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## Use of real-world evidence in pharmacoeconomic analysis

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## **General discussion and future perspectives**

In this thesis, several aspects related to the use of observational data in pharmacoeconomics (PE) for diabetic nephropathy are investigated. The main objective was to investigate the added value of using observational data in PE, with such data being used to analyse comparative effectiveness as well as to measure the cost-effectiveness outcomes in a middle-income country, i.e. China in this thesis. Five sub-aims were addressed in the thesis:

- 1) reviewing the existing PE information on angiotensin converting enzyme inhibitors (ACE inhibitors) and angiotensin II receptor blockers (ARBs) in patients with type 2 diabetes (T2D) and renal disease;
- 2) developing a framework for data quality assessment and preprocessing to improve the quality of observational data in outcomes research;
- 3) conducting the comparative effectiveness of ACE inhibitors and ARBs on renal function decline in T2D patients using observational data;
- 4) analyzing the changes of economic burden of diabetes in urban China based on observational data;
- 5) evaluating the cost-effectiveness and budget impact of ACE inhibitors and ARBs in Chinese patients with T2D and nephropathy using local observational cost data.

## MAIN FINDINGS

### **Box 1.** Main findings of the five sub-aims

- 1.1.** Actual information on drug use and real-world effectiveness were hardly included in previous PE studies in diabetic nephropathy;
- 1.2.** The framework for data quality assessment and preprocessing, based on the ‘fit-for-use’ concept, is useful to identify and act on data accuracy and completeness;
- 1.3.** The comparative effectiveness study using electronic health records (EHRs) data showed that the time to renal function decline in patients with T2D was slightly longer in ARB users, but not significantly compared to ACE inhibitor users in a real-world setting;
- 1.4.** The longitudinal study using electronic insurance claims data showed that the economic burden of diabetes increased significantly in urban China over time;
- 1.5.** The cost-effectiveness analysis (CEA) and the budget impact analysis (BIA) showed that treatment with ACE inhibitors and ARBs to prevent the occurrence or progression of diabetic nephropathy is cost-saving in T2D patients in China, which would therefore cause budget savings for the Chinese basic medical insurance scheme in the long term.

The systematic review of the PE evaluation of ACE inhibitors and ARBs in patients with T2D and nephropathy in **Chapter 2** showed that information on drug use and effectiveness in daily clinical practice was hardly ever included in the PE studies (**Box message 1.1**), indicating a lack of adequate information about the PE value when these drugs are used in real-world practice.

In **Chapter 3**, we showed that a standardized framework, based on the 'fit-for-use' concept, is useful to identify and act on data accuracy and completeness, following the verification of assumptions underlying the use of the data. Instead of categorizing data quality issues into different specific dimensions, our framework emphasizes the suitability (accuracy) and the availability (completeness) of the data for a specific research purpose (**Box message 1.2**). The framework builds step-by-step procedures from deciding what data to extract to solving verified quality problems.

Following the data quality preprocessing framework described in Chapter 3, we used preprocessed EHR data to perform a comparative effectiveness research study that compared the effectiveness of ACE inhibitors and ARBs for protecting T2D patients from renal function decline in **Chapter 4**. ARBs prolonged the time to renal function decline slightly, but not significantly, compared with ACE inhibitors (hazard ratio = 0.80, 95%CI [0.58-1.10], p=0.166) (**Box message 1.3**). The results of this study support earlier studies that ACE inhibitors and ARBs have a similar effectiveness for preventing renal function decline in patients with T2D in the real-world clinical practice.

Besides the effectiveness measurements, cost reflects the other essential element in a PE study. Observational data plays an important role in costing in PE as it can capture the actual disease burden and cost of illness in real-world settings. In **Chapter 5**, we performed a longitudinal study to describe the diabetes costs in Chinese patients using observational electronic claims data. The results showed that the economic burden of diabetes increased significantly in urban China over time, with a significant out-of-pocket cost for patients requiring hospitalization (**Box message 1.4**). For the universal health coverage in China, the increasing economic burden of diabetes will aggravate the contradiction between limited health resources available and increasing health care demand.

