Intermittent claudication is the most frequent clinical manifestation of atherosclerosis affecting the arteries of the lower limb. It is not uncommon in the elderly: from 2 to 5% of the population between the ages of 55 and 75 suffer from claudication. The characteristic symptoms are pain, cramp, or fatigue in muscles of the lower extremity caused by walking, which are completely relieved after 2 to 5 minutes rest by standing. Common sites of obstruction in the peripheral arterial system are the aortoiliac arterial segment and the superficial femoropopliteal arterial segment. General measures in the treatment of peripheral arterial occlusive disease are directed towards reducing the rate of progression of atherosclerosis in the legs and at other sites. This includes the reversal of risk factors, such as smoking, hyperlipidemia, diabetes mellitus, and hypertension, and the use of antiplatelet drugs. More specific measures directed towards improving the symptoms of claudication are exercise programs, drugs, balloon angioplasty, and reconstructive surgery. Over the past few decades percutaneous treatment strategies have become widely used and the success rates have proven to be high, especially in the iliac arteries, with low complication rates.

This thesis deals with the relative benefits and cost effectiveness of percutaneous treatment strategies, more specifically stent placement and balloon angioplasty, for the treatment of patients with intermittent claudication due to atherosclerosis of the iliac arteries. In addition, this thesis addresses some methodological issues concerning quality-of-life and cost assessment.

General considerations concerning both the percutaneous treatment of iliac artery occlusive disease and outcome assessment in the evaluation of medical interventions are described in Chapter 1. In the treatment of iliac artery occlusive disease, percutaneous transluminal angioplasty (PTA) has become an established, safe, and effective procedure. Endovascular stent placement (i.e., a tubular metallic prosthesis that can be placed inside arteries) was developed to overcome the limitations of PTA, such as acute occlusion in the periprocedural period and restenosis within several months. The reported results of endovascular stent placement have been very promising, although the results are difficult to compare with those of angioplasty because of differences in reporting methods and case mix across studies. Currently, stent placement is commonly used to treat iliac artery occlusive disease if intra-arterial pressure measurements or angiographic appearance indicate that the results of iliac
Summary

Balloon angioplasty are suboptimal. However, stents are increasingly being placed primarily. Although placing a stent is expensive, a potential advantage of primary stent placement is that initial and long-term results may be better than those of PTA or secondary stenting. A prospective randomized clinical trial, the Dutch Iliac Stent Trial, was initiated to compare primary stent placement with stent placement after PTA if the results of PTA were suboptimal (defined as a residual pressure gradient of 10 mm Hg or more, with vasodilatation, across the treated site). In addition to the medical effectiveness, quality-of-life and cost outcomes were also assessed and a cost-effectiveness analysis was performed. In assessing quality-of-life and cost outcomes we encountered methodological problems, which we investigated further.

A meta-analysis of cohort studies reporting results of PTA and stent placement to treat aortoiliac occlusive disease was performed with adjustment for differences in case mix and reporting methods (Chapter 2). Six PTA and 8 stent studies published in 1990 or later were included in the analysis. Because risk factors and immediate procedure results were not uniformly defined or measured under identical conditions, a random-effects model was used to combine these proportions. Furthermore, to pool patency results, a meta-analysis technique was used with pooling of life-table data with and without adjustment for covariates (i.e., patient characteristics with prognostic value in predicting failure). The results demonstrated that after treatment the mean ankle-brachial index in the stent studies improved significantly more compared with that in the PTA studies (mean ankle-brachial indices after treatment 0.87 versus 0.76, respectively; p=0.03). The immediate technical success rate was higher after stent placement (96%) than after PTA (91%), although the difference was not significant. The complication rates and the mortality rates of stent placement and PTA did not differ significantly. Following PTA, the 4-year primary patency results were 65% for stenoses versus 54% for occlusions in the treatment of claudication and 53% for stenoses and 44% for occlusions in the treatment of critical ischemia. Following stent placement, the 4-year primary patency results were 77% for stenoses versus 61% for occlusions in the treatment of claudication and 67% for stenoses versus 53% for occlusions in the treatment of critical ischemia. The risk of long-term failure was reduced by 39% after stent placement compared with PTA. These results suggest that in the treatment of iliac artery occlusive disease, stent placement is superior to PTA alone. However, the costs, quality of life, and clinical effectiveness associated with stent placement remained unclear, with respect to primary stent placement and stent placement after PTA (if a failure occurred) and also in comparison with PTA.

In chapters 3, 4, 5, and 6 the quality of life of a health state with intermittent claudication and the costs of the percutaneous treatment strategies were assessed. The methodology to assess these outcomes, however, is not straightforward, e.g., costs and quality of life can be assessed with various measures and from various viewpoints. As a result, the methodology itself became the focus of these chapters. The quality of life of patients was assessed with the short form 36 (SF-36) and seven dimensions of health-status (e.g., physical, role, emotional, mental, and social functioning). To measure the difficulties related to health-status and to the utilities, our long-term approach was to estimate quality-of-life measures from the standard-gamma and standard-life measures.

