Use of real-world evidence in pharmacoeconomic analysis

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Cost-effectiveness and budget impact analysis of improvement of medication utilization in patients with type 2 diabetes and nephropathy from a healthcare payer perspective in China

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ABSTRACT

Objectives:

This study aims to calculate the cost-effectiveness of renin-angiotensin-aldosterone system (RAAS) inhibitors and other active anti-hypertensive agents vs. no anti-hypertensive treatment in delaying progression of nephropathy in patients with type 2 diabetes (T2D) in China. A budget impact analysis (BIA) was also performed to analyze the budget changes of the Chinese urban employee basic medical insurance (UEBMI).

Methods:

For the cost-effectiveness analysis, a discrete-time Markov model was used to simulate the progress of diabetic nephropathy (DN) in a hypothesized cohort with 1,000 T2D patients, consisting of five main health states. Only direct medical costs were considered in the analyses. The model was run with a 1-year cycle length for three different time horizons: 5-year, 10-year, and lifetime. The BIA was conducted in the T2D patient population insured by the UEBMI, estimating cost burden of three scenarios in which the proportions of patients using the three comparators differed.

Results:

RAAS inhibitors were dominant for postponing DN progression compared with other drugs and no treatment within a 10-year time horizon or longer. Next to cost savings, increases were estimated in both patients' length and quality of life. The BIA showed that treating all T2D patients with RAAS inhibitors would save on the insurance fund budget for the UEBMI beyond 4 years.

Conclusion:

Treatment with RAAS inhibitors is dominant to prevent the occurrence or progression of DN in T2D patients in China on the long term. Using RAAS inhibitors in all T2D patients would therefore cause budget savings for the UEBMI scheme.

BACKGROUND

Diabetes imposes a heavy economic burden on national economies and healthcare systems, especially in low- and middle-income countries [1]. In 2015, China had 109.6 million patients with diabetes, making it the largest national population of diabetics in the world [2]. This number is expected to increase to 150 million by 2040 [2]. With the expected sharp increase in the number of diabetic patients over the next few decades, the economic burden associated with diabetes is also projected to rise.

After the implementation of the new healthcare reform in 2009, the basic medical insurance coverage in urban China has gradually increased to exceed 95% of the total population (3]. With the increasing prevalence of diabetes and its complications, the financing of this urban basic medical insurance system will face challenges.

Major costs for diabetes include medical expenditures for blood glucose level control, and for additional medicines and services for the prevention and treatment of diabetes related chronic complications [4]. Additionally, diabetes is a major cause of chronic kidney disease. Interventions that successfully prevent the development or progression of either condition have the potential to substantially reduce healthcare costs. The International Diabetes Federation Clinical Guidelines Task Force's global guideline for type 2 diabetes (T2D) calls for the use of a renin-angiotensin-aldosterone system (RAAS) inhibitor in all patients with T2D, regardless of lipid and blood pressure levels [5]. RAAS inhibitors, including angiotensin-converting enzyme inhibitors (ACE inhibitors) and angiotensin receptor blockers (ARBs), have been proven to have renoprotective effects in diabetic patients [6]. However, there is relatively low use of RAAS inhibitors in the Chinese diabetic patient population [7, 8], suggesting that the current treatment for these patients is sub-optimal. An improved treatment and prevention pathway for diabetes, including the optimized use of RAAS inhibitors, may reduce the financial impact on the urban basic medical insurance system, by preventing future hospitalizations, disability, and medical care costs.

As an essential part of a comprehensive economic evaluation of a pharmaceutical or other healthcare technology, a budget impact analysis (BIA) may help to forecast the impact of health technology changes on financing of health insurance schemes and thus to improve real-world healthcare decision-making [9, 10]. Additionally, a cost-effectiveness analysis (CEA) may help in allocating budgets optimally. Economic evaluation is not mandatory for formulary approval or reimbursement policy adjustment in China, although the Chinese guidelines for pharmacoeconomic evaluations, published in 2011, do recommend taking

it into account [11]. There is little cost-effectiveness evidence with regard to diabetes in China [12, 13]. To our knowledge, no CEA or BIA has been ever published to evaluate the impact of diabetes-related drugs or interventions on the financing of Chinese basic medical insurance schemes. CEA and BIA can contribute to optimizing medication use with cost-effective interventions for patients with diabetes and nephropathy in China.

This study aims to perform a CEA of the use of RAAS inhibitors (ACE inhibitors/ARBs) and other active anti-hypertensive drugs compared with no anti-hypertensive treatment to delay progression of nephropathy, in patients with T2D in China from a healthcare payer perspective. In addition, a BIA is performed to analyze the changes in the urban employee basic medical insurance (UEBMI) budget when different medication strategies are applied.

METHODS

Study design

A cost-effectiveness model was built to evaluate the cost-effectiveness of three treatment comparators to treat a hypothesized cohort with 1,000 T2D patients in China to delay progression of diabetic nephropathy (DN), including RAAS inhibitors, other anti-hypertensive drugs (other drugs), and no anti-hypertensive treatment (no treatment). Using the same parameters as in the CEA model, a BIA was conducted in T2D patients insured by the Chinese UEBMI to determine the estimated insurance budget of three different scenarios in which the proportions of patients having RAAS inhibitors, other drugs, and no treatment differed. The three scenarios included a 'real-world' scenario in which half of the patients use RAAS inhibitors, some use other drugs and the remaining ones have no treatment, an 'improved' scenario in which majority of the patients use RAAS inhibitors and the remaining ones use other drugs, and a 'treat-all' scenario in which patients all use RAAS inhibitors.

