JDI Journal of Diabetes Investigation Open access
Official Journal of the Asian Association for the Study of Diabetes
ORIGINAL ARTICLE

Prevention of renal failure in Chinese patients with newly diagnosed type 2 diabetes: A cost-effectiveness analysis

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Keywords
Cost-effectiveness, Diabetic kidney disease, Screening

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J Diabetes Investig 2018; 9: 152–161

doi: 10.1111/jdi.12653

ABSTRACT

Aims/Introduction: Diabetic kidney disease (DKD) is the second leading cause (16.4%) of end-stage renal disease in China. The current study assessed the cost-effectiveness of preventing DKD in patients with newly diagnosed type 2 diabetes from the Chinese healthcare perspective.

Materials and Methods: A lifetime Markov decision model was developed according to the disease course of DKD. Patients with newly diagnosed type 2 diabetes might receive treatment according to one of the following three strategies: (i) "do nothing" strategy (control strategy); (ii) treatment with angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers (universal strategy); (iii) or screening for microalbuminuria followed by angiotensin-converting enzyme inhibitor/angiotensin II receptor blocker treatment (screening strategy). Clinical and utility data were obtained from the published literature. Direct medical costs and resource utilization in the Chinese healthcare setting were considered. Sensitivity analyses were undertaken to test the impact of a range of variables and assumptions on the results.

Results: Compared with the control strategy, both the screening and universal strategies were cost-saving options that showed lower costs and better health benefits. The incremental cost-effectiveness ratio of the universal strategy over the screening strategy was US $30,087 per quality-adjusted life-year, which was higher than the cost-effectiveness threshold of China. The sensitivity analyses showed robust results, except for the probability of developing macroalbuminuria from microalbuminuria.

Conclusions: Screening for microalbuminuria could be a cost-saving option for the prevention of DKD in the Chinese setting.

INTRODUCTION

Chronic kidney disease (CKD) remains a global health problem, and the population prevalence of CKD exceeds 10%[1]. The prevalence of CKD reached 10.8% in China, which is equivalent to 119.5 million people[2]. Diabetic kidney disease (DKD) is the second leading cause (16.4%) of end-stage renal disease (ESRD) in China[3], the incidence of which increased from 45.8% in 1999 to 61.7% in 2009[2,4]. The tremendous medical costs (nearly US $15,000 per patient per year) and poor outcomes (64% survival rate at 5 years) resulting from renal failure have received increasing attention[4–6]. Hence, it is imperative to delay the onset of DKD. The renin–angiotensin–aldosterone system is the most effective target to prevent worsening of renal disease[7]. Angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin II receptor blockers (ARBs) have been recommended as first-line agents for delaying DKD[8]. Because of the asymptomatic nature of early DKD, early screening is important.

The clinical stages of DKD are generally classified into stages based on the values of urinary albumin excretion; that is, microalbuminuria and macroalbuminuria[8]. Microalbuminuria is defined as a urinary albumin excretion rate ranging from 30 to 300 mg/day, and is deemed to be a surrogate marker for renal

Received 21 September 2016; revised 8 February 2017; accepted 2 March 2017

impairment and a predictor of worsening CKDs, cardiovascular disease (CVD), and cerebrovascular disease and mortality[9–11]. At present, proteinuria has been recognized as a risk factor for developing ESRD, and screening for microalbuminuria should be considered in high-risk populations[12]. However, because the prevalence of microalbuminuria is quite different among races and countries, screening and prevention programs should be tailored depending on the patient's race, place of residence and socioeconomic status[13]. One important issue is the financial impact of kidney disease. Previous economic evaluations in other countries have found that screening for microalbuminuria in patients with type 2 diabetes is cost-effective[14–17], and other studies have shown that the most cost-effective strategy for ACEI/ARB treatment is to initiate such treatment immediately after the diabetes diagnosis[18–20]. However, the findings of these studies cannot be generalized to the Chinese setting because of epidemiological and economic differences. A 4-year prospective study found that the incidence of microalbuminuria during follow up in a Chinese population was 33.1 per 1,000 patient-years[21]. The prevalence of microalbuminuria in the general Chinese population was 24.4% in men and 24.5% in women[22]. A cross-sectional study enrolled 32,208 patients with type 2 diabetes from 33 countries, and found that the overall global and Asian prevalence of normo-, micro-, and macroalbuminuria was 51 and 44%, 39 and 43%, and 10 and 12%, respectively[23].

