Management strategies for intermittent claudication

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SUMMARY

Intermittent claudication is characterized by cramping pain, discomfort, or fatigue in the lower limbs that is elicited by exercise and relieved by rest. Typically, the amount of exercise that initiates the symptoms is more or less constant, forcing a patient to pause at regular distances while walking. Over time, patients may develop more severe symptoms, such as ischemic rest pain, ulcers, or gangrene. In a small minority of the patients amputation of the lower limb is eventually required. The symptoms of intermittent claudication are explained by impaired blood flow to the lower limbs caused by atherosclerotic obstructions in the peripheral arterial system.

Treatment alternatives include exercise, bypass surgery, and, more recently, percutaneous transluminal angioplasty. Traditionally, the approach to treating intermittent claudication has been conservative, because patients face little risk of limb loss and because the risks of perioperative complications from surgical revascularization procedures are significant (*Chapter 1*). Interventions are generally postponed until initial non-interventional options such as exercise have failed. The risks of perioperative complications from angioplasty, are, however, far lower than those of bypass surgery and the question has been raised whether the conservative approach to treating intermittent claudication can still be justified as earlier intervention may prevent unnecessary disability. On the other hand, the costs of both types of vascular interventions are considerable. Considering the limitations of the health care resources, it is even possible that current treatment strategies are not conservative enough and that, from a cost-effectiveness perspective, vascular interventions would better be reserved for patients with more severe symptoms of peripheral arterial occlusive disease.

The primary purpose of the work presented in this thesis was to evaluate the cost-effectiveness of interventional and non-interventional treatment strategies in patients with intermittent claudication. We developed a Markov decision model that simulates outcomes, both costs and effects, under several alternative treatment strategies. Results of the decision analysis are presented in *Chapter 9*. Most of the other studies presented in this thesis were preliminary steps that provided input information for the decision model.

In *Chapter 2* we examined the value of certain patient characteristics and vascular laboratory measures in predicting the outcomes of an exercise program for patients with intermittent claudication. This analysis was presented as an example of the use of autoregressive logistic regression, a statistical technique that may be particularly useful if primary data is analyzed to provide input data for a Markov decision

analysis. We found that age, duration of the symptoms, and the ankle/brachial index may help to predict the outcomes of the exercise program.

The effect measure that was used in the decision analysis adjusts a patient's life expectancy for the effects of disease and disability on the quality of life. Quality weights may be obtained with health value measures, questionnaires that aim to measure quality of life on a 0-1 scale. In *Chapter 3* we used several such measures, including the time trade-off, standard gamble, verbal rating scale, Health Utilities Index, and the EuroQol, and explored their relation with a measure of symptom severity, the symptom-free walking distance, of the respondents. The strongest statistical association between health values and walking distance was found for the EuroQol and the verbal rating scale.

In *Chapter 4* we discussed the use of summary ROC curves in combining data from different published studies of the performance of a diagnostic test. In our study we applied the technique to studies of the diagnostic performance of duplex scanning in peripheral arterial occlusive disease. Usually, such studies report estimates of the sensitivity and specificity of the test. A summary ROC curve adjusts for differences between the studies in the threshold value used that may have caused systematic differences in sensitivity and specificity. The results of the analysis suggest that the addition of color-flow imaging to duplex scanning improves its diagnostic performance and probably reduces the total imaging time.

In *Chapter 5* we determined the costs of a variety of vascular interventions. Data were obtained from the hospital accounting database of Brigham and Women's Hospital (Boston, United States). The results of a regression analysis suggest that perioperative complications may have a significant effect on the total costs of a hospital admission for bypass surgery or angioplasty. Additional effects were found for age, sex, presenting symptoms, and history of coronary artery disease.

Chapter 6 is a meta-analysis of studies of the short- and long-term results of aortic bifurcation bypass surgery in patients with peripheral arterial occlusive disease. An important, but relatively rare long-term complication from this and other similar procedures is occlusion of the bypass. Most studies in vascular surgery therefore use 'graft patency' as their primary outcome measure. Our analysis suggests that the risks of perioperative mortality and morbidity (e.g., myocardial infarction) from this procedure have declined during the past few decades, whereas the graft failure rates remained constant.

A comparison of interventional and non-interventional treatment strategies in peripheral arterial occlusive disease based on literature data is complicated by a fundamental difference in reporting traditions between the different areas in vascular medicine. In vascular surgery and interventional radiology, outcome studies focus on

patency, whereas outcome studies of non-interventional therapy primarily report functional outcomes, such as walking performance. *Chapter 7* aimed to provide a link between changes in ankle/brachial index, as used in patency criteria, and changes in maximum walking distance.

Theoretically, ignoring the possibility that patients develop symptoms in the contralateral limb may bias against therapeutic options that treat both limbs simultaneously (e.g., exercise). In *Chapter 8* we determined the incidence of contralateral symptoms in patients with a unilateral intervention for peripheral arterial occlusive disease. We found that the incidence of contralateral critical ischemia (i.e., rest pain, ulcer, or gangrene) is considerable, especially if the initial ipsilateral procedure was also performed for critical ischemia or if the initial contralateral ankle/brachial index was low.

Chapter 9 presented the results of a Markov decision analysis comparing interventional and non-interventional treatment strategies for intermittent claudication. A Markov decision model defines a number of different health states and simulates how patients may move between the different health states under a particular treatment strategy. The model keeps track of the time spent in each health state and the accumulated costs. Treatment strategies included exercise, exercise and angioplasty, or exercise, angioplasty and bypass surgery as possible therapeutic options for intermittent claudication. We found that, compared to a treatment strategy based exclusively on exercise, interventional treatment strategies improved the quality-adjusted life expectancy, provided that patients did not have a history of myocardial infarction or angina pectoris. The extra costs of interventional strategies, however, were considerable. Relative to the gain in quality-adjusted life expectancy, the extra costs of strategies that included bypass surgery (> 200,000 US-dollar per quality-adjusted life year gained) were in fact much higher than what by most standards would be regarded as acceptable. The exact timing of the intervention did not seem to be a key issue: very similar results were obtained for strategies based on primary intervention vs. those that considered intervention only if exercise failed. These results suggest that current treatment strategies, which in many centers include bypass surgery as a secondary treatment option may not be conservative enough, at least from a cost-effectiveness perspective. Estimates of the extra costs relative to the gains of strategies that included angioplasty as the only interventional therapeutic option were comparable to those of other expensive, but currently accepted technologies, though highly uncertain. We conclude that a future clinical trial among patients with intermittent claudication would probably best be directed at comparing an interventional treatment strategy based on angioplasty to a strictly non-interventional treatment strategy.