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Use of real-world evidence in pharmacoeconomic analysis

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Summary

The main objective of the thesis is to assess the added value of use of observational data in pharmacoeconomic (PE) evaluations. Five sub-aims were addressed in the thesis:

- 1) to describe existing PE studies on renin-angiotensin-aldosterone system (RAAS) inhibitors, including angiotensin converting enzyme inhibitors (ACE inhibitors) and angiotensin II receptor blockers (ARBs), in patient with type 2 diabetes (T2D) and nephropathy in a systematic literature review;
- 2) to develop a framework for improving quality of observational data;
- 3) to conducting a comparative effectiveness study of ACE inhibitors and ARBs, and assess the value of observational data in outcomes research studies;
- 4) to analyze the changes of economic burden of diabetes in China, and assess the value of observational data in health economics studies;
- 5) to evaluate the cost-effectiveness and budget impact of ACE inhibitors and ARBs in Chinese patients with T2D and nephropathy, and assess the use of observational data in PE evaluations.

In order to examine the key features of data from randomized controlled trials (RCTs) and model structure in PE studies, **Chapter 2** reported a systematic literature review of the PE evaluations on RAAS inhibitors (ACE inhibitors and ARBs) in patients with T2D and nephropathy. Our review summarized results evidencing the cost-saving potentials of RAAS inhibitors in T2D patients with nephropathy compared with conventional therapy excluding a RAAS inhibitor. Regarding to the analytic models, these ACE inhibitor studies adopted Markov models to simulate the disease progression with a relatively longer time horizon, and the transition probabilities in the models were usually from different RCTs. The analytic models used for ARBs were relatively consistent in their strong alignment to the available RCTs, which caused similarity of the results for the same ARB drug in different countries. In our efforts to extract some information of drug use patterns or safety from those included studies, we also found that actual drug utilization information was seldom included in the PE evaluations. Hereby, we identified a general lack of observational data in the PE evaluations so far performed on RAAS inhibitors.

Because of the fact that observational studies require well-developed study design and more complex methodology, a need of high-quality data was raised to answer the important research questions in health outcomes studies. Among different types of observational data, the electronic health record (EHR) data provide additional opportunities to study

drug use patterns or drug effects in real-world clinical practice. In **Chapter 3**, we developed a general framework to illustrate the problems and solutions of data quality assessment and preprocessing. The framework is based on the 'fit-for-use' concept and consists of the following four steps: (1) define the general assumptions (data are accurate and complete); (2) define requirements for data quality based on the research task; (3) screen observations of data with possible quality problems and verify whether the general assumptions are not true for those observations; (4) select the best strategies to handle the data with verified quality problems. This framework helps to establish a line of thought to identify and act on data issues, following systematic check of assumptions underlying the data use.

Applying the data quality preprocessing framework described in Chapter 3, we used preprocessed data to perform a comparative effectiveness research. The **Chapter 4** compared the effectiveness of ACE inhibitors vs. ARBs for protecting T2D patients from renal function decline in a real-world setting. We used a propensity score matching method based on multiple imputed datasets. Survival models with competing risks showed that ACE inhibitors and ARBs were similar in protecting T2D patients from renal function decline, although the effect slightly favored ARBs. Compared with earlier RCTs, this real-world study extended the follow-up period and adopted the outcome measurement combining both GFR and albuminuria irrespective of the initial renal function. In addition, the unselected population included in our study enhanced the results to be generalizable to a broader diabetic population. Through the data quality preprocessing and the propensity score matching, we believed that the confounding, which is usually a main consideration in observational studies, was minimized.

Besides the effectiveness measurement, cost is the other essential element in a PE evaluation. Observational study on cost is also important to reflect the real-world disease burden. In **Chapter 5**, we performed a study to describe the changes of diabetes cost in Chinese patients using electronic claims data. Our results showed an increasing trend in total medical cost and diabetes-related cost during 2009-2011. We applied our data quality assessment framework in this study as well. These observational data contained information of patients' healthcare visits occurring in all levels of health institutions in the sample city, which overcomes the main limitation in individual hospital based cost analyses. The prescription data from this observational cost study also showed the use patterns of different anti-hypertensive drug in the real-world diabetic patients. This information of drug use patterns provided the evidence base for our further cost-effectiveness and budget impact analyses.

In **Chapter 6**, we performed a cost-effectiveness analysis of RAAS inhibitors (ACE inhibitors and ARBs) vs. other active anti-hypertensive agents and no anti-hypertensive treatment in patients with T2D and nephropathy in China from a healthcare payer perspective. A budget impact analysis (BIA) was conducted alongside the PE evaluation to analyze the budget changes of Chinese urban employee basic medical insurance (UEBMI) when different strategies of medication use are applied. In this study, we tried to incorporate previous real-world findings in China-specific setting, including cost and drug use patterns from Chapter 5. The results showed that RAAS inhibitors would reduce the budget of UEBMI in the long term for T2D patients.

In the general discussion in **Chapter 7** was the overall thesis discussion for observational data related issues. Concerns on the data quality have increased with the growing use of observational data in health outcomes researches. The quality assessment and preprocessing framework in this thesis builds a step-by-step procedure to decide what data to extract and how to solve verified quality problems. This framework emphasizes that detailed information on data quality assessment should be provided to ensure the validity of study results and to improve the appropriateness of observational data use in different settings. Applying the framework, we used improved data to perform a comparative effectiveness study. We focused on those methodology recommendations from guidelines to conduct an observational study with good quality. We believe that detailed and transparent comparative effectiveness studies in high quality will contribute to the use of real-world evidence in PE studies. PE studies with local observational cost data can be very important for decision makers to develop country-specific strategies with high value for money. The BIA for China in this thesis is an attempt to conduct a PE study using observational data. Such kind of BIA is valuable to formulate appropriate diabetes treatment pathways, optimize the allocation of health resources, and improve patients' quality of life.

