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Use of real-world evidence in pharmacoeconomic analysis

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Introduction

The goal of health economics (HE) is to answer the question of how to allocate scarce resources to improve health [1]. Outcomes research (OR) is to evaluate the clinical outcomes of health care interventions. The integrative area of health economics and outcomes research (HEOR) helps healthcare decision makers to decide which health interventions to invest in based on patients' needs, safety, efficacy and effectiveness of health interventions, cost-effectiveness and budget impact. HEOR is becoming increasingly important as a tool for assessing new health interventions, especially for pharmaceuticals, throughout the world. Challenges still exist for gathering HEOR evidence to support decision-making, e.g. how to interpret clinical efficacy and real-world benefits, the topic of this thesis.

PHARMACOECONOMICS AND DATA SOURCES

As HE research specifically directed at pharmaceuticals, pharmacoeconomics (PE) compares the cost and efficacy/effectiveness of pharmaceutical products to guide the use of scarce resources to achieve best value to patients, healthcare payers and society [2, 3]. Evidence of value for money is increasingly desired along with clinical efficacy/effectiveness by different payers and healthcare systems [4], enhancing the further development of PE.

Although a variety of tools and techniques for conducting PE analyses have been developed, it is commonly recognized that there are two competing approaches to the economic evaluation of pharmaceuticals. In a trial-based study, outcomes and costs data are collected concurrently with the clinical trial. In a decision-model-based study, data from a number of sources are synthesized [5].

Whether PE analyses are trial-based or modeling studies, the overall data requirements are the same: it is about comparative effectiveness, resources, costs and health benefits (**Table 1** [5]).

Table 1. Data required in PE

Required data	Data source
Comparative treatment efficacy/effectiveness (e.g., clinical outcomes, survival)	RCTs, observational studies or systematic literature review / meta analyses
Consumption of healthcare resources	Obtained concurrently during RCTs or observational data such as electronic health records, claims data, local surveys, patient-chart reviews or expert opinions
Costs of resources	Observational data such as claims data from payers or other routine data collection
Health state preference / utility	During RCTs, specific utility studies, or from surveys of the general population

PE, pharmacoeconomics; RCT, randomized controlled trials.

First, data defining comparative treatment efficacy/effectiveness, e.g. clinical outcomes or life-years, are required. Often these come from randomized controlled trials (RCTs), and can be used directly in the economic study. However, in the modelling studies, the effect data could be derived from not only RCTs but also observational sources (e.g., claims databases, epidemiologic studies). RCTs compare the efficacy and safety of a medication vs. a comparator, using pre-defined clinical endpoints and in a controlled environment. In contrast, observational studies usually adopt a cohort or case-control design in a more general clinical practice setting [6]. Despite limitations of ‘external validity’, RCTs remain the main data source at a higher evidence hierarchy level to evaluate the treatment effects in PE, especially for new drugs. But clinical outcomes derived from RCTs are often not valid for real world. In recent years, studies based on observational effectiveness data were published to reflect the value of real-world evidence in PE [7-10].

In order to calculate the total cost or incremental cost of one treatment over another, data describing the quantities of resources consumed by the treatments being compared and the unit costs or prices of resources are required. Based on different perspectives, a range of resources could be used in PE studies [11]. These include drugs, medical care, or other patient family’s own resources, such as traveling to healthcare facilities or providing nursing support at home. These data can either be collected alongside a trial or be derived from a range of other observational sources, including electronic health records (EHRs), claims data, local surveys, and expert opinions.

Finally, data of patients’ preference on health states may be required, especially if the aim of the PE study is to calculate the cost per quality-adjusted life year (QALY) gained. Such

data can also be collected by the survey alongside a trial, or by asking patients to value their own current health states using standard-gamble or time-tradeoff methods, or by surveys in members of the general public [5]. Also, patient-reported outcomes are often combined with valuations derived from the general public [12].

OBSERVATIONAL DATA IN PE

Pros and cons of observational data

Although RCTs are the gold standard to determine a drug's efficacy, it is well recognized that results of RCTs may not sufficiently reflect effectiveness of therapies delivered in real world [13, 14]. For decision-making in PE, policy makers require the best available evidence. Routinely collected and electronically stored healthcare data in routine clinical practice has been widely developed and utilized over the past decades [15]. There is increasing awareness that observational studies can complement RCTs to examine efficacy findings from RCTs in larger patient populations in real-world settings.

