Original Article

Cost-utility analysis of imrecoxib compared with celecoxib for patients with osteoarthritis

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Background: The objective of this study is to compare the long-term cost-utility of imrecoxib and celecoxib for patients with osteoarthritis (OA) from the perspective of the Chinese healthcare system.

Methods: An economic model was built based on the model from the National Institute for Health and Care Excellence (NICE). The simulation was carried out initially for 100 cycles of 3 months each, starting with 10,000 patients. A discount rate of 5% was applied both for cost and utility. Quality-adjusted life years (QALYs) were adopted as the utility indicator, and real-world data from the hospital information systems of 170 hospitals was collected to indicate cost. The relative incidence rates of adverse events (AEs) with imrecoxib and celecoxib were collected from randomized controlled trials. Sensitivity analysis was performed to validate the robustness of the model.

Results: In the base case analysis (6-month treatment duration, 55 years old and above), imrecoxib was the more cost-effective option compared to celecoxib, with an incremental cost-effectiveness ratio (ICER) of $3,041.14. This finding remained unchanged after varying the treatment duration and the age of the patients. The main drivers of the results were the relative incidence of myocardial infarction (MI), the cost of imrecoxib, and the utility of OA patients without any AEs. Probability sensitivity analysis (PSA) showed that there was a 59.02% probability of imrecoxib as the more cost-effective option, with a threshold of $30,000.

Conclusions: Although there were uncertainties, imrecoxib was the more cost-effective option compared to celecoxib, with a definite possibility. Due to the limitations of the original model and this study, the results of this study should be adopted with caution.

Keywords: Imrecoxib; celecoxib; cost-utility; osteoarthritis (OA)

Submitted Dec 23, 2020. Accepted for publication Mar 29, 2021.
doi: 10.21037/atm-21-290
View this article at: http://dx.doi.org/10.21037/atm-21-290

Introduction

Arthritis is listed as a type of 'immortal cancer' by the World Health Organization (WHO), and osteoarthritis (OA) is the most common arthritic disease (1,2). OA is a chronic degenerative disease characterized by joint pain throughout the body, which may be caused by fibrosis, chap, ulcers, and loss of articular cartilage (3). The prevalence of OA in China warrants close attention, as it reached 25.03%, 21.51%, 20.46%, and 8.99% for the lumbar, knee, cervical, and hand joints, respectively (4). In addition, as a chronic

joint disease, it is especially harmful to the health of the elderly, and the prevalence of OA increases with age (5). China entered into an aging society in 1999 (6). Given the age-related prevalence of OA and the growing number of elderly people in China, the number of patients with OA in China will increase year by year. Furthermore, OA is a disease with a high disability rate, and can increase the incidence of cardiovascular diseases (CV) and all-cause mortality. For example, symptomatic OA of the knee can increase all-cause mortality by nearly 100% (3). According to the Chinese Guidelines for Diagnosis and Treatment of Osteoarthritis, there are six main types of drugs for managing osteoarthritis: Nonsteroidal anti-inflammatory drugs (NSAIDs), analgesics, intraarticular injection of drugs, disease-modifying antirheumatic drugs (DMARDs), Chinese patent medicine and antidepressants (3). Among the six types, NSAIDs are first-line used drugs, and widely prescribed to patients with OA. The anti-inflammatory mechanism of NSAIDs is to inhibit cyclooxygenase (COX), which is required for prostaglandin synthesis (7). COX exists in 2 isoforms: COX-1 is a ubiquitous constitutive isozyme producing prostaglandins, and is responsible for homeostatic functions, while COX-2 is largely a cytokine-induced isozyme producing prostaglandins that mediates pain and inflammation. There is a known link between NSAID therapy and gastrointestinal (GI) bleeding, with a reported 3,200 deaths in the US a year as a result of complications from GI bleeding using NSAIDs (8). Because COX-1 exists in the stomach, intestine, kidneys and platelets, and COX-2 is expressed during inflammation, the therapeutic effects of NSAIDs are mainly the result of inhibition of COX-2, whereas the toxic effects (e.g., gastrointestinal) are mainly due to the inhibition of COX-1 (9). Therefore, an ideal NSAID should selectively inhibit COX-2 without inhibiting COX-1 (7). COX-2 inhibitors include: etodolac, meloxicam, celecoxib, rofecoxib, etoricoxib, valdecoxib and lumiracoxib, among which celecoxib is a common COX-2 inhibitor for managing OA and widely prescribed for managing OA (1). Imrecoxib, approved by the Chinese Food and Drug Administration (CFDA) in 2011, is a novel and moderately selective COX-2 inhibitor that possesses anti-inflammatory effects by inhibiting COX-2 (10,11).