The aim of the present study was to assess the cost-effectiveness of prevention strategies for delaying DKD in patients with newly diagnosed type 2 diabetes in the Chinese setting. Our evaluation was carried out from a healthcare perspective.

METHODS

Economic model overview

A decision-analytic model was used to project the lifetime cost-effectiveness of different screening strategies for the prevention of DKD for patients with newly diagnosed type 2 diabetes. The model incorporated both a decision-tree module for the screening phase (Figure 1a), and a Markov process module for the long-term disease course of DKD (Figure 1b); this structure was adopted from previously published reports[14,17]. At the beginning of the tree, patients with newly diagnosed type 2 diabetes would receive treatment according to one of the following screening strategies: no microalbuminuria screening and no ACEI/ARB treatment (control strategy), no microalbuminuria screening and all patients received ACEI/ARB treatment (universal strategy), or annual microalbuminuria screening and patients received ACEI/ARB treatment as described below (screening strategy). We assumed the characteristics of the patients to be similar to those in the previously published Chinese cohort with newly diagnosed type 2 diabetes[24], which enrolled 382 patients (mean age 51 years [standard deviation

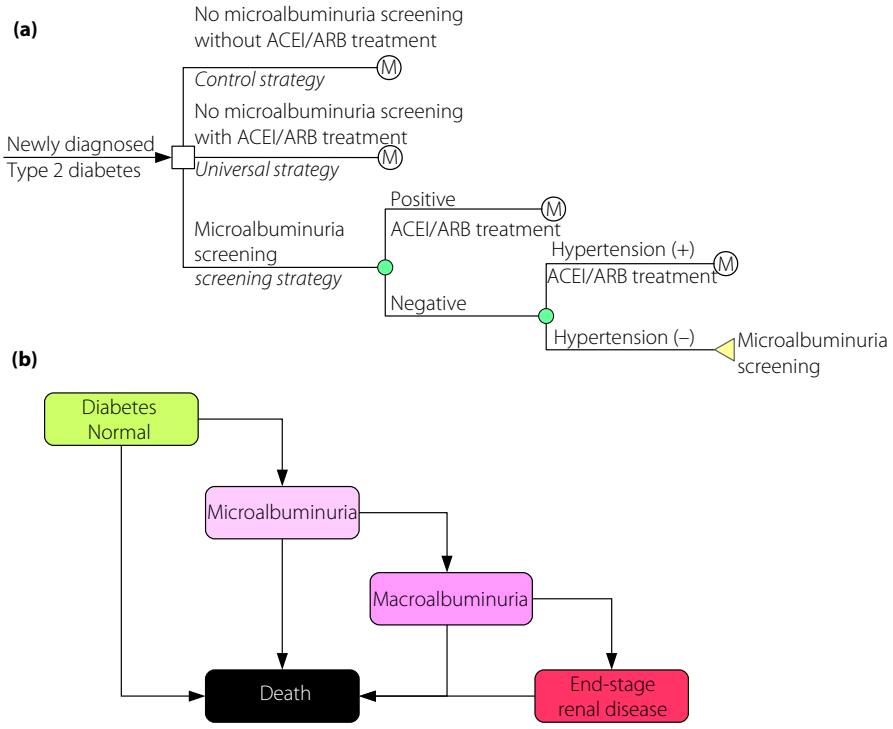

Figure 1 | Structure of the decision model with (a) a decision tree for the screening phase and (b) a Markov model for the long-term disease course. During each Markov cycle, patients either remained in their assigned health state or progressed to a new health state (straight arrow). Transition rates between health states were derived either from systematic reviews of the literature or from previous studies. ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker.