Cost-effectiveness model overview

We adopted a discrete-time Markov model to simulate the progress of DN (**Figure 1**), which has been previously used for American and German DN patients using RAAS inhibitors [14, 15]. The Markov model consisted of five main health states: T2D with normoalbuminuria, T2D with microalbuminuria, T2D with macroalbuminuria, end-stage renal disease (ESRD) and death (**Figure 1**). The definition of albuminuria level is based on the recommendations of the American Diabetes Association [16]. Normo-, micro- and macro-albuminuria were defined as urinary albumin excretion <30 mg/day, ≥30 to <300 mg/day, and ≥300 mg/

day, respectively. ESRD was defined as requiring dialysis, including hemodialysis and peritoneal dialysis. Kidney transplantation was not included in the ESRD state, because of the extreme rarity of transplantation in China [17]. We assumed that DN progresses without skipping any stage and would not remit from a more severe state to a less severe state. Furthermore, it was assumed that patients could die in any health state. In addition to costs, health outcomes were measured in quality-adjusted life years (QALYs). The Markov model simulated the course of a cohort of 1,000 patients at the age of 50 years over an analytic time horizon (lifetime in the main analysis; 5 and 10 years in scenario analyses) with a 1-year cycle length. Patients started in different health states before developing ESRD (normo-, micro- and macro-albuminuria), based on the prevalence of those states derived from literature [18-20].

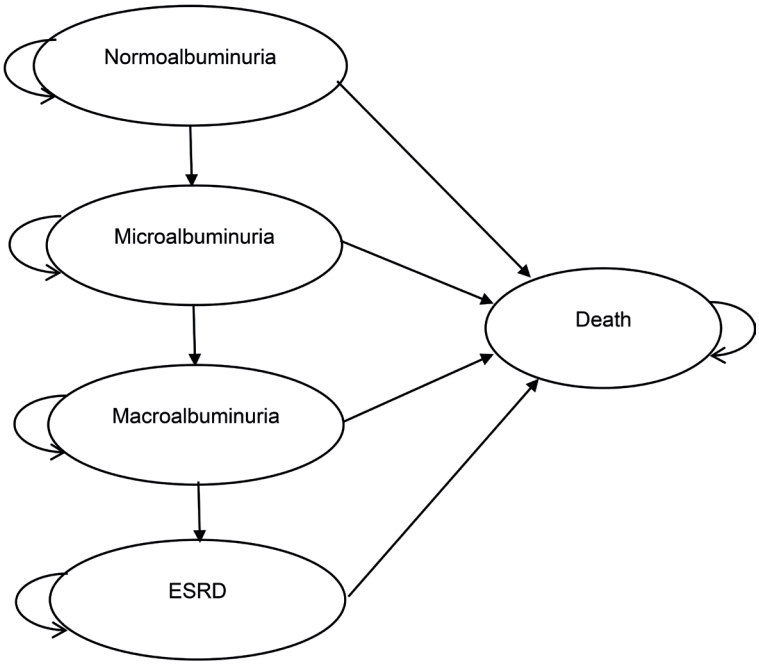

Figure 1. Structure of the Markov model

Intervention and comparators in the cost-effectiveness model

The CEA simulation model analyzed three comparators of medication use. Use of RAAS inhibitors, which includes ACE inhibitors and ARBs, was the main investigated strategy. Use of other anti-hypertensive drugs, including diuretics, calcium channel blockers and

beta blockers, was the second treatment strategy, because those agents were the main comparators of RAAS inhibitor for postponing DN progress in previous studies [21, 22]. Both treatment strategies were compared with no anti-hypertensive treatment in terms of cost-effectiveness. A previous study showed that approximately 30% of Chinese diabetic patients do not take any RAAS or other drugs [8], illustrating the relevance of the present CEA for the Chinese patient population.

Transition probabilities

To determine the distribution of the population over the initial health states, we performed a literature search in PubMed to acquire information about the prevalence of microalbuminuria and macroalbuminuria. The search strategy in the PubMed database was: (Diabetes Mellitus, Type 2[Mesh]) AND China[All Fields] AND prevalence[All Fields] AND (microalbuminuria[All Fields] OR macroalbuminuria[All Fields]). Three epidemiological studies conducted in China were screened to provide the most recent prevalence data of microalbuminuria and macroalbuminuria. Based on these, the distribution of initial health states was determined as: 22.8% microalbuminuria [18], 3.4% microalbuminuria (similar in two studies) [19, 20], and the remaining 73.8% normoalbuminuria.

Due to the lack of comparative effectiveness evidence for the three treatment comparators in the Chinese population, the transition probabilities between health states were extracted from the literature. We performed a literature search in PubMed using the search strategy: ('Meta-Analysis'[pt]) AND (Diabetic Nephropathies[Mesh]) AND (Angiotensin Receptor Antagonists[Mesh]) AND (Angiotensin-Converting Enzyme Inhibitors[Mesh]) AND (microalbuminuria[All Fields] OR macroalbuminuria[All Fields] OR (end stage renal disease[All Fields]) OR mortality[All Fields]). The major inclusion criteria for the literature were that analyses must provide evidence of comparative effectiveness between ACE inhibitors/ARBs vs. other drugs or placebo/no treatment on any stage of DN progress or mortality.

