Health technology assessment of treatment for peripheral arterial disease

SUMMARY

PAD is a widespread cardiovascular disease, in 2010 an estimated 40.5 million people lived with PAD in the European region (1), and patient numbers are increasing worldwide (2). Some patients with PAD experience chronic pain, have a reduced walking distance or may become dependent on other people to handle everyday life (3). Additionally, patients with PAD have a high risk for cardiovascular events such as heart attack or stroke, and for death from cardiovascular causes. Treatment of PAD therefore includes physiotherapy, lifestyle interventions, treatment with drugs i.e. pharmacological treatment, and (repeated) invasive treatment, this can include surgery or minimally-invasive interventions to improve the blood flow to the affected extremities (2, 4, 5). New pharmacological treatment options and invasive treatment techniques and materials are becoming available, potentially reducing the burden of the disease to the patient, but also potentially increasing treatment costs and economic burden of PAD (6-17). In this context, the evaluation of costs, clinical outcomes, and the value for money i.e. cost-effectiveness of such new PAD treatments becomes increasingly relevant.

The objective of the thesis was to 1) investigate current PAD treatment patterns, 2) measure the quality of life of patients with PAD and to estimate the costs of PAD treatment, and 3) to assess the cost-effectiveness of new pharmacologic treatment strategies for PAD.

The first sub-objective aimed to identify groups of PAD patients with different treatment needs according to their cardiovascular risk and their probability of undergoing invasive PAD treatment, i.e. revascularization probability. Purpose of the identification of these groups was to explore if patient characteristics available at PAD diagnosis could be used to anticipate these treatment needs. Chapter 2, addressing this first sub-objective, described the analysis of characteristics of 274 patients newly diagnosed with PAD, and their treatment following diagnosis. Groups of PAD patients who developed different treatment needs were identified, and the relationship between group membership and patient characteristics were explored. This relationship was analysed in two ways: 1) Venn diagrams identified combinations of characteristics that were related to increased cardiovascular risk and reduced revascularization eligibility, 2) a regression analysis was used to analyse predictors of increased revascularization probability. On the one hand, the Venn diagrams identified four combinations of characteristics that characterized patients with reduced revascularization eligibility due their cardiovascular profile. These combinations were (a) insulin-dependent diabetes and impaired renal function, (b) History of MI and obesity, (c) insulin-dependent diabetes and history of MI, and (4) Age > 75, obesity and insulin-dependent diabetes. Within the patient cohort analysed, 5.1% of patients had such a combination of characteristics that identified them as likely ineligible for revascularization and thus dependent on stringent pharmacological cardiovascular prevention. Treatment for such patients who are at increased cardiovascular risk and need for extra measures to prevent PAD progression as well as cardiovascular events may

benefit from intensified and individualised pharmacological treatment. On the other hand, the regression analysis showed a number of characteristics of patients who are at higher risk of undergoing invasive PAD treatment. These characteristics were younger age, lower physical functioning, and lower quality of life, as well as more severe Fontaine stages and worsening complaints. Identifying this group of patients who are more likely to need revascularization may help GPs treating PAD patients refer patients with such characteristics and signs of worsening of the disease to the vascular surgeon earlier. By involving the vascular surgeon earlier, the decision to switch from conservative to invasive treatment will not be delayed, which may benefit the patient. The findings of the study presented in Chapter 2 may help develop guidance for PAD treatment in the primary care setting, where additional information on a patient's future treatment needs may help doctors determine the best treatment approach for newly diagnosed PAD patients.