10], body mass index 25.0 kg/m^2 [3.0] and mean fasting plasma glucose 11.2 mmol/L [3.1]); nearly 38.61% of the patients in this cohort had hypertension[25]. The initial prevalence of microalbuminuria and macroalbuminuria was derived from the Shanghai diabetic complications study[26]. If the patients in the screening strategy were diagnosed with hypertension or microalbuminuria, ACEI/ARB would be prescribed based on the Chinese recommendation of managing microalbuminuria[27]. The initial health states in the Markov model included "no DKD," "microalbuminuria," "macroalbuminuria," "ESRD" and "death (absorbing state)"; these were assigned to patients based on their condition when type 2 diabetes was diagnosed. In each 1-year cycle of the Markov process, patients could remain in their state or progress to a new health state (straight arrow). The all-cause mortality risk adjusted by the patient's health state was assigned to all patients. The average number of cycles (from the diagnosis to death or 100 years-of-age) that individuals reside in each state can be used in conjunction with state values (e.g., life years, health-related quality of life, cost) to measure life expectancy, quality adjusted life expectancy and expected costs[28].

The primary outcome measures were quality-adjusted life-years (QALYs) and cost (US dollars), which were annually discounted at 5% in agreement with Chinese guidelines for pharmacoeconomic evaluations[29]. A QALY places a weight on time in different health states, and is the arithmetic product of life expectancy and a measure of the quality of the remaining life-years, which has been widely recommended to inform the allocation of healthcare resources across a broad range of conditions and interventions[30]. Incremental cost-effectiveness ratios (ICERs), presented as the cost per additional QALY gained, were also calculated. When the ICER was lower than the per capita gross domestic product of China in 2014 ($7,380), cost effectiveness was assumed according to the recommendation of World Health Organization[31–33].

Clinical data

Model inputs for epidemiology data were obtained from Chinese studies to the greatest possible extent; however, the paucity of epidemiological DKD studies in China necessitated the use of data from other countries, especially from East Asia because of the racial/ethnic differences in the prevalence of proteinuric and non-proteinuric DKD[34,35]. The model inputs are summarized in Table 1.

The incidence of microalbuminuria reported by a Korean study was 52/1,000 person-years, which included 188 Korean type 2 diabetes patients with initial normoalbuminuria who were followed prospectively for 5.5 years[35]. The Randomized

Table 1 | Model inputs

Parameters	Base-case value	Range tested	Reference
Probability of transition per year (without ACEI/ARB treatment)			
Normoalbuminuria to microalbuminuria	0.038	0.03–0.052	35–37
Microalbuminuria to macroalbuminuria	0.094	–0.02–0.2	15
Macroalbuminuria to ESRD	0.109	0.104–0.114	39, 40
HR for progression with ACEI/ARB treatment			
Normoalbuminuria to microalbuminuria	0.82	0.64–1.05	41
Microalbuminuria to macroalbuminuria	0.45	0.26–0.79	41
Macroalbuminuria to ESRD	0.8	0.69–0.93	41
HR for all-cause mortality			
Normoalbuminuria	1.462	1.042–2.051	46
Microalbuminuria	1.35	0.79–2.33	47
Macroalbuminuria	1.83	1.53–2.19	45
ESRD	4.46	3.26–6.1	43
Initial disease prevalence (%)			
Normoalbuminuria	77.4%	70.4–82.5%	26
Microalbuminuria	21.9%	16.4–27.4%	26
Macroalbuminuria	0.7%	1.1–2.2%	26
Preference weights (utility)			
Normoalbuminuria, Microalbuminuria and Macroalbuminuria	0.876	0.736–1	52
ESRD	0.6	0.39–0.81	53
Resource utilization and cost data (US $)			
Managing diabetes per year	828.95	387.14–1,395	48
Microalbuminuria test per unit	4.09	2.38–6.35	Local charge
Managing ESRD per year	14,241	13,571–15,031	49
ACEI/ARB treatment per day	0.73	0.013–1.81	Local charge

ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; ESRD, end-stage renal disease; HR, hazard ratio.

Olmesartan and Diabetes Microalbuminuria Prevention (ROADMAP) trial found that the probability of microalbuminuria in Japanese patients without microalbuminuria was 9.8%, with a median of 3.2 years of follow up[36]. A cross-sectional study that enrolled 1,827 Taiwanese individuals found that the median duration of microalbuminuria among type 2 diabetes patients was 23 years[37]. The annual mean probability based on these three studies was used in the current analysis. The risk of new-onset macroalbuminuria from microalbuminuria was obtained from a published report[15], which calibrated the probability of microalbuminuria to macroalbuminuria based on a meta-analysis that included 17 studies and 2,036 patients[38]. The probability of developing ESRD from macroalbuminuria was estimated from an Olmesartan Reducing Incidence of End-stage Renal Disease in Diabetic Nephropathy Trial (ORIENT) and the Reduction of Endpoints in NIDDM with the Angiotensin II Antagonist Losartan (RENAAL) study[39,40]. The risk reduction caused by ACEIs/ARBs was obtained from a systematic review[41].