We found two network meta-analyses (NMAs) [22, 23] and five meta-analyses [21, 24-27] including one Cochrane review [21], which provided the relative risk (RR) of RAAS inhibitors compared with other treatment comparators. In order to keep the populations - on which the estimates of comparative effectiveness of the three treatment comparators were applied - comparable [28, 29], we chose one NMA as the main evidence source for treatment effectiveness measurements [22]. Compared with no treatment, RAAS inhibitors reduce the risk of deterioration from normoalbuminuria to microalbuminuria (RR = 0.82)

[22], the progression from microalbuminuria to macroalbuminuria (RR = 0.45) [22], and the progression to ESRD (RR = 0.80) [22]. We used another meta-analysis of observational studies, which studies ACE inhibitors and ARBs as a single group, to set the RR of all-cause mortality between RAAS inhibitors and no treatment (RR = 0.83) [27]. The RR of other drugs compared with no treatment, was calculated using the indirect treatment comparison method [30], combining the RRs of RAAS inhibitors vs. other drugs and RRs of RAAS inhibitors vs. no treatment collected in the same NMA and meta-analysis of observational studies [22, 27].

To determine the annual transition probabilities between different disease stages for patients, we extracted the number of events (microalbuminuria, macroalbuminuria and ESRD) and the total patient population from the individual studies included in the meta-analyses [21, 22, 27]. The annual transition probabilities were calculated by dividing the number of events by the total person-years during the study period (number of patients multiplied by follow-up time), assuming a constant annual hazard rate over the study time horizon. This calculation method was recommended in economic evaluation literature when estimating the annual transition probabilities from non-patient-level data [31]. The transition probabilities of no treatment were then multiplied by the RRs to derive other probabilities for patients using other drugs or RAAS inhibitors. The annual transition probabilities to death in stages before ESRD were calculated by multiplying by age-specific mortality rates of the Chinese population [32] with a standardized mortality ratio for patients with diabetes compared with the general population [33, 34]. For patients with ESRD, an annual ESRD-driven mortality of 6.4% was derived from one Chinese local observational study for ESRD patients who required hemodialysis [35]. The age-specific annual mortality for the ESRD stage was then obtained by adding 0.064 to the age-specific mortality for the other stages. We assumed above-mentioned age-specific mortalities were for the general patient population (without any specific treatment), thus they were multiplied by 0.83 (RR of mortality between RAAS inhibitors and no treatment) to derive the mortalities for RAAS/other drugs users. All parameters regarding the RRs and the annual transition probabilities are listed in **Table 1**.

Table 1. Summary of parameters for the Markov cost-effectiveness model

Variables	Base-case estimate	Data source
Initial disease prevalence		
Normoalbuminuria	73.8%	
Microalbuminuria	22.8%	Hao G, et al [18]
Macroalbuminuria	3.4%	Jia W, et al [19]; Chen YY, et al [20]
Annual transition probabilities (with RAAS inhibitors)		
Normo- to Microalbuminuria	2.9%	
Micro- to Macroalbuminuria	3.1%	Vejakama P, et al [22]
Macroalbuminuria to ESRD	3.2%	
ESRD to death	5.4%	Gao L and Zuo L [35]; Chinese Health Statistic Yearbook 2011 [32]
Normo-/micro-/macroalbuminuria to death	Age-dependent	Chinese Health Statistic Yearbook 2011 [32]
Relative risk with RAAS inhibitors comparing with no treatment		
Normo- to microalbuminuria	0.82	
Micro- to macroalbuminuria	0.45	Vejakama P, et al [22]
Macroalbuminuria to ESRD	0.80	
All-cause mortality	0.83	Qin Y, et al [27]
Relative risk with RAAS inhibitors comparing with other drugs		
Normo- to microalbuminuria	0.84	
Micro- to macroalbuminuria	0.70	Vejakama P, et al [22]
Macroalbuminuria to ESRD	0.82	
All-cause mortality	1.0	Lv J, et al [21]
Utilities		
Normoalbuminuria	0.785	
Microalbuminuria	0.737	
Macroalbuminuria	0.737	Beaudet A, et al [36]
ESRD	0.617	
Hemodialysis (90%)	0.621	
Peritoneal dialysis (10%)	0.581	
Annual costs (USD,2011, from sample city in east China)		

Table 1. Continued

Variables	Base-case estimate	Data source
General diabetes-related medical costs	2021.35	Huang Y, et al [8]
Diabetes with microalbuminuria	3052.31	
Diabetes with macroalbuminuria	4896.46	
ESRD	26252.63	
RAAS inhibitors	152.68	
Other drugs	91.38	
Cost ratio for national level	1.42	GDP per capita in the sample city [8] divided by the national GDP per capita
Standardized mortality ratio for diabetes	1.41	Lewis EJ, et al [34]; Bertoni AG, et al [33]
Discount rate of costs	5%	China Guidelines for Pharmacoecnomic Evaluations [11]
Discount rate of utilities	5%	

RAAS, renin-angiotensin-aldosterone system; ESRD, end-stage renal disease; USD, US dollar; GDP, gross domestic product.

Utilities

We performed a literature search to collect data on quality of life from existing evidence. The search strategy in PubMed was: (Quality of Life[Mesh]) AND (Diabetes Mellitus, Type 2 [Mesh]) AND (Diabetes Complications [Mesh]) AND (microalbuminuria[All Fields] OR macroalbuminuria[All Fields] OR (end stage renal disease[All Fields]) OR nephropathy[All Fields]). There were no specific studies summarizing health-related quality of life in Chinese patients with DN. To incorporate the evidence at the highest available hierarchy level, the synthesized utility measurements in DN patients from one systematic review were used [36]. This review included studies conducted in Europe, America, Australia and Asia to identify a reference set of utility values for T2D and its complications in line with the UK's National Institute of Health and Care Excellence requirements. The EuroQol five-dimensional (EQ-5D) questionnaire index value, which is also recommended by the Chinese pharmacoeconomic evaluation guidelines [11], was reported in the review. Evidence showed that the EQ-5D preference weights between the Chinese population and UK population had equivalent psychometric properties [37]. Thus, the utility values from the review were assumed to be valid for our model. The utility of ESRD was calculated as

a weighted average of the utilities of different types of dialysis based on the prevalence of dialysis from a Chinese domestic study [17]. The calculation was performed as follows:

Utility of ESRD = utility of hemodialysis (0.621) * prevalence of hemodialysis (0.900) + utility of peritoneal dialysis (0.581) * prevalence of peritoneal dialysis (0.100) = 0.617

Utilities for different health states are listed in **Table 1**.