In **Chapter 6**, we performed a CEA of renin-angiotensin-aldosterone system (RAAS) inhibitors (ACE inhibitors/ARBs) and other active anti-hypertensive agents vs. no anti-hypertensive treatment in patients with T2D and nephropathy in China. A BIA was conducted alongside the PE evaluation to analyze the changes of the Chinese urban

employee basic medical insurance (UEBMI) budget when different medication use strategies are applied. Results from the modeling study showed that treatment with RAAS inhibitors to prevent the occurrence or progression of diabetic nephropathy is cost-saving in T2D patients in China in the long term. Using RAAS inhibitors in all T2D patients would therefore cause budget savings for the Chinese UEBMI scheme (**Box message 1.5**). Our BIA using observational data and other synthesized data with likely good validity is valuable for healthcare decision makers in China to formulate appropriate diabetes treatment pathways, optimize the allocation of health resources, and improve patients' quality of life.

## QUALITY OF OBSERVATIONAL DATA – A FRAMEWORK FOR DATA QUALITY ASSESSMENT AND PREPROCESSING

### **Box 2.** Role of the data preprocessing framework

- 2.1.** Published observational studies seldom reported or discussed data quality issues, therefore there is ample room for improvement;
- 2.2.** The 'fit-for-use' concept in our data preprocessing framework entails that the dimensions of data quality do not have objective definitions, but are task-dependent;
- 2.3.** Our framework builds step-by-step procedures from deciding what data to extract to solving verified quality problems;
- 2.4.** Considering that different EHRs have a lot in common, we believe the framework could be applied to other research settings to assess and report on data quality.

With the growing use of EHRs in observational studies, concerns on data quality have increased. To date, the literature on data quality of observational data in comparative effectiveness studies focuses primarily on the infrastructure for carrying out studies [1-4]. Published comparative effectiveness studies using EHRs usually report more details of study design and analytical methods to validate causal inferences in the absence of randomization, with limited focus on data quality issues (**Box message 2.1**). Although published guidelines of comparative effectiveness research emphasize the importance of data quality, those recommendations are still general. Despite the fact that solutions for data quality issues will vary between individual studies using different data sources, transparency of addressing data quality issues for observational data will help to improve the consistency in data quality measures and to facilitate best practices and trust in the clinical evidence [5,6].

Existing literature regarding to data quality distinguished various quality dimensions [7,8]. In our Chapter 3, we integrated different data quality dimensions into two major ones, accuracy and completeness, based on the 'fit-for-use' concept [9]. This concept entails that the dimensions of data quality do not have objective definitions, but are task-dependent (**Box message 2.2**). Accuracy could be considered extensively as the extent to which the data are suitable for a specific study's requirements. Analogously, completeness could be considered as whether all required data are available. Therefore, the underlying general assumption in our data quality assessment framework, is that the data are accurate and complete.

For large-scale outcomes studies, especially multisite studies or studies in distributed data networks, some frameworks and recommendations were published to support the improvement of assessing and reporting the data quality issues [10,11]. But still, there is a need to develop a generalized data quality assessment and preprocessing toolkit for comparative effectiveness research or other observational studies. Our framework builds step-by-step procedures from deciding what data to extract to solving verified quality problems (**Box message 2.3**). These procedures encourage researchers to understand their data, verify quality problems based on potential mechanisms and use other information as much as possible to solve quality problems.

Our framework developed in Chapter 3 was applied to the comparative effectiveness study in Chapter 4 and proved useful to a research setting with laboratory test data, diagnosis data and prescription data. The framework helps to provide detailed information on data quality assessment which is emphasized by guidelines to ensure the validity of study results, and improves the appropriateness of the use of observational data in different settings. Considering that various electronic health data have a lot in common, we believe the framework could serve for other research settings to assess and report on data quality (**Box message 2.4**).

## OBSERVATIONAL DATA IN OUTCOMES RESEARCH STUDIES

### **Box 3.** Observational data in outcomes research studies

**3.1.** With the need of real-world evidence to inform healthcare decision-making, the demand for high-quality comparative effectiveness research has increased over the past several years;

**3.2.** The comparative effectiveness research in this thesis addressed several important topics, including selecting clinically meaningful endpoints, assessing and minimizing biases, and evaluating missing data, in order to produce an outcomes research study with good quality;

**3.3.** Compared with earlier studies, our comparative effectiveness study differs in several aspects: the combined renal function outcome allowed a more general population and the observational design allowed a longer follow-up.