Background mortality could be incurred by a patient at any point in the model. The model used a normal life table from the life tables for World Health Organization member states (2011) to adjust the mortality risk for patients with type 2 diabetes without DKD, microalbuminuria, macroalbuminuria and ESRD[42–47].

Costs

Because our analysis was carried out from the healthcare perspective of China, only direct medical costs were considered. Costs of ACE inhibitors, ARBs, annual screening procedures and treatment for ESRD, as well as health care expenditures related and unrelated to diabetes, were considered (Table 1). The annual costs of patients with type 2 diabetes were applied to all health states except for ESRD, which was derived from a comparative study on medical expenditures for diabetes mellitus and non-diabetes mellitus in nine provinces of China[48]. The annual costs related to ESRD were obtained from a national survey that calculated the heath resource expenditure of different types of dialysis in 837 patients with ESRD[49]. To calculate the daily consumption associated with ACEI/ARB therapy, the most frequently recommended ACEIs/ARBs in China, including the generic and name brand versions of telmisartan, irbesartan, olmesartan, candesartan, valsartan, benazepril, captopril, perindopril and enalapril, were considered, and their daily dose was based on the Defined Daily Dose suggested by the World Health Organization[50]. The median daily cost of ACEIs/ARBs was used in the base-case analysis, and the impact of the lowest and highest costs was tested in the sensitivity analysis. An immunonephelometric method was used for a quantitative screening test for microalbuminuria[51], and three tests were administered for confirmation if the first test was positive, as recommended by the Chinese expert consensus[27]. The cost of the test per unit was derived from a local hospital.

Utility scores

The economic evaluation for patients with type 2 diabetes used preference weights (utility) to adjust the length of life for quality of life (Table 1). A utility value of 1 is equivalent to being in perfect health, and a value of 0 is equivalent to death. The values for patients without DKD were based on a recent health-state utility study in Chinese patients with type 2 diabetes[52], and those for patients with ESRD were derived from an Asian cohort in Singapore[53] that used the EuroQol five dimensions questionnaire for measuring the utility scores[54]. Similar to previous reports, we assumed that patients without ESRD have the same quality of life[14,15].

Sensitivity analyses

To address the uncertainty of the model, probabilistic sensitivity analysis was carried out using a second-order Monte Carlo technique. In this analysis, statistical distributions were adopted to the corresponding model parameters and values sampled by 1,000 Monte Carlo simulations for jointly examining the uncertainty in all model parameters. In particular, a beta distribution was used to represent the uncertainty in utility, probability and proportions, because these are binomial parameters and are constricted in the interval from zero to one. A triangle distribution was used for cost data, because costs are limited from minimum to maximum values and are often highly skewed. For continuous data, such as the hazard ratio, a normal distribution was used. Based on the results of probabilistic sensitivity analysis, a cost-effectiveness acceptability curve was plotted to show the proportion of cost-effective simulations at different levels of willingness-to-pay per QALY gained. Furthermore, one-way sensitivity analyses were used to examine the robustness of the results by changing individual variables between lower and upper limits, as shown in Table 1. All statistical calculations were carried out using the R software package (version 3.2.2; R Development Core Team, Vienna, Austria).

RESULTS

Base-case analysis

The outcomes for the three strategies in the base-case analysis are shown in Table 2. If no prevention was available (control strategy), 43.8%, 45.3% and 27.9% of newly diagnosed patients would develop microalbuminuria, macroalbuminuria and ESRD, respectively, in their lifetime; the calculated total cost, QALYs and expected life years per person were $22,419, 10.91 and 20.94, respectively. Compared with the control strategy, the universal and screening strategies resulted in a lower incidence of ESRD, more health benefits and lower costs; that is, both strategies dominated the control strategy.

The comparison between the universal and screening strategies showed that the universal strategy yielded more QALYs, but involved greater costs. The ICER per QALY gained for the universal strategy over the screening strategy was $30,087 (Figure 2).

