PEER REVIEW HISTORY

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ARTICLE DETAILS

<table>
<thead>
<tr>
<th>TITLE (PROVISIONAL)</th>
<th>Economic Analysis of Endovascular Drug-eluting Treatments for Femoropopliteal Artery Disease in the United Kingdom</th>
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<tbody>
<tr>
<td>AUTHORS</td>
<td>Katsanos, Konstantinos; Geisler, Benjamin; Garner, Abigail; Zayed, Hany; Cleveland, Trevor; Pietzsch, Jan Benjamin</td>
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VERSION 1 - REVIEW

<table>
<thead>
<tr>
<th>REVIEWER</th>
<th>Monika Herten, PhD</th>
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<tbody>
<tr>
<td>Clinic for Vascular and Endovascular Surgery, University Hospital Muenster, Germany</td>
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| REVIEW RETURNED | 15-Feb-2016 |

GENERAL COMMENTS

The summary of information given in this review is new and analysis the situation for the United Kingdom is similar as previously published for the United States and Germany. (Pietzsch et al. Economic analysis of endovascular interventions for femoropopliteal arterial disease: a systematic review and budget impact model for the United States and Germany. Catheter Cardiovasc Interv. 2014 Oct 1;84(4):546-54.)

The manuscript is concise with a great amount of information and well structured. The analysis is performed very thoroughly. The figures/tables at the end of the manuscript are clear and demonstrate what is stated in the text. The search of literature is performed very accurately and the references were cited correctly.

On minor recommendation:

As stated at page 7 in the methods section, the analysis included all relevant studies of endovascular interventions for treatment of de novo SFA lesions. Therefore, this limitation “de novo SFA lesions” should be mentioned in the results section of the abstract. Otherwise three more trials for DCB on SFA ISR would have to be included: the DEBATE ISR and the FAIR trial, both using also the IN.PACT admiral DCB with quite high TLR (40%) at 24 months for the DEBATE ISR. Additionally the COPA CABANA trial using the Cotavance DCB with about 30 % TLR at 12 months would have to be included.

Summary:

I would strongly recommend the manuscript to be accepted for publication.

<table>
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<tr>
<th>REVIEWER</th>
<th>Miltiadis Krokidis</th>
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<tr>
<td>Cambridge University Hospitals NHS Foundation Trust, Cambridge, UK</td>
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| REVIEW RETURNED | 27-Feb-2016 |
| GENERAL COMMENTS | This is a very interesting health economics manuscript on a very important topic. My main concern- that is not included in the study limitations and probably needs to be included is the fact that the existing data that supports the use of drug eluting technology is based on studies outside the UK. We may accept the fact that the expression of atherosclerotic peripheral arterial disease is following the same pattern worldwide however we need to recognise a different distribution even in the same country.

Another major point is that the majority of the patients included in the studies are suffering from intermittent claudication and only 15-20% from critical limb ischemia. Again this is a result of using as a source non-UK based trials. We know that the best treatment for claudicants is the modification of life style prior to reaching the angiographic table. Unfortunately in various health systems outside the NHS there is an abuse of invasive methods - like the drug eluting technologies - that would not be applicable for NHS patients. Regarding NHS patients drug coated technology needs to be addressed mainly to patients with critical limb ischemia and the claudicants where the other options are exhausted.

A final point lays on the fact that your analysis is focused on the results of a specific product versus others (the IN.PACT Admiral balloon). If the purpose of the study is to compare this product with the rest of the existing technology it needs to be mentioned on the title of the manuscript.

Otherwise, I need to congratulate you for the thorough and extensive analysis of the existing data in this very complex and continuously evolving area of medicine. Health systems need to adapt to new data and integrate new technologies when they become cost effective. |

| VERSION 1 – AUTHOR RESPONSE |

Reviewer: 1 (Monika Herten, PhD; Clinic for Vascular and Endovascular Surgery, University Hospital Muenster, Germany)

Reviewer’s comment: The summary of information given in this review is new and analysis the situation for the United Kingdom is similar as previously published for the United States and Germany. (Pietzsch et al. Economic analysis of endovascular interventions for femoropopliteal arterial disease: a systematic review and budget impact model for the United States and Germany. Catheter Cardiovasc Interv. 2014 Oct 1;84(4):546-54.). The manuscript is concise with a great amount of information and well structured. The analysis is performed very thoroughly. The figures/tables at the end of the manuscript are clear and demonstrate what is stated in the text. The search of literature is performed very accurately and the references were cited correctly. As stated at page 7 in the methods section, the analysis included all relevant studies of endovascular interventions for treatment of de novo SFA lesions. Therefore, this limitation “de novo SFA lesions” should be mentioned in the results section of the abstract. Otherwise three more trials for DCB on SFA ISR would have to be included: the DEBATE ISR and the FAIR trial, both using also the IN.PACT admiral DCB with quite high TLR (40%) at 24 months for the DEBATE ISR. Additionally the COPA CABANA trial using the Cotavance DCB with about 30 % TLR at 12 months would have to be included. I would strongly recommend the manuscript to be accepted for publication.