Comparative effectiveness research concerns the generation and synthesis of evidence that compares the benefits and harms of alternative interventions to prevent, diagnose, treat and monitor a clinical condition or to improve the delivery of care [12]. In recent years, the interest in comparative effectiveness research, with growing demand for observational data to support healthcare decision-making, has increased the exploration of data sources other than randomized controlled trials (RCTs) (**Box message 3.1**). In addition, sometimes head-to-head comparisons of two interventions may be absent in RCTs for targeted populations. While meta-analysis / network meta-analyses and RCTs provide evidence at the top level of the clinical evidence hierarchy [13], comparative effectiveness research based on observational data provides additional supportive information to reflect the real-world effectiveness in actual practice. In the real-world settings, patients are more diversified and treatment use patterns vary more.

Consensus of the most important aspects of quality of observational data in comparative effectiveness research has been summarized in recommendations [14]. These recommendations include use of clinically meaningful endpoints; use of appropriate measures of exposure and statistical techniques; assessing and minimizing bias; evaluation of missing data and measure validity; adaptation of the interpretation of study results for different stakeholders; interpretation of study limitation in the context of the population studied, etc. Especially, the transparency in statistical analysis is emphasized in comparative effectiveness research, allowing for public critique of methodologies as well as reproducibility of results. For the clinical endpoints, our study in Chapter 4 focused on the renal decline progression based on both glomerular filtration rate (GFR) and albuminuria.

The advantage is that the results apply to patients with different baseline renal function stages. To minimizing the influence of confounding by indication, patients starting on ACE inhibitor and ARB treatment were matched on a propensity score, adjusting for all available baseline characteristics. To assess imbalance in individual baseline characteristics, the standardized mean difference was calculated. For the missing data and other data quality issues, we followed our framework in Chapter 3 to solve verified quality problems (**Box message 3.2**).

Compared with earlier studies, our comparative effectiveness study differs in several aspects. Earlier studies usually used outcomes based on single measurement, e.g. GFR, albuminuria, or end-stage renal disease outcomes. The combined renal function outcome allowed including a more general population, in which patients ranging from normal to severe renal impairment. In addition, our study had a longer follow-up than the relatively short follow-up in RCTs (**Box message 3.3**) [15-17]. A general problem in real-world studies, insufficiency of patient numbers, still existed in our study. The large datasets with accurate and complete information that have adequate power to identify the statistical significance are not available on a large scale.

## OBSERVATIONAL DATA IN HEALTH ECONOMICS STUDIES

### **Box 4.** Observational data in health economics studies

**4.1.** Observational data are important in adding country-specific information in PE studies;

**4.2.** Compared with previous Chinese studies using data from individual hospitals or patient interviews and usually with a cross-sectional design, our cost analysis used longitudinal electronic claims data that reflected the real-world resource use and costs in a larger urban Chinese population.

**4.3.** Improving data quality is needed to ensure validity and reliability of results in health economics studies.

Most PE guidelines are developed in the context of value assessment using clinical and cost-effectiveness criteria for decision-making [18]. In the long-term PE evaluations, both effectiveness and costs for a drug are usually estimated by modeling. This requires a variety of clinical input parameters. RCT data may remain the main data source for the majority of parameters, especially when decision-making is needed on new drugs' reimbursement. However, additional real-world evidence is needed as well and observational data become



an important information source. This can, for example, be clearly observed in PE appraisals in various countries, such as NICE in UK [19]. Resource use and cost parameters required for PE modeling should reflect the healthcare system's service delivery patterns and more importantly, routine clinical settings. Therefore, it is not appropriate to include resource use from RCTs. In addition, because it is important for a PE study to use country-specific costs, cost data are better to be obtained from observational data sources including EHRs, claims data and chart reviews (**Box message 4.1**).

The cost analysis in Chapter 5 aimed to analyze the development of disease burden of diabetes in China. The main limitation for cost in the Chinese PE studies is that the cost data is usually obtained from hospital surveys, expert surveys, public price data source or existing literature [20-22]. Especially for disease burden analyses of diabetes, studies usually adopted a cross-sectional design using data from individual hospitals or patient interviews [23-25]. Our study used longitudinal electronic claims data instead of reported or surveyed data (**Box message 4.2**). These data contained information on medical visits occurring in all levels of health institutions, which overcome the main limitation in individual hospital based studies.