Costs

This study was conducted from a healthcare payer perspective. This means that only direct medical costs were considered. The cost data were derived from a retrospective, longitudinal observational study in an open cohort of Chinese patients with diabetes previously performed by the authors [8]. This study analyzed patients' outpatient visits and hospitalization records from an electronic medical insurance claims database including diabetic patients covered by the provincial UEBMI in a provincial capital city in eastern China. Diabetes related costs, defined as costs associated with diabetes-related medical visits, were used as model inputs. Different health states were identified from the datasets using the standardized diagnoses based on the Chinese diagnosis names. The mean diabetes-related costs per patient in 2011 of those patients categorized in the specific diagnosis groups (without complications, micro/macroalbuminuria, hemodialysis/peritoneal dialysis) were used as the costs for different health states in the model. Drug costs for RAAS inhibitors and other drugs were also derived from the datasets using the recoded Anatomical Therapeutic Chemical (ATC) code information based on the Chinese medication names. Drugs with ATC codes starting with 'C09' were categorized as RAAS inhibitors, and drugs with ATC codes starting with 'C03', 'C07' and 'C08' were categorized as other drugs. Mean drug costs per patient in 2011 for those two groups were used as the drug costs in the model. Costs were calculated in 2011 US dollars using the exchange rate between US dollars and Chinese Yuan in 2011 (1 US dollar = 6.459 Chinese Yuan). All costs information is listed in **Table 1**. In order to inflate the costs from the sample city to the national level, all costs were multiplied by a cost ratio (1.42), equal to the gross domestic product (GDP) per capita in the sample city, divided by the national GDP per capita [38].

Cost-effectiveness analysis

For the CEA base-case analysis, the model was run with a 1-year cycle length for 50 years (lifetime). Both utilities and costs were discounted at an annual rate of 5% in accordance with the Chinese guidelines for pharmacoeconomic evaluation [11]. Half-cycle correction was applied to both costs and utilities, using Simpson's 1/3 method [39, 40]. Outcomes

are displayed in incremental cost-effectiveness ratios (ICERs), which are equal to mean incremental costs, divided by mean incremental health outcomes. Analyses over two shorter time horizons, 5-year and 10-year, were also conducted to compare with the base-case lifetime analysis.

To address uncertainty around the ICER, one-way deterministic sensitivity analyses (DSA) were conducted over the lifetime horizon. The parameters varied in the DSA included the initial disease prevalence, annual transition probabilities, RRs with RAAS inhibitors, utilities, annual costs and discount rate. For costs, the standard deviation was used to define the upper and lower values for sensitivity analyses. If a standard deviation was not available, the lower and upper limits of the range of other variables were defined as 0% and 100% (disease prevalence, discount rate) or lowest/highest value from identified literature (effectiveness and utilities).

In order to assess how a simultaneous change in several variables affects the ICER, we performed a probabilistic sensitivity analysis (PSA). We ran 1,000 of simulations by repeatedly drawing samples from probability distributions of input parameters, including relative treatment effectiveness between comparators, costs, and utilities, over the lifetime horizon. Relative risks in the analyses were assumed to follow a lognormal distribution [41]. Probabilities and utilities were assumed to follow a beta distribution because they are restricted to take on values between 0 and 1 [42]. Costs were sampled from a gamma distribution, which has the property of being always positive [43].

Budget impact analysis

The BIA targeted the T2D population covered by UEBMI in 2011 (34.1 million), which was estimated using data from national statistical yearbooks (**Table 2**) [32, 44, 45]. The BIA analyzed the changes in the budget of UEBMI when three scenarios are applied. The proportions of patients having the three treatment comparators (RAAS inhibitors, other agents, and no anti-hypertensive treatment) differed in the three scenarios. In the first 'real-world' scenario, the proportions of users of the three treatment comparators was derived from the same real-world study as that used for the cost input in the CEA (52% patients prescribed with RAAS inhibitors, 20% patients prescribed with other drugs, 28% patients with no treatment [8]). In the comparator BIA scenario 2, 80% of patients were prescribed RAAS inhibitors (the 28% patients with no treatment in the scenario 1 were prescribed RAAS inhibitors instead) and 20% of patients were prescribed other drugs ('improved' scenario). In the comparator BIA scenario 3, 100% of patients were prescribed

RAAS inhibitors ('treat-all' scenario). The mean proportion of UEBMI reimbursement payment in total diabetes-related costs (70%), as derived from the observational costing study [8], was applied to all costs in the BIA. The BIA did not apply discounting.

Table 2. Patient population calculation for the budget impact analysis

Population/Prevalence	2011
Population in China	1347.35 billion
Prevalence of T2D	14.3%
Coverage of UEBMI	17.7%
Estimated T2D population covered by UEBMI	34.10 million
Average proportion of insurance reimbursement payment in total diabetes-related medical cost	70%

T2D, type 2 diabetes; UEBMI, urban employee basic medical insurance.

