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The aim of the dissertation is threefold: first, to assess whether costs for consumption and leisure activities need to be considered in the incremental cost-effectiveness ratio (ICER) in cost-effectiveness analyses (*Part Ia – methodological aspects, utility measurement, chapter 2*), second, to review evidence and highlight important bias types in trial-based as well as in model-based economic evaluations (*Part Ib – methodological aspects, bias in economic evaluation, Chapters 3 and 4*) and third, to assess the cost-effectiveness of angiotensin-converting enzyme (ACE) inhibitors and angiotensin II receptor blockers (ARBs) in diabetic as well as non-diabetic renal disease in different countries (*Part II – economic evaluation studies, Chapters 5 to 7*).

*Chapter 2* of the thesis presents the results of a randomized study on patients with inflammatory bowel disease in Germany (n=104). The purpose of the study was to conduct an empirical survey on whether the effects of ill health on consumptive activities are spontaneously considered in a health state valuation exercise and how much this matters. Patients were randomly provided or not provided with explicit instructions regarding the consideration of consumption and leisure effects in a time trade-off (TTO) exercise. The study showed that explicit instructions to consider non-health-related utility in TTO exercises did not influence TTO scores. However, spontaneous consideration of non-health-related utility in patients without explicit instruction (60% of respondents) led to significantly lower TTO scores. Based on these findings, we recommend that consumption costs be included in the numerator of the ICER, at least for those respondents who spontaneously consider non-health-related utility from treatment. However, double-counting always has to be avoided.

To the best of our knowledge, for the effects of ill health on consumptive activities, no such empirical evidence has been gathered so far, although this study shows that it plays an important role in the valuation of utilities. Results also showed that exercises eliciting health valuations from the general public may include a description of the impact of disease on consumptive activities. Overall, this research might contribute to a more accurate ICER by providing further insights into the TTO understanding of patients.
Chapters 3 and 4 complete the methodological part of the thesis, both dealing with bias types and addressing the second aim of the thesis. Chapter 3 aims to give an overview of the potential risks of bias in trial-based economic evaluations and to identify how key sources for bias can be revealed and overcome. In total, eleven biases were identified and assigned to a particular trial phase. A distinction was made between pre-trial biases, biases during the trial and biases that are relevant after the actual trial. We discussed these bias forms in detail and presented strategies to detect and overcome them in a systematic way. The biases identified also account for model-based studies. Chapter 4 is directly related to Chapter 3. Here, we focused on bias types in model-based economic evaluation. It is obvious that bias types relevant for trial-based economic evaluation are usually relevant for model-based studies as well. So in this chapter, we focused on selected model-specific issues, using the Philips checklist as a tool to structure our results.

Eleven specific biases for model-based economic evaluations were identified and classified related to structure, data and consistency of the model, including structural assumptions, model type, time horizon, data selection (such as treatment effects), assessment of uncertainty and internal validation. In the end, together with biases which account for trial-based as well as for model-based studies identified in Chapter 3, a checklist for assessing bias in economic evaluations was developed (ECOBIAS). The ECOBIAS checklist encompasses a common part for model- and trial-based economic evaluation and a model-specific part. Part A of the checklist incorporates eleven biases that account for both types of economic evaluation, whereas Part B covers eleven model-specific aspects of bias.

Both studies demonstrated that there are several ways that biases can influence the final results of trial-based as well as model-based economic evaluations, which could change a result from being cost-effective to not being cost-effective at all. Combining the biases that can occur in trial-based with those in model-based economic evaluations identified in a previous article by the author group, the ECOBIAS checklist for identifying and avoiding bias in economic evaluation is introduced. To our current knowledge, we provide the first checklist (ECOBIAS checklist) on biases in trial-based and model-based economic evaluations. It is important to understand that different bias types can be related to each other and that the elimination of one can introduce another. The checklist can be used by researchers and
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can be completed with submission of an article, but it can also be used by policymakers to check for bias in a systematic way.

In Chapter 5, a cost-utility analysis on the cost effectiveness of ACE inhibitors in newly diagnosed type 2 diabetes was performed. The aim of this study was to assess the most cost-effective time to start an ACE inhibitor in the event of cough in patients with type 2 diabetes in Germany. Three strategies were compared: treating all patients at the time of diagnosing type 2 diabetes, screening for microalbuminuria and screening for macroalbuminuria. A lifetime Markov decision model with simulated 50-year-old patients with newly diagnosed diabetes mellitus was developed using published data on costs and health outcomes and simulating the progression of renal disease. We showed that the treat-all strategy is associated with the lowest costs and highest benefit and therefore dominates screening both for macroalbuminuria and microalbuminuria. Our results were robust, even when considering a variety of different assumptions of uncertainty. It was concluded that patients with type 2 diabetes should be treated with an ACE inhibitor immediately after diagnosis if they do not have contraindications.