Same as using observational data in outcomes research, improving data quality also needs to be emphasized to enhance the validity and reliability of results in health economics studies (**Box message 4.3**). Much effort has to be spent on data standardization in order to make the observational data fit for research purpose. The unified coding of diagnosis and medications needed for reliable and valid input, is still not used in many parts of the world, including China. When internationally valid coding systems as the International Classification of Diseases (ICD) and the Anatomical Therapeutic Chemical (ATC) codes for medications are used in an existing dataset in our cost analysis, specific effort and several checks have to be included to assure accuracy and completeness. Some inherent limitations by using the observational claims data cannot always be solved. For example, the definition of diabetic cost in Chapter 5 included all costs happening in diabetes and complication visits. We assumed that those complication visits were all diabetes-related. However, in the real-world clinical practice, those complication visits could have been caused by other reasons than diabetes, e.g. a hospitalization visit for nephropathy could be caused by high blood pressure alone. Despite such limitations, the observational data are essential information for assessing economic burden of disease.

## OBSERVATIONAL DATA IN PE IN COUNTRY-SPECIFIC SETTINGS

### **Box 5.** Value of observational data in PE in country-specific settings

**5.1.** Inadequate treatment is usually accompanied with heavier disease burden and costs, also in low- and middle-income countries like China;

**5.2.** PE studies with local observational data are highly important for decision makers to develop country-specific strategies with high value for money;

**5.3.** BIA using observational data with likely good validity is valuable to predict the impact of treatment pattern changes on healthcare financing and thus to improve healthcare decision-making.

Diabetes poses a heavy economic burden on national economies and healthcare systems, especially in low and middle-income countries. In this thesis, China has been selected as the country of interest. With the largest diabetes population around the world, the economic burden associated with diabetes in China will rise dramatically in the next few decades. Among the diabetic population, approximately one fourth to one third of patients will develop renal manifestations. However, evidence showed the treatment pattern for diabetic patients in China is sub-optimal (**Box message 5.1**). Our study in Chapter 5 also demonstrated that the number of RAAS inhibitor users in Chinese diabetic patient population is low although guidelines suggest that RAAS inhibitors are recommended for all patients with T2D [26].

Inadequate treatment is usually accompanied with heavier disease burden, also in low- and middle-income countries like China. Observational data are valuable to improve diabetes treatment pathways, since the long-term outcomes may only be reflected in the real-world setting. Unfortunately, evidence from observational comparative research of treatment strategies in diabetes is rarely reported in China [27], due to the lack of well-established long-term cohort and large-scale EHR databases, especially in mainland of China. In the absence of country-specific observational data that can be directly used for PE evaluations, the use of synthesized data from meta-analysis or network meta-analysis were adopted in different cost-effectiveness studies for diabetes in China [28,29]. We also incorporate the results from a network meta-analysis in the cost-effectiveness study in Chapter 6. Until more evidence of direct observational comparisons are reported, synthesized data from network meta-analyses are still at the top level of the evidence hierarchy for effectiveness measurements. The synthesized evidence can provide a complete picture for the effectiveness measurements of different treatments associated with different major outcomes among patients with diabetes. Compared with rarity of

real-world effectiveness data in Chinese population, real-world cost data were reported more commonly in China [23-25]. PE studies with local observational cost data are highly important for decision makers to develop country-specific strategies with high value for money. The large scale cost data that represent stronger external validity would be valuable for PE studies. In addition, the real world cost data can contribute in predicting the impact of treatment pattern changes on health insurance financing and thus to improve healthcare decision-making (**Box message 5.2**). As for T2D patients in China, those improvements in decision-making may influence the healthcare budget more crucially compared with other countries, considering two facts: 1) Asian individuals with diabetes are at increased risk of microvascular complications and albuminuria compared with Caucasians [30]; 2) China will have the most rapid growth rate of diabetes-related health expenditure from 2015 to 2040 (41.2%) around the world, as predicted by International Diabetes Federation [31].

Our study in Chapter 6 also performed a BIA using real-world cost data and drug use information derived from our cost analysis in Chapter 5. To our knowledge, no BIA studies in T2D patients in China-specific settings have been published. The results showed that RAAS inhibitors would save expenditures of the insurance funding over a 50-year time horizon, although the incremental drug cost would lead to additional cost in the first few years. The effectiveness of RAAS inhibitors to increase quality of life would further reduce the societal cost in the working-age population, which becomes increasingly significant in the light of the growing economic burden in T2D. Our BIA using observational data or other data with likely good validity may be valuable to aid healthcare decision makers in China to formulate appropriate diabetes treatment pathways, optimize the allocation of health resources, and improve patients' quality of life (**Box message 5.3**).

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