Table 2 | Lifetime results of the base-case analysis

Strategy name	Control strategy	Universal strategy	Screening strategy	Difference (vs control strategy)	
				Universal strategy	Screening strategy
Cumulative incidence					
Microalbuminuria	43.8%	38.7%	43.8%	−5.1%	0.0%
Macroalbuminuria	45.3%	27.7%	30.0%	−17.6%	−15.3%
ESRD	27.9%	14.7%	15.9%	−13.2%	−12.0%
Cost (US $)					
Microalbuminuria	2,454	4,105	4,424	1,651	1,970
Macroalbuminuria	1,114	920	984	−194	−130
ESRD	12,602	6,027	6,405	−6,575	−6,197
Total	22,419	19,782	18,232	−2,637	−4,187
QALY	10.91	11.25	11.20	0.34	0.29
LY	20.94	21.70	21.53	0.76	0.59
ICER (US $/QALY)†		−7,697	−14,380		

†Compared with the control strategy. ESRD, end-stage renal disease; ICER, incremental cost-effectiveness ratios; LT, life-years; QALY, quality-adjusted life-years.

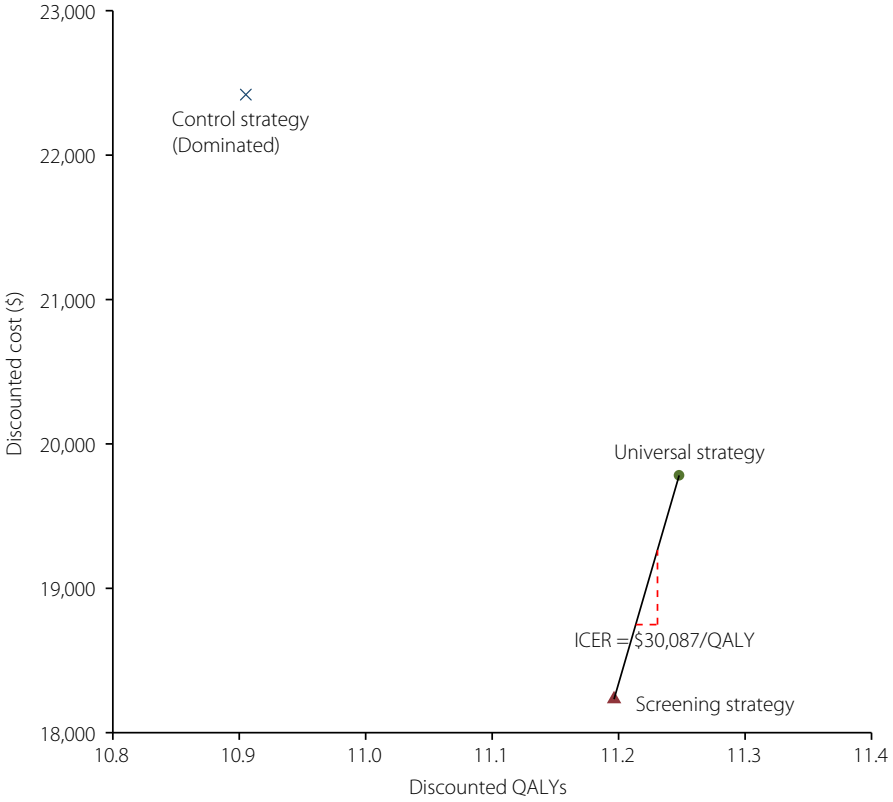

Figure 2 | The cost-effectiveness frontier shows the most efficient options among the three competing prevention strategies. The *x*-axis shows the discounted lifetime quality-adjusted life-years (QALYs) for each strategy, and the *y*-axis shows the total discounted lifetime costs (in US dollars). The oblique line connects interleukin-2 and the most cost-effective strategies; strategies above the straight lines were dominated or extended dominated. In the cost-effective plane, the values of the most incremental cost-effectiveness ratios (ICER) are shown.

