A simulation model for peripheral arterial disease: Methods and application of a Markov model

Walzer S1,2, Droeschel D1,4, Shannon R2,5
1 MArS Market Access & Pricing Strategy GmbH, Weil am Rhein, Germany
2 MArS-imulation UG (h.b.), Weil am Rhein, Germany
3 State University Baden Wuerttemberg, Loerrach, Germany
4 Riedlingen University, SRH FernHochschule, Riedlingen, Germany
5 Global Health Economics Project LLC, New York, USA

Corresponding author:
Dr. Stefan Walzer
MArS Market Access & Pricing Strategy GmbH
GeoffBaechlein 4
79576 Weil am Rhein
Germany
Contact: stefan.walzer@marketacess-pricingstrategy.de

INTRODUCTION:
- Peripheral Arterial Disease (PAD) can cause heavy, tired or painful legs and feet (claudication), if allowed to progress, it can lead to severe lack of blood flow in the legs or feet, resulting in Critical Limb Ischemia.
- If left untreated PAD can also result in amputation, morbidity, and even death.
- There has been a rapid increase in the use of endovascular treatment especially in percutaneous transluminal balloon angioplasty (PTA).
- Revascularisation strategy is individual to the patient, and treatment by vascular specialists, or within specialised vascular centres, is recommended by the European Society of Cardiology (ESC) guidelines.
- Furthermore developments include drug-eluting stents (DES), drug-eluting balloons, cryotherapy, and endovascular and drug treatments.
- The aim of the underlying analysis was to develop a flexible health economic model for adaptation to various health care systems in order to routinely analyze PAD therapies systematically and comparatively.

METHODS:
- The scientific research question can be summarized as follows: “What is the scientific evidence of health economic models in PAD?”
- In order to establish the currently available published health economic models a systematic literature search was conducted.
- For a systematic literature search the following databases were searched:
  - Health Technology Assessment Database: http://www.demid.de/static/de/db/dtbn/info/health.txt
  - NHS Economic Evaluation Database: http://www.crd.york.ac.uk/CRDWeb/AboutHIHSEED.asp
- In the search the following PICOC criteria were applied:
  - Population: Patients with any therapy in PAD
  - Intervention: Peripherale Arterielle Erkrankungen (PAD), Interssestentklemmungs (IC): critical limb ischemia (CLIA) Therapy, Diagnostics
  - Comparator: Therapy: Patients with any therapy in PAD
  - Outcomes: Cost, cost-effectiveness, cost per QALY, cost minimization, cost comparison, cost of illness, health economic model, economic evaluation
  - The search was limited to the last 10 years (2006 to 2016).
- The key focus for the evaluation of the articles was the description of the underlying model.
- Based on the available evidence a new health economic model was developed.

RESULTS:
- Currently there is no health-economic model available which included all relevant interventions in PAD with two exceptions:
  - Sculpher et al. included all relevant interventions, however only as a subgroup analysis
  - The key model comparing all interventions against each other was published by Simpson et al. 2014. However, when comparing the Simpson model against current medical guidelines new interventions might not easily be included.
- Hence a new health economic model for PAD was developed with a baseline of interventions in which the addition of further new interventions can be included rapidly.
- For that the advantages of Markov modeling was utilized. A deterministic Markov model with 30 day cycle was developed. The time frame for the model was fixed for five years.
- The average patient in the model is assumed to be 68 years on average with a diagnosed PAD Fontaine IIb, III, IV.
- Currently there is no health economic model available which included all relevant interventions in PAD with two exceptions.
  - Sculpher et al. included all relevant interventions, however only as a subgroup analysis
  - The key model comparing all interventions against each other was published by Simpson et al. 2014. However, when comparing the Simpson model against current medical guidelines new interventions might not easily be included.
- Hence a new health economic model for PAD was developed with a baseline of interventions in which the addition of further new interventions can be included rapidly.
- For that the advantages of Markov modeling was utilized. A deterministic Markov model with 30 day cycle was developed. The time frame for the model was fixed for five years.
- The average patient in the model is assumed to be 68 years on average with a diagnosed PAD Fontaine IIb, III, IV.