The second sub-objective of the thesis was to measure the quality of life of patients with PAD and to estimate the costs of PAD treatment in the first two years after diagnosis. Chapter 3 describes the quality of life of patients with new PAD, and the effect of invasive and conservative treatment using two different measurement instruments, the SF-6D and EQ-5D. Quality of life data from 229 patients with newly diagnosed PAD was analysed. The data had been collected during a time period of two years starting from diagnosis of PAD. The analyses compared the effect of non-invasive, i.e. conservative vs. invasive PAD treatment one and two years after diagnosis. To enable a comparison between the conservative and invasive treatment groups, differences in characteristics of the groups were adjusted for using a matching technique (propensity score matching). The effects of invasive treatment and conservative treatment were estimated, patient characteristics that influenced the extend of the treatment effect were identified. At year one, 30.6% of patients had received invasive treatment, 7.4% received invasive treatment during the second year. The EQ-5D instrument indicated that QoL after invasive treatment was higher, and more patients reported 'no problems' with pain/discomfort, mobility and usual activities after invasive treatment. The SF-6D instrument indicated that physical functioning, role limitations physical and pain were improved after invasive treatment. Both treatments showed a positive effect on quality of life measured by the EQ-5D, the SF-6D measured a small negative effect of conservative treatment. The comparison between patients who received invasive treatment and patients who received conservative treatment showed that the effect of treatment on quality of life was dependent on the quality of life at PAD diagnosis. Patients with lower quality of life and patients who experienced rest-pain at diagnosis gained more quality of life with PAD treatment. The difference in effect between conservative and invasive treatment was not statistically significant. The effect of invasive treatment was numerically larger. The analysis highlighted that both conservative and invasive treatment improved the quality of life of

patients with PAD. The EQ-5D was more sensitive to changes in quality of life and differences between patient groups.

In Chapter 4 we quantified the costs of PAD and PAD treatment by estimating the costs of mild PAD and moderate PAD, of peripheral revascularization i.e. invasive treatment and the cost of illness of PAD in the Netherlands overall (Chapter 4). Based on a bottom-up approach, using data from a smaller cohort of patients with PAD to estimate the costs within a much larger population, we estimated the cost of illness of PAD of the entire population of PAD patients in the Netherlands. Resource use and costs of 245 new Dutch PAD patients over a period of two years starting from PAD diagnosis were analysed. The impact of patient characteristics on PAD costs was explored using generalized linear regression. The costs of all new and all prevalent cases of PAD in the Netherlands were estimated. Over the first two years of treatment, 64.5% of patients exclusively received conservative treatment and 35.5% received invasive treatment at least once. Patients reported going to the GP and to the physiotherapist most often. The costs of PAD treatment were highest 3 months after diagnosis, and lowest 24 months after diagnosis. This was largely driven by the costs of invasive treatment. During the three months before PAD diagnosis, the majority of costs were related to specialist care. The total cost over the 27 months period (3 months before hospital-based diagnosis up to the 24 months after diagnosis) were €7,504 per patient; €4,265 (BCI €3,836 – €4,796) in the first year and €2,789 (BCI €2,307 – €3,324) in the second year. Costs were higher in patients with a high BMI and patients undergoing (repeated) invasive treatment, and lower in patients using cholesterol-lowering drugs and in patients with a high quality of life at diagnosis. The annual healthcare costs of patients with mild PAD and moderate PAD were €2,031 and €2,318, respectively. The costs of a revascularization were €4,422. Considering there are 26,489 new PAD patients in the Netherlands per year, the costs of new PAD are estimated to be €113.1 million in the first year and €72.4 million in the second year of PAD treatment (18). The annual costs of 613,000 prevalent PAD cases amount to €1.26 billion (19). This is comparable to the estimated €1.3 billion spent on the treatment of other cardiovascular disease such as ischemic heart disease in the Netherlands according to the European cardiovascular disease statistics (19).

The third and last sub-objective was to assess the cost-effectiveness of a new pharmacological treatment, rivaroxaban plus aspirin, for cardiovascular disease including PAD. In Chapter 5 we used a health-economic model to assess the costs and clinical outcomes of dual pathway inhibition (DPI) with 2.5mg rivaroxaban twice daily plus 100mg aspirin compared to aspirin alone for the prevention of heart attacks, strokes and death from cardiovascular disease in patients with coronary artery disease (CAD) or/and PAD. In patients with PAD, treatment with DPI and with aspirin were also compared to treatment with clopidogrel. A state transition model was developed, i.e. a model that simulated how a hypothetical cohort of patients treated with either of the treatment options would over