Sensitivity analysis

Because the universal strategy showed the greatest health benefits, it was used to carry out a one-way sensitivity analysis compared with the control strategy. The analyses showed that the results of the model were more sensitive to the probability for developing macroalbuminuria from microalbuminuria,

because this variable was found to have the greatest impact on ICER, which showed that the universal strategy would become non-cost-effective when the risk decreased. The remainder of the sensitive variables, such as diagnosing diabetes and the daily cost of ACEI/ARB, had a medium effect (Figure 3). It is worth noting that in all adjustments for the remainder of the variables, the universal strategy maintained its cost-effectiveness, as the ICER per QALY gained remained well below the threshold of $7,380.

In probabilistic sensitivity analysis, the ICERs per QALY gained for the universal and screening strategy over the screening strategy were $ –5,713 (95% confidence interval –6,280 to –5,145) and $ –14,862 (95% confidence interval –15,565 to –14,159), respectively. Cost-effectiveness acceptability curves showed that the screening strategy produced nearly 90% probability of cost-effectiveness when the threshold was equal to the per capita gross domestic product of China in 2014, showing that it was the most cost-effective intervention (Figure 4).

DISCUSSION

To the best of our knowledge, this is the first economic analysis in the Chinese setting to compare annual microalbuminuria screening (screening strategy) and the treatment of all patients with ACEIs/ARBs (universal strategy) with the "do nothing" (control) strategy during the lifetime of patients with newly diagnosed type 2 diabetes. The present results showed that the screening and universal strategies provided greater health benefits and lower costs. In terms of health outcomes, the screening and universal strategies were more effective, because they reduced the frequency of ESRD in comparison with the control strategy, resulting in higher QALYs and also decreased health resource utilization (Table 2). Hence, both the universal and screening strategies were found to be cost-saving prevention alternatives, resulting in an ICER equal to $ –7,697 and $ –14,380 per QALY gained, respectively. Compared with the screening strategy, the universal strategy gained greater health outcomes with a higher cost, leading to an ICER equal to $30,087 per QALY gained, which was higher than the cost-effectiveness threshold recommended by the World Health Organization[31–33]. These results show that the screening strategy might be a favorable option for Chinese patients.

The present findings are generally in agreement with previously reported economic studies showing that early detection and intervention are cost-effective measures by offsetting their costs through reducing the disease burden related to DKD, although their analyses were carried out in diverse settings with different study designs[14–20]. More specifically, a cost-utility study carried out in another Asian country (Thailand) showed that annual screening for microalbuminuria was a cost-effective method for preventing renal failure in insulin-dependent diabetes patients with an ICER of THB3,035 per QALY in comparison with a "do nothing" scenario[17]. However, an evaluation, which was undertaken in the USA, showed that treating all patients with ACEIs/ARBs was cost-effective compared with screening for microalbuminuria, with an ICER of $7,500 per QALY[18]. Similar findings were procured in an