Compared with RCTs, observational studies are usually not limited by strict patient selection criteria, which may enhance their external validity [16]. For example, patients with serious comorbidities are often excluded from RCTs but can be included in observational studies.

However, observational studies may have the limitation of lower internal validity due to the potential for selection bias and the wide range of confounders [5, 17]. Unless the presence of those biases and confounders can be minimized and/or corrected for, the estimated treatment effectiveness from observational studies may not necessarily always imply a valid cause and effect relationship [18].

Use of observational data

If the impact of bias and confounders can be precisely estimated and minimized in observational studies, observational studies may contribute to providing informative real-world evidence to PE.

For example, cost-effectiveness of a treatment may vary over time, which can be observed in a real-world setting. In these cases, observational studies can be performed to compare the results from a RCT with the outcomes of the same treatment after it is in general use. These comparisons may show the differences between efficacy of a treatment under strict assessment conditions and the effectiveness seen during actual use [19]. Such information

can help decision makers to potentially adjust their decision on the reimbursement of a treatment. For example, in the Netherlands, the Dutch authorities previously determined that data on the actual effectiveness of a new drug, rather than efficacy, needed to be collected in an outcomes study during a period of conditional reimbursement, to better understand what the cost-effectiveness of the drug will be in daily practice [20]. Of note, in the meantime the conditional reimbursement system in the Netherlands has already been transformed again.

In addition, with the development of PE worldwide, it has become evident that economic evaluations are not generalizable between countries [21, 22]. This is mainly attributable to differences in patients' characteristics, healthcare resource utilization, clinical practice, and costs. This also introduces a particular problem in trial-based economic evaluations where efficacy of the treatment and resource use are evaluated across study sites, as the result data may not be applicable to a specific location. In these cases, evidence from observational studies may help to bridge the gap for the translation of results from RCTs to country-specific settings. For example, information with respect to resource use and costs as well as prevalence of illness severity and patient comorbidity need to be collected from local observational data sources to reflect the actual situation of local patient populations.

Methods for observational data analysis

The reason for the reluctance to use observational data by healthcare decision makers was mainly due to the uncertainty about the reliability and robustness of results derived from observational studies. Three main issues related to using observational data were usually encountered, in particular confounding by indication, missing data, and insufficient numbers of comparable patients [23]. To include sufficient patient population for observational studies, different organizations have put efforts in building large-scale healthcare data sources, e.g. databases representing integrated healthcare-delivery networks. Infrastructures have also been developed to ensure evidence can be generated more transparently from those large-scale databases [24]. For the other two issues, a number of analytical methods have been developed over the years. Those analytical approaches include matching, regression analysis, propensity scores, instrumental variables, difference-in-differences approach, and control functions to minimize selection bias [18], and multiple imputation methods to deal with missing data which are missing at random.

Although healthcare policymakers, payers, and providers are increasingly turning to those observational analyses to answer a variety of questions, assessment of the comparative treatment effectiveness through the analysis of secondary data sources is still controversial due to the study design and data quality. Matching methods can act as an important pre-processing method on the data before concluding the comparative effectiveness in observational studies. This approach allows the analyst to consider problems of imbalance in covariates and assess overlap between treatment groups before and after matching [25]. Yet, improvements of matching methods in economic studies are still required. A review from 2013 showed that economic evaluations using matching methods often didn't report details of the matching [18]. For example, solutions relying on the propensity score require post-match balance in the entire distribution of individual covariates.

PE IN DIABETES AND NEPHROPATHY

The rapid growth of non-communicable diseases represents an enormous disease burden on different healthcare systems around the world. The worldwide incidence of diabetes and especially the diabetes-related complications highlight the relevant economic burden of the disease [26]. Among those complications, diabetic nephropathy occurs in up to 40% of diabetic patients with microalbuminuria, and is the major cause of end-stage renal disease (ESRD) in many regions of the world [27, 28].

The high costs of diabetes and ESRD clearly put forward the need for improved prevention strategies. Effective allocation of resources remains a significant challenge to many healthcare systems given the need for long-term planning of resources, the emerging of new drugs and technologies, and the benefits vs. costs of implementing new prevention strategies [29]. PE is increasingly used to inform decision makers about the value for money of alternative treatment strategies in diabetes and diabetic nephropathy [30].

Observational data are likely to be particularly valuable for formulating appropriate diabetes treatment pathways and improving patient outcomes, since the long-term outcomes may only be reflected in the real-world setting and the resources use pattern may be distinct from RCTs. For those countries without available national-specific RCT data, studies using the observational data such as EHRs may act as an important role for PE studies.