Figure 1: The peripheral arterial disease model

- It is assumed that all patients start in a static health state with PAD (HS 1).
- Therefore patients can transition within a 30 day outcome to a patient health state (HS 2), which would require a PTA intervention.
- Patients could respond positively on the re-intervention or progress further which would require the utilization of stents (HS 3).
- PTA after stents the ultimate last intervention before an amputation would be implementing a bypass (HS 4).
- If all reinterventions (HS 4) have been ruled-out, the last resort intervention is amputation (HS 5).
- Final absorbing state is mortality (HS 6).
- It is assumed that patients in the different intervention arms have different mortality outcomes.
  - Thus there is a transition from HS 2 to HS 7 which is the general mortality of the 30 day patency.
  - The transition from HS 2 to HS 8 is the intervention specific mortality of the 30 day patency.
  - Similar transitions are given from HS 3 to HS 9, which is the general mortality of the 30 day non-patency.
  - The transition from HS 3 to HS 10 is the intervention specific mortality of the 30 non-patency.
  - Further a re-intervention specific mortality (HS 4 to HS 11) and an amputation specific mortality (HS 6 to HS 12) is given.

Figure 2: Base case efficacy results in the Peripheral Arterial Disease (PAD) Model

- Mortality based on the different health states for a defined patient population is available in Figure 3.
- Furthermore cost and resource utilization which are required in the different health states are computed.
- The total cost per patient are calculated on which basis a budget impact analysis could be run.
- Additionally the models includes utilities and allows for cost utility analysis.
- The model will now extensively be validated with external and internal sources:
  - Face validity with clinical PAD experts in different countries
  - Face validity with health economic (modeling experts)
  - Testing of functionality of the model
  - Comparison of model results with external results based on clinical studies
  - Additionally, the probabilistic component of the model will be programmed and included.

Figure 3: Mortality results in the Peripheral Arterial Disease (PAD) Model

- The possibility of adding further new procedures in the model is provided for each health state and adds to the flexibility of this model.
- The base case input values are provided in table 1.

Table 1: Base case input values for the Peripheral Arterial Disease (PAD) Model

<table>
<thead>
<tr>
<th>Model health state</th>
<th>Monthly probability (base case)</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>PTA to PTA (HS 0 to HS 1)</td>
<td>0.100</td>
<td>Start of the model</td>
</tr>
<tr>
<td>PTA to HS (HS 1 to HS 2)</td>
<td>0.006</td>
<td>Harrev et al. 1994</td>
</tr>
<tr>
<td>Stent to bypass (HS 9 to HS 10)</td>
<td>0.253</td>
<td>NICE 2012</td>
</tr>
<tr>
<td>Bypass to amputation (HS 7 to HS 9)</td>
<td>0.000</td>
<td>Assumption</td>
</tr>
<tr>
<td>PTA to PTA mortality (HS 2 to HS 3)</td>
<td>0.05</td>
<td>de Vries et al. 2002</td>
</tr>
<tr>
<td>Stent to stent mortality (HS 6 to HS 7)</td>
<td>0.26</td>
<td>Assumption</td>
</tr>
<tr>
<td>Bypass &amp; bypass mortality (HS 10 to HS 11)</td>
<td>0.87</td>
<td>Assumption</td>
</tr>
<tr>
<td>Amputation to mortality (HS 8 to HS 6)</td>
<td>0.15</td>
<td>Assumption</td>
</tr>
</tbody>
</table>

CONCLUSIONS:
- The developed Markov simulation model is consistent with the medical practice in PAD in Europe and the US.
- Additionally the model reproduces flexibly various finance and reimbursement realities and can hence be seen as a recommended health-economic model for analyses in PAD for new and existing therapies.
- However, an internal and external validation with published datasets is currently being executed and will be published.