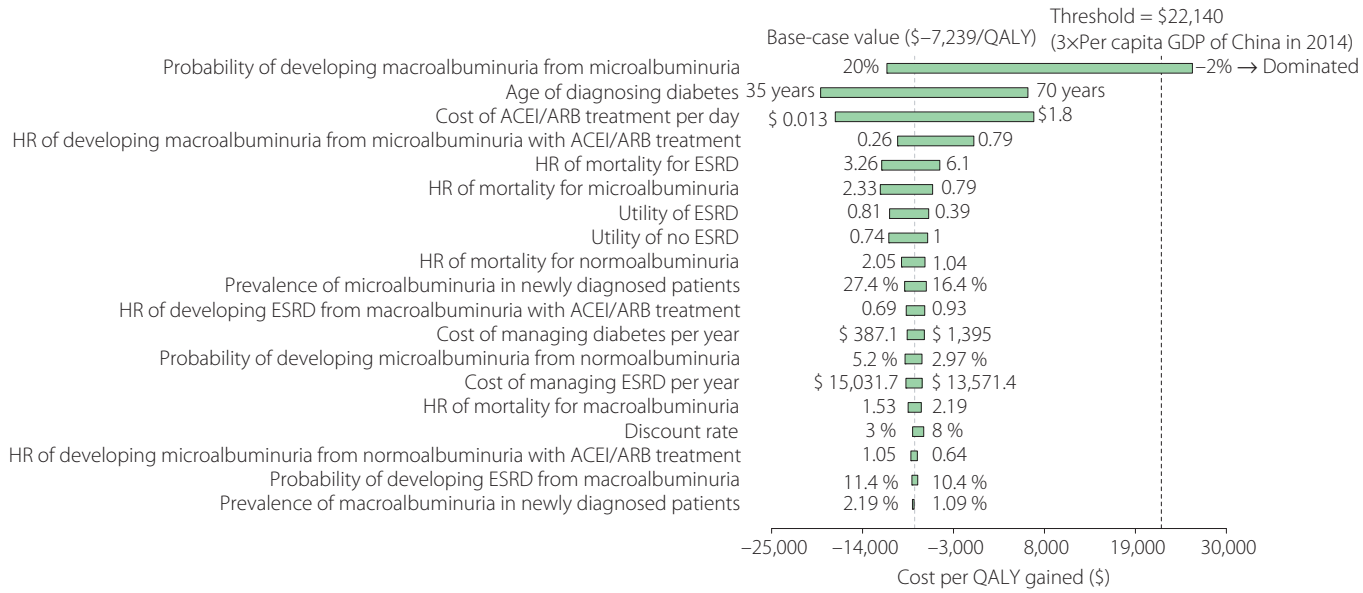

Figure 3 | Tornado diagram representing the cost per quality-adjusted life-year (QALY) gained in one-way sensitivity analysis for universal strategy vs control strategy. The width of the bars represents the range of the results when the variables were changed. The vertical grey and black dotted lines represent the base-case results and threshold, respectively. The width of the bars represents the range of results when the variables are changed. The vertical dotted line represents the base-case results. ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; ESRD, end-state renal disease; GDP, gross domestic product; HR, hazard ratio.

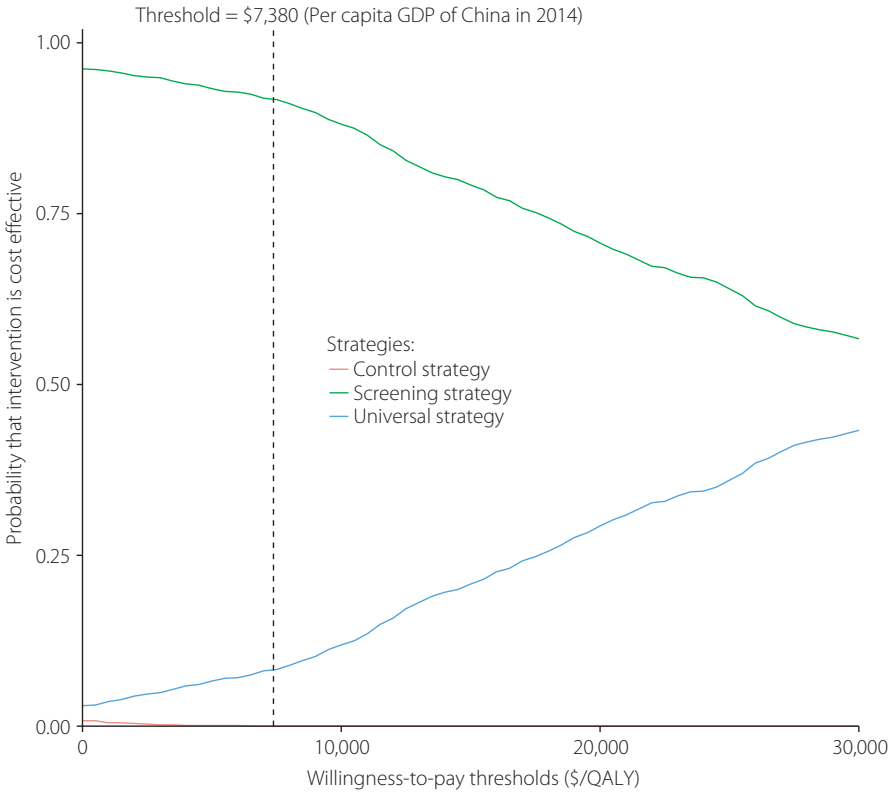

Figure 4 | Cost-effectiveness acceptability curves for the different strategies for preventing the diabetic kidney disease. The *y*-axis shows the probability that a strategy is cost-effective across the willingness to pay per quality-adjusted life-year (QALY) gained (*x*-axis). The vertical dashed line represents the thresholds for China. GDP, gross domestic product.

evaluation carried out in the Netherlands and Germany[15,20], suggesting that treating all newly diagnosed type 2 diabetes patients with ACEIs/ARBs might save costs. One potential reason for this result is that the cost of ACEI/ARB treatment might be less offset by reducing ESRD in the Chinese setting than in the USA, the Netherlands and Germany, because their annual costs related to ESRD are much higher than those in China. Additionally, a randomized, placebo-controlled trial carried out in the USA showed that the use of captopril in diabetic nephropathy provided significant savings in healthcare costs with a broader societal benefit[55].