time transition through a set of health states representing the different health conditions the patients could be in. In this case, these health conditions reflected stable disease, cardiovascular events as heart attack, or ischemic and haemorrhagic stroke, worsening of PAD, bleeding events, and death. To estimate the health outcomes and costs of each treatment option, costs and quality of life consequences were attached to each health state and summed up considering the amount of time patients would spend in each health state. Evidence from two clinical trials were used to model the effect of treatment with DPI, aspirin and clopidogrel. The model evaluated the treatments by estimating health outcomes and costs over a lifetime horizon. The results were standardized units of health gained, which was expressed in quality-adjusted life years (QALY), and costs. The cost per QALY was compared against the willingness-to-pay threshold per unit of health gained by the Dutch health authorities (€50,000 per QALY). This reflected the value for money provided by the treatments from a Dutch healthcare perspective. The analysis showed that in CAD patients and in PAD patients, DPI provided the best health outcomes (longer survival, higher number of QALYs) and the highest costs. The additional costs stemmed largely from higher drug costs. This resulted in a cost per QALY of €32,109 for the treatment of CAD, and of €26,381 for the treatment of PAD when comparing DPI to aspirin. Treatment with clopidogrel was less cost-effective than with DPI. The probability of DPI being cost-effective was 92% and 56% in CAD and PAD patients. The annual healthcare costs would increase by €38.7 million if DPI was implemented for the treatment of CAD and would increase by €29.0 million if DPI was implemented for the treatment of PAD. The relationship between costs and effects of treatment with DPI differed in some subgroups of CAD and PAD patients. The costs per QALY was lowest in PAD patients with additional diseases and in CAD patients younger than 65, this indicated that treatment would be most cost-effective in these patients. The costs per QALY were highest in PAD patients with carotid artery disease and in CAD patients older than 75, this indicated that treatment with DPI would be less cost-effective. Chapter 5 ended with a discussion of limitations of the study and of the evidence used, and how these impact the decision uncertainty. It was highlighted that unavailability of detailed trial data contributed considerable uncertainty as assumptions had to be made where data from clinical trials should ideally be used, but these were not made available. The level of evidence informing the effectiveness of clopidogrel was identified as another uncertainty, specifically regarding the cost-effectiveness of DPI for the treatment of patients with PAD.

Chapter 6 continued by exploring the feasibility of a comprehensive uncertainty assessment of health economic models, using the model described in Chapter 5 as a case study. The aim was to parameterize all influential uncertainties and reflect them in the cost-effectiveness probability and risk associated with the adoption decision. The uncertainties applying to the model were identified and added to the probabilistic sensitivity analysis if possible. Parameter distributions were obtained by expert elicitation, and structural uncertainties were either parameterized or explored in scenario analyses

which were model averaged. The case study highlighted that a truly comprehensive uncertainty assessment could not be achieved, and several subjective judgments and decisions were necessary in the process of the uncertainty assessments, which potentially reduced the comprehensiveness and transparency of the approach. Expert elicitation regarding the value of parameters that were uncertain showed to be a useful tool in parameterizing previously unexplored uncertainties, and in reflecting them in the cost-effectiveness results. Guidance regarding the use of applicable methodologies, such as the selection of uncertainties, the use of expert elicitation, the aggregation of elicited and existing data, the use of model averaging, and reporting the results in a comprehensive and transparent manner was missing and perceived as a barrier to the comprehensive uncertainty assessment. The use of existing tools such as TRUST for the assessment of uncertainties (20), and EXPLICIT for the elicitation of expert opinion (21) were perceived as facilitators. The study provided an example of how comprehensive uncertainty assessment can be conducted by utilizing existing tools and available sources of expert knowledge. It also underlined that the requirements for comprehensive uncertainty assessment need better definition by those potentially using it – decision makers in healthcare – and more attention regarding the development of guidance and instructions for the appropriate use of methodologies is needed.

The last chapter (Chapter 7) of this dissertation summarizes the main findings and discusses implications on HTA methodology. Furthermore, implications on clinical and policy decisions making regarding care for PAD patients are outlined. Based on the research conducted, areas that require further research are described. Regarding the field of HTA, these include the handling of missing cost data, the systematic identification and parameterization of uncertainties relating to health economic models and the use of expert elicitation tools in HTA. Regarding the clinical and policy aspects of care for PAD patients, these include the further development of prediction tools for the anticipation of future treatment needs, the use of intensified conservative treatment and the role of non-clinical characteristics in the treatment pathway of PAD patients.

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