The results demonstrated that the SF-36 and standard-gamma and standard-life measures were related to the standard-gamma. Furthermore, the quality-of-life measures were related to the standard-gamma, which was used to estimate utilities. The standard-life measures were related to the standard-gamma, which was used to estimate utilities. The standard-life measures were related to the standard-gamma, which was used to estimate utilities. The standard-life measures were related to the standard-gamma, which was used to estimate utilities.
Outcome assessment of the percutaneous treatment of iliac artery occlusive disease

of patients with intermittent claudication is described in Chapter 3. Quality of life was assessed with a health status measure (the RAND36-item Health Survey 1.0 (RAND-36)) and several valuational measures (i.e., time tradeoff, standard gamble, rating scale, McMaster health-utilities index) and the relationships between the health-status measure and the valuational measures were assessed. Because of the practical difficulties related to the assessment of time-tradeoff values and standard-gamble utilities, our long-term goal is to derive a predictive instrument for value and utility estimation based on answers to descriptive health-status questionnaires. All quality-of-life measures showed reduced quality of life in patients with intermittent claudication. The results demonstrated that the mean values of the scores on all RAND-36 health dimensions were significantly lower (i.e., implying poorer functioning and greater role limitations) compared with the mean values of the scores obtained from a random sample of the general population (matched for age and gender). The relationships between the RAND-36 dimensions and the values and utilities varied from poor to moderate. Conventional multiple regression analysis demonstrated that the health-status dimensions explained only 28% and 14% of the variance in the time tradeoff and standard gamble scores, respectively, and 62% and 53% of the variance in the McMaster health utilities index and rating-scale scores, respectively. These results suggest that answers to descriptive health-status questions cannot reliably predict standard-gamble utilities or time-tradeoff values.

The poor relationships between the standard-gamble utilities and the health-status scores, however, may be attributable to heterogeneity among patients in the weights they assign to different health-status dimensions. It seems plausible that certain health-status dimensions, e.g., bodily pain or physical functioning, are more important for some patients than for others. The study in which we investigated this hypothesis is described in Chapter 4. The study population was the same as the one of the study described in chapter 3. The assumption that the population consisted of two separate classes yielded superior representation of the data. The method of latent-class analysis was used to estimate the unknown parameters and class memberships. It was demonstrated that different health-status dimensions occurred in the regression equations of the two classes and the overall explained standard-gamble variance was 49%, which was much higher than the percentages of utility explained by health-status dimensions so far. Thus, these results suggest that patients with intermittent claudication belong to a variety of classes, all with class-specific relationships between the standard-gamble utility and the RAND-36 health-status dimensions.

Finally, a cost-effectiveness analysis from the societal perspective requires societal preferences for the health state intermittent claudication. Because it was not feasible to use existing methods to obtain preferences from a general population sample, we developed a new method using a single binary standard-gamble question. Furthermore, we assessed the societal preference for the health state amputation due
to peripheral arterial occlusive disease and investigated the difference between generic and disease-specific vignettes. This study is described in Chapter 5. A random sample of the general population in the United States was randomly divided into 10 subgroups with a different mortality risk for each subgroup in the standard-gamble question. The mean utility was estimated by the area above the proportional distribution of responses indicating acceptance of the gamble. In addition, each group was subdivided into two subgroups responding to vignettes with either a general description or a more disease-specific description of the health states. Mean societal utilities for intermittent claudication were demonstrated to be similar to the mean utilities obtained from patients with intermittent claudication. Although the validity and reliability need further testing, our results suggest that the binary standard-gamble question can be used in the general population to obtain societal preferences for health states. Furthermore, the results from our study suggest that disease-specific descriptions yield lower utilities than do generic descriptions of health states.

In Chapter 6 the costs of the percutaneous treatment strategies were assessed from various viewpoints in different countries. In practice, many different approaches are used to assess costs. Possible differences caused by different methodologies may have major implications for policy making. To investigate the results of different methodologies and the generalizability across countries, we assessed costs from the perspectives of the interventional radiology department, the hospital, the patient, and the health care system both in the Netherlands and in the United States. We used a cost-accounting method and charges to estimate the costs. It was demonstrated that actual costs were not significantly different from charges in the Netherlands. In the United States, however, charges were significantly higher compared with actual costs. Furthermore, by performing the cost analysis in both countries we demonstrated that reported costs are not by definition generalizable across countries. However, by doing a cost analysis of various cost components across countries, cost-saving strategies may be identified. We concluded that cost analyses may yield different results depending on the chosen perspective and country.

The results of the meta-analysis, quality-of-life assessment, cost assessment, and the other results of the Dutch Iliac Stent Trial were included in a cost-effectiveness analysis comparing stent placement and PTA for iliac artery occlusive disease (Chapter 7). A Markov decision model was developed and the analysis was performed from a societal perspective. The baseline analysis considered 60-year-old male patients with lifestyle-limiting claudication due to stenoses in the iliac arteries for whom a percutaneous intervention was indicated. A sensitivity analysis was performed using different costs, quality of life, age, sex, disease severity, and lesion type. The results demonstrated that primary stent placement compared with selective stent placement yielded no additional benefits and was more expensive ($957). Selective stent placement compared with PTA alone yielded higher patency results (relative risk of long-term failure 0.6).
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long-term failure 0.61) and quality-adjusted life expectancy (0.2 QALYs gained), and an incremental cost-effectiveness ratio below $20,000 per QALY gained.

The main conclusion (see also Chapter 8) of the outcome assessment of percutaneous treatment in iliac artery occlusive disease is that in the treatment of patients with claudication and a stenosis, primary stent placement yields no additional benefits and is more expensive compared with stent placement as an adjunct to PTA. In addition, our results suggest that the gain in effectiveness of selective stent placement compared with PTA alone justifies the additional costs. In the treatment of patients with critical ischemia or an occlusion, the role of primary stent placement as opposed to selective stent placement remains to be elucidated. Finally, although we found that differences in quality-of-life outcomes and costs did not influence the clinical decision in our study, providers, payers, and policy makers need to be aware of the methods used to assess quality of life and costs in cost-effectiveness analysis in order to make informed decisions.