We carried out extensive sensitivity analyses to examine the robustness of our results. The probability for developing macroalbuminuria from microalbuminuria was the most influential factor for clinical and economic outcomes; this was in agreement with the study reported by Adarkwah *et al.*[15] When the risks increased, such as in patients with poor glucose and blood pressure control[56], the cost-effectiveness of the prevention strategy might become more favorable. As shown in Figure 3, for younger patients, such as patients diagnosed at 35 years-of-age, the ICER of the universal strategy over the control strategy decreased to $19,074/QALY gained. However, for older patients, such as those diagnosed at 70 years-of-age, the ICER would increase to $5,999/QALY gained. These findings show that the prevention program could be tailored according to patient age, which might improve the cost-effectiveness of prevention strategies. Another considerable variable was the daily cost of ACEI/ARB treatment, which yielded a more favorable economic outcome when the lower cost of ACEI/ARB was used. Because of limited health resources in the Chinese healthcare system, the utilization of generic ACEIs/ARBs might be a favorable option[57]. Another economic study from the USA also found that the results were sensitive to the age at diagnosis and the cost of ACEI treatment[18].

Potential weaknesses of this analysis should be considered. First, the clinical data were derived from different published studies, although it was assumed that these data were applicable to the Chinese healthcare setting. The use of these data might lead to uncertainties; however, given the absence of local related data, this choice was considered a favorable approach to obtain relevant clinical data. In an effort to minimize the impact of potential bias and uncertainty in the results, we examined the robustness of the data using sensitivity analyses. Second, in the current analyses, because of the absence of relevant epidemiological studies in Asia, factors associated with the risk of developing DKD, such as estimated glomerular filtration rate, urinary albumin-creatinine ratio and glycated hemoglobin levels, were not stratified by risk factors

as in previous reports[58]. Third, the current study was undertaken from the healthcare perspective, and as such, only direct medical costs were considered. However, because of the great impact of CKD on families[59,60], a more complete evaluation from a broader (societal) perspective might also be necessary. Indeed, direct non-medical and indirect costs, such as the loss of productivity, are likely higher than those included in the current study; therefore, the economic outcome might be more favorable from a societal perspective. Fourth, to simplify the model as previous studies did[14–20], the present study did not consider the impact of ACEI/ARB on cardiovascular disease, which might improve the diabetes outcomes by reducing the risks of stroke and heart disease. Thus, the omission might underestimate the cost-effectiveness of ACEI/ARB. Fifth, because of the lack of local data, the impact of adherence to screening and treatment was not considered in the current analysis. A Danish study found that just 57.2% of type 2 diabetes patients had been screened for microalbuminuria with any method within the preceding 12-month period. If the adherence was low, the results and the conclusions of the study might be different. Finally, the present study did not consider the consequence caused by DKD, such as heart disease, stroke and infections, which would underestimate the benefits of the interventions. Nevertheless, because the results of the present analysis reflect the clinical conditions of managing DKD in China, we believe that the results can serve as important reference points for Chinese decision makers.

The present study suggests that annual microalbuminuria screening in normoalbuminuria type 2 diabetes patients proved to be a cost-saving measure when compared with the "doing nothing" strategy; screening was also cost-effective when compared with treating all patients with ACEIs/ARBs. Therefore, a compulsory screening program should be initiated by Chinese policy makers.

ACKNOWLEDGMENTS

This study was supported by grants from the National Natural Science Foundation of China (no. 71373160 and 81300603), and the Fourth Round of a Three-year Action Plan on Public Health Discipline and Talent Program (Evidence-based Public Health and Health Economics, no. 15GWZK0901). The funding agency had no role in study design, data collection and analysis, decision to publish or preparation of the manuscript.

DISCLOSURE

The authors declare no conflict of interest.

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