strategy and around 36% with current standard of care as per NICE guidance. In addition, compared with standard of care, we found single-digit NNTs of 5 in case of a DCB-first treatment and 6 in case of a DES-first treatment, highlighting the high efficacy of drug-eluting technologies in improving clinical outcomes of the femoropopliteal artery.

Most interestingly, these improved clinical outcomes were found to be associated with limited increases in overall cost for the NHS budget. For the base case scenario assuming current tariffs and market forces, drug-eluting treatments resulted in an incremental budget impact of only £43–£44, or around 2%, per patient at 24 months, with a favourable projected ICER



**Figure 1** Twenty-four-month cost, by index and reintervention procedure, and 24-month TLR projection for the primary analysis and subset analysis of DCB type. BMS, bare metal stent; DCB, drug-coated balloon; DES, drug-eluting stent; PTA, percutaneous transluminal balloon angioplasty; TLR, target lesion revascularisation.

of around £4000–£4500 per QALY gained. Considering that clinical results of individual DCB have been found to differ significantly on the basis of different balloon pharmacokinetics and paclitaxel bioavailability,<sup>15 16</sup> we explored the potential effect of different DCB catheters. Our DCB subgroup analysis revealed that a 3.5 µg/mm<sup>2</sup> paclitaxel balloon with a urea-based excipient was associated with the lowest rate of TLR totalling 11.2% at 24 months and a calculated cost impact of £33 per patient, a NNT of 4 and a most favourable ICER of around £2300 per QALY gained.

While the current NICE guidance<sup>3</sup> does not consider DCB or DES as the first-line treatment in the SFA, the authors suggest that a subsequent revised version should carefully consider the aforementioned options, based on the presented robust clinical data and favourable health economic analysis. The economic impact of the different SFA treatments is based on the higher initial treatment costs versus the current standard of care, and the subsequent differential of the avoided or delayed TLRs—a classic ‘spend now to save later’ scenario. Costs per procedures avoided, based on the inverse of the absolute risk difference (or NNT), seem to provide very reasonable value not just for the healthcare system but also for the patients who can be spared repeat invasive procedures and may enjoy improved quality of life. We have identified very small NNT (range 4–11) in all of the explored scenarios of the base case and sensitivity analyses confirming the high efficacy of DES and DCB as first-line SFA therapies. Arguably, DES and DCB are not only protecting patients from recurrent symptomatic disease that may mandate reinterventions, but are also saving them from the inherent risk of potential complications, anxiety and inconvenience of having to undergo a repeat procedure.

To account for variable SFA lesion complexity, we expanded our analysis to include 1.5 drug-eluting devices on average. As expected, the latter approach

showed an increase of incremental cost impact of around £280–£300 per patient at 24 months with a substantial increase of the corresponding ICER values. On the other hand, the results of our health economic decision analysis were sensitive in magnitude and direction to the actual list prices of the devices. Notably, a 10% price reduction raised both DES and DCB as dominant healthcare technologies by saving money for the NHS budget, while offering superior clinical outcomes. Hence, considering the fiercely competitive open market and ongoing pressure for cost savings in the current economic challenges facing the NHS, this analysis shows that drug-eluting endovascular technologies are potentially a new paradigm shift in the treatment of femoropopliteal disease.

The literature on economic analyses of DESs or DCBs is sparse to date. While there is a recent British cost-utility analysis on DCBs for infrainguinal disease<sup>1</sup> projecting both lower costs and higher QALYs (ie, DCB was found dominant) for intermittent claudication and CLI, the analysis does not take newer studies into consideration. A Swiss cost-effectiveness study from 2013<sup>48</sup> revealed that a DCB strategy, compared with PTA, is likewise economically dominant; however, that study was only based on clinical input parameters from one study.<sup>17</sup> Three of the authors of the current study participated in a prior study investigating budget impact of endovascular strategies in the German and US healthcare systems.<sup>6</sup> That study, based on clinical data available up to early 2013, found drug-eluting therapies to be associated with cost savings in both healthcare systems, when compared with PTA and BMS over a 2-year horizon.

In the present economic analysis, we performed an in-depth synthesis of numerous studies in the femoropopliteal segment. We first explored the options of DES or DCB as first-line treatments (primary analysis) and then also as secondary treatments during potential



**Table 3** Base case results, primary analysis

Strategy	24-Month cost	24-Month TLRs (%)	Cost difference	TLRs avoided	NNT to avoid 1 TLR in 24 months	Cost per TLR avoided	QALY gain (estimated)	ICER (£/QALY) (estimated)
PTA with bailout	£2863	36.2	£0	–	NA	NA	–	NA
BMS→PTA with bailout								
BMS								
BMS→PTA with bailout	£2975	26.9	£112	0.093	10.8	£1204	0.005	£20 719
BMS								
DCB→PTA with bailout	£2906	17.6	£43	0.187	5.4	£231	0.011	£3983
BMS								
DES→PTA with bailout	£2907	19.4	£44	0.168	6.0	£264	0.010	£4534
BMS								

BMS, bare metal stent; DCB, drug-coated balloon; DES, drug-eluting stent; ICER, incremental cost-effectiveness ratio; NA, not available; NNT, number needed to treat; PTA, percutaneous transluminal balloon angioplasty; QALY, quality-adjusted life year; TLR, target lesion revascularisation.

revascularisation to account for the wide variation of real-life clinical practice in the UK (secondary analysis). In the latter analysis, incremental cost per patient increased modestly (range £162–£259) compared with the primary analysis base case (range £43–£44). However, we consider those economic estimates as quite conservative because the present study considered a time horizon of only 2 years; hence, our model did not allow enough time for the expected clinical benefit of secondary drug-eluting treatments to materialise. Still, we note that the DCB with urea-based excipient produced more favourable clinical and economic results under all scenarios and conditions (see online supplementary appendix).