The BIA applied the same transition probabilities and cost parameters as used in the CEA. All patient populations and treatment comparators used in the CEA and BIA were summarized in **Table 3**. Model building and data analyses were performed using computing environment R 3.3.2 (R Development Core Team, 2005).

Table 3. Summary of the treatment comparators in the CEA and the scenarios in the BIA

Analyses	Comparators	Patient population	Outcomes	Time horizon
CEA	RAAS inhibitors, including ACE inhibitors and ARBs	1,000 hypothesized Chinese T2D patients	ICER (RAAS vs. other drugs/no treatment)	5-year, 10-year, lifetime (50-year)
	Other anti-hypertensive drugs, including diuretics, calcium channel blockers and beta blockers (other drugs)		ICER (other drugs vs. No treatment)	
	No anti-hypertensive treatment (no treatment)		As reference treatment comparator	
BIA	Scenario 1 'real-world': 52% patients using RAAS inhibitors, 20% patients using other drugs, 28% patients with no treatment	34.10 million Chinese T2D patients insured by UEBMI	As reference scenario	Lifetime (50-year)
	Scenario 2 'improved': 80% of patients using RAAS inhibitors (the 28% patients with no treatment in the scenario 1 were prescribed RAAS inhibitors instead), 20% of patients using other drugs		Budget difference (Scenario 2 vs. Scenario 1)	
	Scenario 3 'treat-all': 100% of patients using RAAS inhibitors		Budget difference (Scenario 3 vs. Scenario 1)	

ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blockers; CEA, cost-effectiveness analysis; BIA, budget impact analysis; RAAS, renin-angiotensin-aldosterone system; T2D, type 2 diabetes; UEBMI, urban employee basic medical insurance.

RESULTS

Base-case cost-effectiveness analysis

The base-case CEA showed that RAAS inhibitors were dominant as compared to other drugs and no treatment within the 10-year time horizon or longer (lifetime horizon) (**Table 4**). In the short time horizon (5-year), RAAS inhibitors showed slightly increased QALYs with increased cost, due to the incremental drug cost that exceeded the reduced diabetes related savings. However, RAAS inhibitors can be still considered as cost-effective (ICER = 18,220 USD per QALY) versus no treatment, when compared with the 3-times

GDP threshold recommended by the Chinese guidelines [11] (approximately 20,000 USD in Chinese urban areas) in the short time horizon.

Table 4. Results of the base-case analysis

Treatment comparators	Costs (USD) (discounted)	QALYs (discounted)	ICER (USD/ QALY) (vs. no treatment)	ICER (USD/ QALY) (RAAS inhibitors vs. other drugs)
Lifetime				
No treatment	30,890	9.195	-	-
Other drugs	31,367	9.596	1,190	-
RAAS inhibitors	29,138	9.662	Dominant	Dominant
5-year				
No treatment	5,830	2.503	-	-
Other drugs	5,990	2.511	20,090	-
RAAS inhibitors	6,002	2.513	18,220	6,000
10-year				
No treatment	13,275	5.160	-	-
Other drugs	13,420	5.201	3,624	-
RAAS inhibitors	13,188	5.208	Dominant	Dominant

QALY, quality-adjusted life year; ICER, incremental cost-effectiveness ratio; USD, US dollar; RAAS, renin-angiotensin-aldosterone system.

Sensitivity cost-effectiveness analysis

In the DSA, the variable with the largest impact on the ICER for RAAS inhibitors was the RR of progression from micro- to macroalbuminuria when compared with no treatment (**Table 5**). With an RR of 0.77 for the progression from micro- to macroalbuminuria (0.45 in the base case), RAAS inhibitors would no longer be dominant compared with no treatment. For the comparison between other drugs and no treatment, the RRs of progression from micro- to macroalbuminuria, and from macroalbuminuria to ESRD were also parameters with a large impact. Assuming a higher risk reduction in progression to macroalbuminuria or ESRD with other drugs (RR = 0.95), other drugs would also be dominant compared to no treatment.

Table 5. Results of one-way deterministic sensitivity analyses (ICERs)

Parameters	Upper and lower limits	Other drugs vs. no treatment	RAAS inhibitors vs. no treatment	RAAS inhibitors vs. other drugs
Initial disease prevalence				
Proportion of normoalbuminuria (lowest/highest value from identified literature)	down to 68% (26% microalbuminuria, 6% macroalbuminuria)	1,314	Dominant	Dominant
	up to 100%	2,276	Dominant	Dominant
Annual transition probabilities (with RAAS inhibitors) (lowest/highest value from identified literature)				
Normo- to microalbuminuria	Down to 0.015	1,714	Dominant	Dominant
	Up to 0.07	82	Dominant	Dominant
Micro- to macroalbuminuria	Down to 0.015	2,211	Dominant	Dominant
	Up to 0.06	1,154	Dominant	Dominant
Macroalbuminuria to ESRD	Down to 0.015	6,848	Dominant	Dominant
	Up to 0.06	211	Dominant	Dominant
Relative risk with RAAS inhibitors compared with other drugs (lowest/highest value from identified literature)				
Normo- to microalbuminuria	Down to 0.50	7,967	Dominant	Dominant
	Up to 0.95	137	Dominant	Dominant
Micro- to macroalbuminuria	Down to 0.26	19,778	Dominant	Dominant
	Up to 0.95	Dominant	Dominant	Dominant
Macroalbuminuria to ESRD	Down to 0.70	2,964	Dominant	Dominant
	Up to 0.95	Dominant	Dominant	Dominant
Relative risk with RAAS inhibitors compared with no treatment (lowest/highest value from identified literature)				
Normo- to microalbuminuria	Down to 0.34	1,190	Dominant	Dominant
	Up to 0.92	1,190	Dominant	Dominant
Micro- to macroalbuminuria	Down to 0.29	1,190	Dominant	Dominant
	Up to 0.77	1,190	1,554	Dominant
Macroalbuminuria to ESRD	Down to 0.77	1,190	Dominant	Dominant
	Up to 0.93	1,190	Dominant	Dominant
Utilities (lowest/highest value from identified literature)				
Normoalbuminuria	Down to 0.681	1,264	Dominant	Dominant
	Up to 0.889	1,124	Dominant	Dominant