In low- and middle-income countries, the high economic burden of diabetes and diabetic nephropathy is usually compounded with inadequate resource use for diabetes care when compared with high-income countries. In addition, there is usually a lack of local cost data in these countries [31]. As a result, studies evaluating diabetes costs in these countries are relatively scarce. PE studies with local observational cost data can be highly valuable for decision makers to develop country-specific strategies with high value for money.

AIMS AND OUTLINE OF THE THESIS

In this thesis, several aspects related to the use of observational data in PE studies for diabetic nephropathy will be analyzed and discussed. The main objective of the thesis is to assess the added value of use of observational data in PE. The thesis has five sub-aims:

- 1) to synthesize the information from existing PE studies evaluating angiotensin-converting enzyme inhibitors (ACE inhibitors) and angiotensin II receptor blockers (ARBs) in patients with type 2 diabetes (T2D) and nephropathy (**Chapter 2**);
- 2) to explore the methods for improving quality of observational data (**Chapter 3**);
- 3) to assess comparative effectiveness of ACE inhibitors and ARBs on renal function decline in patients with T2D and nephropathy using observational data (**Chapter 4**);
- 4) to assess the development of disease burden of diabetes in China using observational data (**Chapter 5**);
- 5) to explore the cost-effectiveness and budget impact of ACE inhibitors and ARBs in Chinese patients with T2D and nephropathy (**Chapter 6**)

We start with a systematic review of the economic evaluation of ACE inhibitors and ARBs in patients with T2D and nephropathy in **Chapter 2**. Treatment guidelines recommend ACE inhibitors and ARBs as the first-choice agents for treating diabetic nephropathy. Although different PE evaluations of ACE inhibitors and ARBs have been published based on RCT results, a systematic PE comparison of ACE inhibitors and ARBs in patients with T2D and nephropathy is still lacking. In this chapter, the similarities and differences in cost-effectiveness analyses for ACE inhibitors and ARBs in patients with diabetic nephropathy are addressed.

In **Chapter 3**, we turn to the issue of data quality in observational data sources. In recent years, the increasing availability of EHRs provides opportunities to study drug use patterns

or drug effectiveness in comparative effectiveness research. This has resulted in a request of high-quality data and data processing approaches to ensure the validity of comparative effectiveness research. Details of data quality and how quality issues were solved have scarcely been reported in published comparative effectiveness studies. In this chapter we apply a general framework to illustrate the problems and solutions of data quality assessment and pre-processing.

In **Chapter 4**, a comparative effectiveness study is performed to evaluate drugs' effectiveness using observational data in the Netherlands, still focusing on ACE inhibitors and ARBs. Due to the lack of head-to-head comparisons between the ACE inhibitors and ARBs for protecting patients from renal function decline in an unselected T2D population, this study is aimed to compare effectiveness of ACE inhibitors and ARBs on nephropathy in T2D patients in primary care. Data quality pre-processing as illustrated in Chapter 3 is applied to improve the internal validity of the results.

In **Chapter 5**, we choose China as example to show the use of observational data in cost evaluation in a middle-income country. Although the Chinese Diabetes Society has published a guideline of prevention and treatment for T2D, the guideline is often not followed in real-world treatment. This may lead to non-optimal control of the course of disease compared with high-income countries. This chapter describes the longitudinal development of the economic burden of diabetes in urban China using electronic claims data. The cost analysis using valid observational data could help to improve PE evaluation, disease management and reimbursement policy-making in China.

In **Chapter 6**, a cost-effectiveness and budget impact analysis is performed to evaluate the use of ACE inhibitors and ARBs in Chinese patients with T2D and nephropathy. Evidence from Chapter 5 showed that the use of ACE inhibitor/ARB was not optimal in patients with T2D in China. With the increasing prevalence of diabetes and its complications, the financing of Chinese urban basic health insurance system will face more challenges if the treatment strategies are not optimized. This chapter performs a modeling analysis to evaluate the cost-effectiveness of ACE inhibitor/ARB or other active drugs vs. no treatment. Budget impact analysis is also performed to evaluate how optimal use of ACE inhibitor/ARB in Chinese patients with diabetes may influence the health insurance financing.

We finish with a discussion in **Chapter 7** of the research presented in this thesis regarding the use of observational data in PE.

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