There are several limitations to this health economic study. First, we pursued a decision-analytic budget impact model, albeit based on true study data from a number of studies and including various competing balloon and stent endovascular treatments. Second, the index procedure in this study pertains to de novo lesions; however, we felt that this was the area with the greatest unmet clinical need, practice patterns are likely to vary in restenosis, and much less published evidence is currently available for restenoses. Third, our analysis was limited to a 2-year time horizon, and the ICER projections were based on simplified computer simulations under certain health utility assumptions. We speculate that a time horizon of at least 5 years would be more applicable for the femoropopliteal segment and ideally a cost-effectiveness study would take place within the context of a prospective randomised controlled trial. Notably, promising 5-year results have been recently released for a paclitaxel-eluting stent<sup>49</sup> and a paclitaxel-coated balloon<sup>50</sup> in the femoropopliteal segment. In addition, a quality of life and cost-effectiveness analysis of the randomised IN.PACT SFA trial at 2 years has been recently released from the perspective of the US health-care system.<sup>51</sup> The health economic findings from the IN.PACT SFA randomised trial are in line with the present results from the NHS perspective in the UK and also corroborate the fact that a 3.5 µg/mm<sup>2</sup> urea excipient-based DCB may be a dominant femoropopliteal treatment option.<sup>51</sup> Fourth, most of the currently available evidence was derived from outside of the UK. While disease biology and risk factors might be similar in other countries, the timing and type of intervention might lead to effect modification in terms of the lesions at the time of endovascular therapy. Last but not least, the synthesised evidence mostly applied for intermittent claudication and the population of CLI was under-represented, resembling only 15–20% of enrolled participants in the included studies. Still, a recent meta-analysis and metaregression study of all available randomised trials investigating different DCB in the femoropopliteal segment has identified only a weak adverse relationship between incidence of CLI and reduction of TLR rates by paclitaxel-coated balloons—on the other hand, paclitaxel dose was the strongest,

**Table 4** Base case results, secondary analysis

Strategy	24-Month cost	24-Month TLRs (%)	Cost difference	TLRs avoided	NNT to avoid 1 TLR in 24 months	Cost per TLR avoided	QALY gain (estimated)	ICER (£/QALY) (estimated)
PTA with bailout	£2863	36.2	£0	–	NA	NA	–	NA
BMS→PTA with bailout								
BMS								
PTA with bailout	£3014	36.2	£151	–	NA	NA	–	NA
BMS→DCB/DES 50% split								
DCB→PTA	£2893	17.6	£30	0.187	5.4	£159	0.011	£2739
DCB→DCB	£2983	17.6	£120	0.187	5.4	£641	0.011	£11 033
DCB with bailout	£3022	19.4	£159	0.168	6.0	£949	0.010	£16 335
BMS→PTA with bailout								
BMS								
DCB with bailout	£3122	19.4	£259	0.168	6.0	£1543	0.010	£26 538
BMS→DCB with bailout								
BMS								
DCB with bailout	£3103	19.4	£240	0.168	6.0	£1432	0.010	£24 629
BMS→DCB/DES 50% split								
DES→PTA	£2892	19.4	£29	0.168	6.0	£175	0.010	£3005
DES→DCB	£2992	19.4	£129	0.168	6.0	£767	0.010	£13 194
BMS→PTA	£2954	26.9	£91	0.093	10.8	£982	0.005	£16 890
BMS→DCB	£3092	26.9	£229	0.093	10.8	£2465	0.005	£42 413

BMS, bare metal stent; DCB, drug-coated balloon; DES, drug-eluting stent; ICER, incremental cost-effectiveness ratio; NA, not available; NNT, number needed to treat; PTA, percutaneous transluminal balloon angioplasty; QALY, quality-adjusted life year; TLR, target lesion revascularisation.

highly significant predictor of the expected biological effect size of DCB treatment.<sup>16</sup> Hence, the authors consider the present results generalisable for different treatment indications for femoropopliteal disease.

In conclusion, the widespread adoption of drug-eluting endovascular therapies for femoropopliteal disease would add meaningful clinical benefit at reasonable additional costs to the NHS and should be carefully considered in future revised guidelines. Based on currently available data, both DES and DCB offer the highest clinical and economic value compared with uncoated balloon angioplasty and/or BMS. Contrary to DES, DCB leave no permanent metal implant behind and—in particular with the use of a 3.5 µg/mm<sup>2</sup> urea-based DCB—might be associated with added clinical benefit and a potentially more favourable economic profile. More randomised trials with an a priori clinical effectiveness and cost-effectiveness design, especially in the case of CLI, are warranted.

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**Contributors** The study was initiated by JBP. All authors were involved in the design of the study. The systematic literature review and its update were performed by JBP, AMG and BPG. The clinical and economic analyses were performed by JBP and BPG. The manuscript was written by KK, JBP and BPG, with the other authors providing critical review and editing. All authors have approved the final submitted version of the manuscript.

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