Table 5. Continued

Parameters	Upper and lower limits	Other drugs vs. no treatment	RAAS inhibitors vs. no treatment	RAAS inhibitors vs. other drugs
Microalbuminuria / macroalbuminuria	Down to 0.694	1,236	Dominant	Dominant
	Up to 0.780	1,147	Dominant	Dominant
ESRD	Down to 0.504	1,172	Dominant	Dominant
	Up to 0.730	1,208	Dominant	Dominant
Annual costs (lowest/highest value defined by standard deviation)				
ESRD	Down to 11251.1	2,175	Dominant	Dominant
	Up to 26252.6	205	Dominant	Dominant
RAAS inhibitors	Down to 64.5	1,190	Dominant	Dominant
	Up to 150.5	1,190	Dominant	Dominant
Other drugs	Down to 38.6	378	Dominant	Dominant
	Up to 90.1	2,002	Dominant	Dominant
Discount rate of costs (lowest/highest value defined by 0% and 100%)	Down to 0	6,105	Dominant	Dominant
	Up to 10	351	Dominant	Dominant
Discount rate of utilities (lowest/highest value defined by 0% and 100%)	Down to 0	406	Dominant	Dominant
	Up to 10	2,802	Dominant	Dominant

RAAS, renin-angiotensin-aldosterone system; ESRD, end-stage renal disease.

The PSA showed that the probability of RAAS inhibitors being dominant (less costly and more effective), was very stable. The plot of the cloud of RAAS inhibitors vs. no treatment showed 100% probability of cost-saving for use of RAAS inhibitors (**Supplementary Figure 1A**). In contrast, other drugs had higher costs with a high probability as compared to no treatment (**Supplementary Figure 1B**).

Budget impact analysis

The increased use of RAAS inhibitors in T2D patients (both 'improved' scenario and 'treat-all' scenario) would cause an increased budget for the UEBMI in China during the first 4 years compared with the 'real-world' scenario. However, this difference in budget would gradually decrease during that 4-year period. The increased annual budget in the first year in the 'treat-all' scenario compared with the 'real-world' BIA scenario was estimated at 740 million USD (**Table 6**), which accounted for 1.2% of the total UEBMI fund expenditure in 2011 (62,210 million USD) [44].

Table 6. Results of budget impact analysis (undiscounted, USD million, 2011)

Scenarios	Scenario 1* 'Real-world'	Scenario 2* 'Improved'	Scenario 3* 'Treat-all'	Budget difference (S2 vs. S1)	Budget difference (S3 vs. S1)
1st year	41,221	41,832	41,961	610	739
2nd year	42,011	42,506	42,583	495	572
3rd year	42,874	43,222	43,236	347	362
4th year	43,803	43,974	43,919	171	115
5th year	44,790	44,761	44,627	-28	-162
6th year	45,825	45,579	45,360	-246	-465
7th year	46,647	46,182	45,873	-464	-773
8th year	47,490	46,800	46,397	-689	-1,092
9th year	48,345	47,429	46,928	-916	-1,417
10th year	49,206	48,064	47,464	-1,142	-1,742
Total 10-years budget impact				-1,862	-3,863
Total lifetime budget impact				-21,657	-49,019

*The base-case scenario: 52% patients prescribed with RAAS inhibitors, 20% patients prescribed with other drugs, 28% patients without any anti-hypertensive agents;
The 'improved' scenario: 80% patients prescribed with RAAS inhibitors (the 28% patients with no active drugs in base-case were prescribed with RAAS inhibitors instead), 20% patients prescribed with other drugs;
The 'treat-all scenario: 100% patients prescribed with RAAS inhibitors.

From the fifth year onwards, both 'improved' and 'treat-all' scenarios start to show reductions in the budget for the UEBMI, whereas the budget would only rise again after about 30 years due to the better survival rate of patients on RAAS inhibitors and other agents (**Figure 3**). Regarding the long-term budget, both 'improved' and 'treat-all' scenarios would save on total expenditures for the UEBMI during the 10-year and the lifetime periods. With the dominant cost-effectiveness of RAAS inhibitors, the 'treat-all' scenario would save 3,864 million USD in total in 10 years and 49,019 million USD in total for current T2D patients' lifetime treatments.