Although a significant number of newly diagnosed type 2 patients may receive blood pressure medications, it has not been shown that these patients are primarily prescribed an ACE inhibitor, which underlines the significance of this analysis. Treatment guidelines in Germany and the Netherlands do not strictly recommend prescribing an ACE inhibitor in this patient population, so our analysis should lead to a correction of current treatment guidelines in a way that newly diagnosed type 2 diabetic patients should receive a low dose ACE inhibitor, even in the absence of hypertension or heart failure, which are currently the standard indications for this drug class. It is therefore clear that an ACE inhibitor should be considered a first-line treatment for hypertensive diabetic patients as well. As the topic investigated in Chapter 5 is of great importance not only from patient’s perspective but also from an economic viewpoint since diabetes is a huge burden for healthcare systems, at least in the Western world, Chapter 6 investigated this research question in the Dutch setting. The majority of data taken into consideration for the model in Chapter 5 were country-specific or at least adapted to the German setting. So the generalizability of the results is not given. We therefore built a new model for examining the cost-effectiveness of ACE inhibitors (or angiotensin II receptor blockers (ARBs) if coughing occurs as a side effect) in patients with newly
diagnosed type 2 diabetes in the Netherlands. We showed a similar trend as in the German setting: In the base-case analysis, the treat-all strategy was associated with the lowest costs and highest benefit and therefore dominates screening both for macroalbuminuria and microalbuminuria. A multivariate sensitivity analysis shows that the probability of savings was 70%. It was concluded that also in the Netherlands, patients with type 2 diabetes should be prescribed an ACE inhibitor immediately after diagnosis if they do not have contraindications. An ARB should be considered for patients who develop a dry cough when treated with an ACE inhibitor. In addition, accounting for both models, the potential for cost savings would be even larger if the prevention of cardiovascular events due to the ACE inhibitor treatment were considered.

Although effectiveness was shown in different trials, cost-effectiveness models did not yet exist in this area for the Dutch and German settings. A systematic review on ACE inhibitors and ARBs in type 2 diabetic nephropathy was published recently. Here, 30 articles were evaluated, including Chapters 5 and 6 of this thesis. Our articles were the only two studies that discussed that dry cough, as a possible side effect of ACE inhibitors, could potentially have an impact on the cost-effectiveness of the latter.

With respect to diabetes, diabetic nephropathy, with its final state of end-stage renal disease (ESRD), is a sequela that causes an enormous economic burden for healthcare systems due to high costs for either dialysis or renal transplantation. Considering this burden, other causes for ESRD are worth investigating in more detail. Diabetes itself accounts for about 40% of patients in renal replacement therapy and therefore represents the main cause for ESRD. Contrariwise, about 60% of patients with ESRD suffer from non-diabetic renal disease, which is focused on in Chapter 7. There is evidence that ACE inhibitors need to be handled with care in this patient population. Therefore, national as well as international clinical guidelines do not consistently recommend treating non-diabetic proteinuric patients with advanced renal disease with an angiotensin-converting enzyme (ACE) inhibitor. This study aimed to determine the cost-effectiveness of ACE inhibitor therapy in this patient population in the Netherlands by comparing two strategies: treating patients with advanced renal disease with an ACE inhibitor versus no treatment. A lifetime Markov decision model was developed to simulate the progression of renal disease using country-specific published data on costs.
and health outcomes. We found that treatment with ACE inhibitors leads to higher benefits and lower costs and dominates the no-treatment strategy. So it could be concluded that ACE inhibitor treatment for non-diabetic patients in the Netherlands, even those with advanced renal disease, is highly cost-effective and should therefore be considered. This should have a strong impact on current treatment guidelines. Our study was the first cost-effectiveness study to investigate this patient population with respect to ACE inhibitor treatment.

Assessing cost-effectiveness in diabetic as well as non-diabetic patients with renal disease represented the second part of the thesis, addressing the third objective as mentioned above. Even though most guidelines recommend using a social perspective, where all costs and outcomes are considered important regardless of who pays for the costs and who will experience the effects, our analyses were performed from a healthcare perspective, which was considered more suitable and was stated clearly as well as justified in detail. Here, only costs and outcomes relevant to the healthcare system were considered. Not stating the perspective correctly or stating a societal view but not including all costs and outcomes might induce bias, which was also systematically described and investigated in this thesis as mentioned above.

The overall findings of this research lead to a number of recommendations for clinical practice, policymaking and future research, which are mentioned and discussed in detail in the final part of the general discussion (see Chapter 8).