Authors’ response: We thank the reviewer for her comments and have included the limitation that the subject of our study are de novo lesions (as opposed to restenoses):
Abstract, results section, second sentence: “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.”

Methods section, first sentence: “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.”

Limitations section, third sentence: “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.”

Reviewer 2 (Miltiadis Krokidis; Cambridge University Hospitals NHS Foundation Trust, Cambridge, UK)

Reviewer's comment: Dear Authors,

This is a very interesting health economics manuscript on a very important topic. My main concern- that is not included in the study limitations and probably needs to be included is the fact that the existing data that supports the use of drug eluting technology is based on studies outside the UK. We may accept the fact that the expression of atheroscretotic peripheral arterial disease is following the same pattern worldwide however we need to recognise a different distribution even in the same country.

Authors’ response: We thank the reviewer for his comments. We appreciate that the etiologies and pathogenesis is likely similar inside and outside of the U.K. However, disease progression and distributions in the type of lesions might be subject to effect modification by both different risk factor profiles and timing and type of therapies. We have worded this as follows:

Limitations section, ninth sentence: “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.”

Reviewer’s comment: Another major point is that the majority of the patients included in the studies are suffering from intermittent claudication and only 15-20% from critical limb ischemia. Again this is a result of using as a source non-UK based trials. We know that the best treatment for claudicants is the modification of life style prior to reach the angiographic table. Unfortunately in various health systems outside the NHS there is an abuse of invasive methods - like the drug eluting technologies - that would not be applicable for NHS patients. Regarding NHS patients drug coated technology needs to be addressed mainly to patients with critical limb ischemia and the claudicants where the other options are exhausted.

Authors’ response: We appreciate reviewer’s comment. We agree – and mention in the manuscript - that there is guidance in the UK that intervention should only be considered when supervised exercise therapy has failed. However, the question remains how the substantial number of patients should be treated who are getting supervised exercise therapy but then still have lifestyle-limiting intermittent claudication. This is the health-economic question addressed in our analysis. Our analysis does not aim to estimate current utilization of conservative and endovascular therapy use, or take a position about appropriate implementation of current guidance. Nor is it intended to assess the health-economic profile of the studied interventions in patients with isolated critical limb ischemia. We agree that future clinical data collection and related analyses should focus more heavily on the subset of CLI patients. Such data would complement our current analysis.

Reviewer's comment: A final point lays on the fact that your analysis is focused on the results of a
specific product versus others (the IN.PACT Admiral balloon). If the purpose of the study is to compare this product with the rest of the existing technology it needs to be mentioned on the title of the manuscript.

Otherwise, I need to congratulate you for the through and extensive analysis of the existing data in this very complex and continuously evolving area of medicine. Health systems need to adapt to new data and integrate never technologies when they become cost effective.

Authors’ response: We appreciate the reviewer’s comment. The overarching objective of our analysis is to compare the health economic profiles of endovascular therapies for SFA disease, with primary focus on drug-eluting therapies. As no head-to-head comparison exists between the two types of DCB, we opted to combine all DCB study evidence for the base case, as this is the most appropriate methodological approach for the base case analysis. However, given the observed substantive difference in pooled TLR rates between urea excipient-based vs. other DCB (11.2% vs. 21.9% at 24 months), and differences in current pricing between these types of DCB, we believe the additional subset analyses provide useful additional information to decision makers.

VERSION 2 – REVIEW

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<td>Monika Herten, PhD; Clinic for Vascular and Endovascular Surgery, University Hospital Muenster, Germany</td>
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| REVIEW RETURNED | 22-Mar-2016 |

| GENERAL COMMENTS | Thank for including the suggested revisions. I also like to congratulate the authors for the excellent analysis of endovascular drug eluting treatments for femoropopliteal artery disease. |

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<tr>
<th>REVIEWER</th>
<th>Krokidis, Miltiadis</th>
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<td>Cambridge University Hospitals NHS Foundation Trust, UK</td>
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| REVIEW RETURNED | 28-Mar-2016 |

| GENERAL COMMENTS | I think the authors adequately addressed the raised issues in their repose and the manuscript may now reach priority for publication. |
Economic analysis of endovascular drug-eluting treatments for femoropopliteal artery disease in the UK

Konstantinos Katsanos, Benjamin P Geisler, Abigail M Garner, Hany Zayed, Trevor Cleveland and Jan B Pietzsch

BMJ Open 2016 6:
doi: 10.1136/bmjopen-2016-011245

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