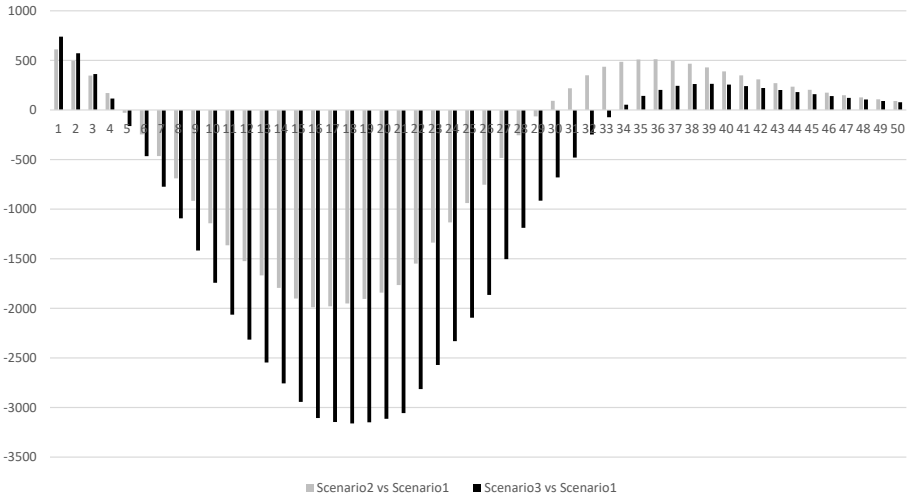

Figure 2. Lifetime (50 years) budget impact of UEBMI in China*
*Scenario 1, base-case: 52% patients prescribed with RAAS inhibitors, 20% patients prescribed with other drugs, 28% patients without any anti-hypertensive agents; this info should also be in methods
Scenario 2, 'improved': 80% patients prescribed with RAAS inhibitors (the 28% patients with no active drugs in base-case were prescribed with RAAS inhibitors instead), 20% patients prescribed with other drugs;
Scenario 3, 'treat-all': 100% patients prescribed with RAAS inhibitors

DISCUSSION

This cost-effectiveness modeling study showed that RAAS inhibitors are cost saving over the lifetime of patients with T2D in China, compared with other active anti-hypertensive drugs or no anti-hypertensive treatment, by delaying the progression of nephropathy. The results were robust to a variety of different assumptions in the DSA and in the PSA. The BIA showed that treating all T2D patients with RAAS inhibitors would save the insurance fund's budget for UEBMI in China in the long term, in addition to increases in patients' length and quality of life.

Our cost-effectiveness results for RAAS inhibitors were in line with previous economic evaluations performed alongside randomized controlled trials for both ACE inhibitors and ARBs. For example, based on the RENAAL trial, all the economic evaluation over 3.5 years indicated that losartan was cost-saving or cost-neutral compared with placebo/ conventional therapy. The cost savings per patient ranged from 2,079 EUR (2,631 USD) in Greece [46] to 4,641 EUR (6,513 USD) in France [47]. Based on the IDNT trial, early

irbesartan initiated at the onset of microalbuminuria was cost-saving compared with control, being more cost-saving than late irbesartan initiated at overt nephropathy [48, 49]. Similar cost-effectiveness results between ACE inhibitors and ARBs were summarized in a systematic review, which strengthened the recommendation that ACE inhibitors or ARBs should be used for patients with DN as both were cost-effective [50]. Compared with previous cost-effectiveness models, which were mainly based on individual clinical trial data, this study used a much broader evidence base for the transition probabilities in the model, including an NMA, a meta-analysis and other country-specific observational evidence. The NMA has been shown to increase the power of the tests and reduce type I errors with expanded sample size in data synthesis [51, 52]. At the moment, until evidence from direct active comparisons is reported, the NMA used in our study represents the top evidence level in the evidence hierarchy [53]. The NMA evidence used in our study provided a useful and complete picture for the renoprotective effectiveness measurements of different antihypertensive treatments associated with major outcomes among diabetic patients.

In pharmacoeconomic studies conducted for China, the cost data was usually obtained from hospital surveys [54], expert surveys [55], public price data sources or existing literature. The limited availability of large-scale cost data would restrict the internal and external validity of the cost-effectiveness results. The cost data in our study used evidence from a longitudinal cost analysis based on electronic insurance claims data [8] instead of reported or surveyed data. Because insurance identity cards are mandatorily used when patients see a doctor in China for the UEBMI insured, those electronic data were trusted to be accurate and credible for calculating complete medical costs covered by the insurance in the real-world setting. These data also contained information on medical visits occurring at all levels of health institutions, which was the main limitation in individual hospital-based cost analyses. The prescription information from the observational study also showed the real-world distribution of different anti-hypertensive drugs used in the general diabetic patients, which provided the evidence base for the BIA scenario analyses.

To our knowledge, no BIA studies in T2D patients in China-specific settings have been published. Our analyses showed that RAAS inhibitors would save expenditures for the insurance in the long term, although the incremental drug cost would lead to additional costs in the first few years. The effectiveness of RAAS inhibitors to increase QALYs and to avoid productivity loss 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 [56, 57]. Compared with high-income countries, the high economic burden of T2D is usually accompanied by inadequate resources for diabetes care in China, a middle-income country [58]. 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.

There are several limitations in both our CEA and BIA substudies. First, the model did not take into account the protective effectiveness of RAAS inhibitors for cardiovascular events, which leads to an underestimation of cost savings. Second, we assumed that the mortality rate was the same for patients with normo-, micro-, and macroalbuminuria. Although a slightly higher mortality rate in patients with more severe DN could be assumed due to other comorbidities, there were no valid data showing that a significant difference exists. Third, although the efficacy was derived from an NMA, the effectiveness of RAAS inhibitors and other drugs may be different in the Chinese population in the real-world setting. However, such data are limited due to the availability of well-established pharmacoepidemiologic studies conducted in T2D patients in China. Finally, our study did not incorporate the societal cost due to productivity loss. As studies adopting the societal perspective have shown improved cost-effectiveness in other country settings [59-61], inclusion of productivity loss will likely improve the cost-effectiveness of RAAS inhibitors in Chinese patients and therefore save more budget for the society. Future studies could provide evidence related to the societal cost of diabetes to further support health decision-making in China.

CONCLUSION

Treatment with RAAS inhibitors to prevent the occurrence or progression of DN is a dominant treatment strategy (cost-savings and QALY gains) in T2D patients in China in the long term. Using RAAS inhibitors in all T2D patients would therefore bring about budget savings for the Chinese UEBMI scheme. Both the CEA and the BIA are likely to be valuable for healthcare decision makers in China to improve diabetes treatment and control the increasing economic burden.

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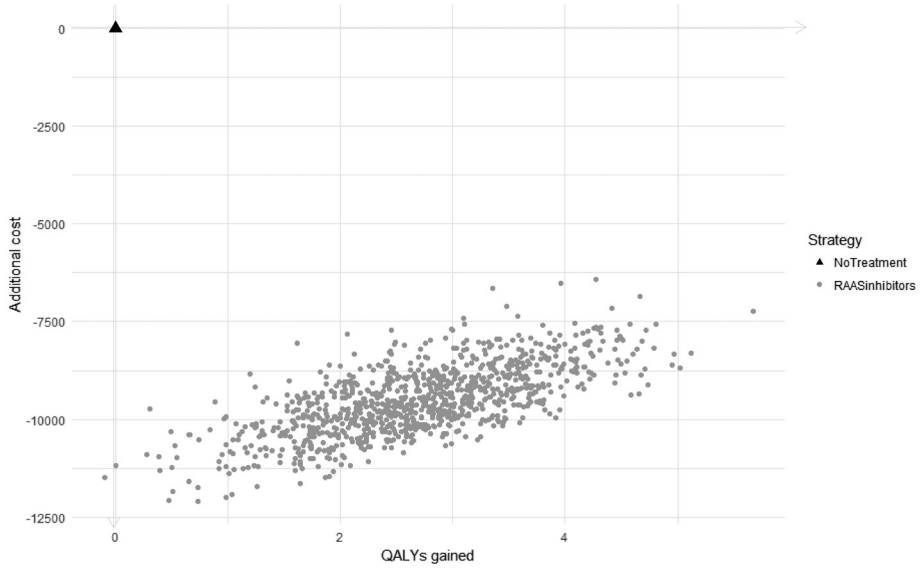
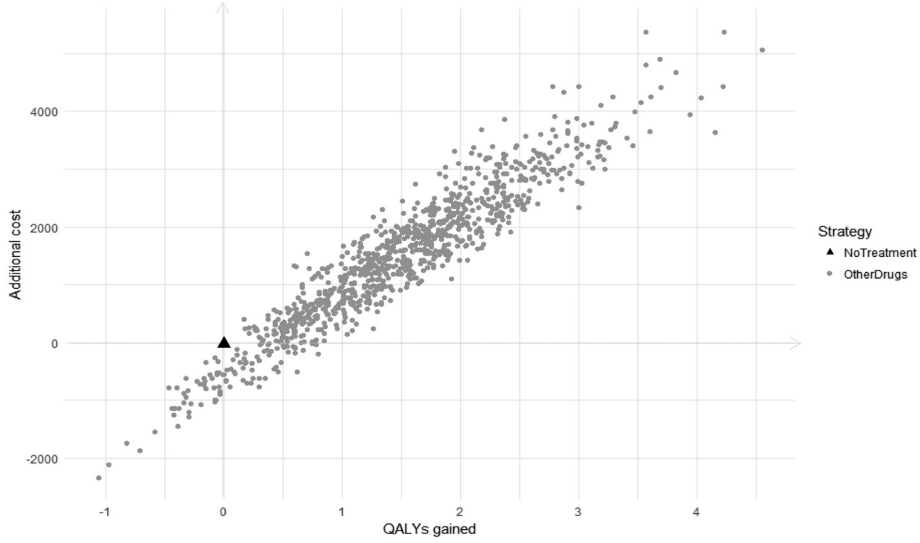
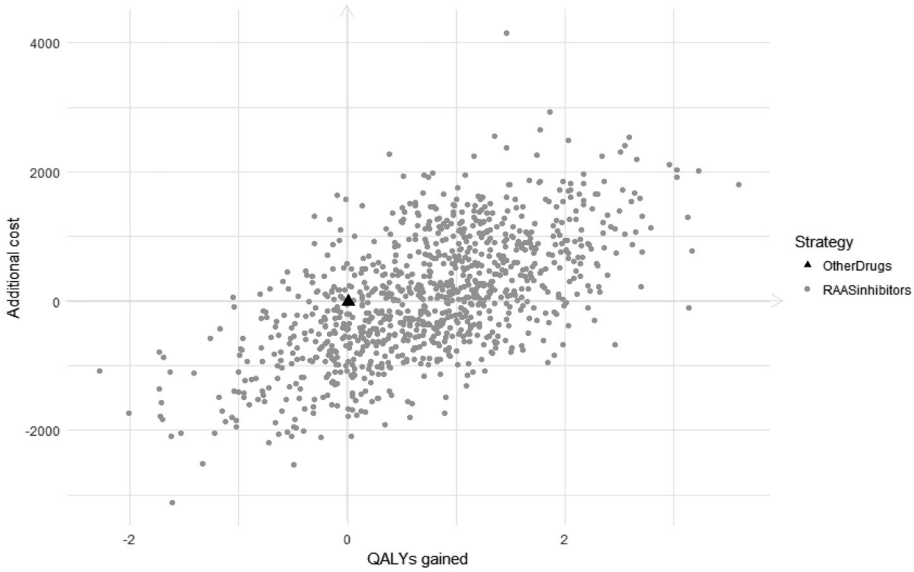


A) RAAS inhibitors vs. no anti-hypertensive treatment.



B) Other drugs vs. no anti-hypertensive treatment.



C) RAAS inhibitors vs. other drugs.

Supplementary Figure 1. 1,000 resampling results from the probabilistic sensitivity analysis