Several studies have reported similar efficacy between celecoxib and imrecoxib, though with different prices and incidences of adverse events (AEs) (12-14). A review of the literature showed that there is a lack of cost-effectiveness analyses on imrecoxib and celecoxib, causing great confusion for patients, hospitals, medical insurance departments, and policy makers. Meanwhile, the National Institute for Health and Care Excellence (NICE) developed an economic model for the cost-effectiveness analysis of drugs treatments for OA in 2008, which has been adopted in different countries (8,15,16). The OA model was built based on the adverse events occurred due to the drugs used for osteoarthritis, which were also common adverse events in Chinese population. Therefore, the objective of this study is to compare the cost-effectiveness of imrecoxib and celecoxib for the treatment of OA based on the NICE OA model, with an update including Chinese real-world data from the perspective of the Chinese healthcare system. It is hoped that these results can be a reference for both related stakeholders in China and international experts who may be interested in the cost-effectiveness of different treatments for OA.

We present the following article in accordance with the CHEERS reporting checklist (available at http://dx.doi.org/10.21037/atm-21-290).

Methods

The model built in this study was an economic model for OA from the NICE, which was first built in the 2008 OA guidelines (guideline code: CG59), and was updated with data from the CONDOR trial in 2012 (16,17). In the present study, the perspective was from the Chinese healthcare system, and the comparators were imrecoxib and celecoxib.

Model structure

The model was a combination of a Markov model and a decision tree model, with the aim to explore the cost-effectiveness of 2 drug treatments for OA. The health states in this model were divided by the most frequent AEs caused by different drug treatments. There were 15 health states in this model: (I) 7 initial health states according to the main AEs caused by most NSAIDs, including OA without any AEs, GI discomfort (dyspepsia), symptomatic ulcer, complicated GI events, myocardial infarction (MI), stroke, and heart failure (HF); (II) 5 post-AE health states (as GI discomfort was assumed to be a mild AE which could be cured without any post-treatment), including post symptomatic ulcer, post complicated GI events, post MI, post stroke, and post HF; (III) 1 post-treatment state, where after treatment, patients without any AEs and with

GI events transitioned to the post-treatment state; (IV) 1 withdraw state, where patients withdrew due to GI events; (V) 1 absorbed state, and the dead state was applied as the absorbed state.

To start with, it was supposed that all patients were in the state of "OA without any AEs", and in each cycle, patients transitioned to the 6 AE health states, then from the AE health states to the post-AE states. Patients in the state of "GI discomforts" were seen as not stopping the drug treatment, therefore, there was a possibility for patients to transition from "GI discomforts" to another AE state. After treatment, patients transitioned to the post state and would stay in the post state until death (patients without any AEs and GI discomforts transitioned to the post treatment state, and patients with AEs transitioned to the corresponding post-AE states). There was a possibility for all patients to die in each state in each cycle. For patients taking the medications, there was possibility for them to withdraw due to GI events. When patients stopped taking imrecoxib or celecoxib, the topical diclofenac solution was assumed to be adopted as a medication to manage OA.

Model running parameters

The time horizon of this model was a lifetime, and the model was terminated when patients reached 80 years old or death. In the base case analysis, the age of patients was set to 55 years old. The simulation was carried out initially for 100 cycles with 3 months in each cycle. Cohort simulation with 10,000 patients per cycle was performed. The annual discount rate of 5% was applied according to the Chinese Guidelines for Pharmacoeconomics Evaluations (18). Scenario analyses were adopted for different start-ages (65 years old) and different treatment durations (6, 12, 24 months treatment).

Inputs

The model had 3 key parameters, which were also the inputs: cost, utility, and transition probability (*Table 1*). Both qualitative and quantitative analyses were applied to collect the input data. Half-cycle corrections were applied when it came to cost and utility.

Utility values

Quality-adjusted life years (QALYs) were adopted as the utility values. Utility values for the health states were extracted from the NICE OA model (17). According to the guidelines, for OA without any AEs, the utility values depend on the utility of OA itself and the efficacy of different treatment strategies. The Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) is widely used to assess the severity level of disease, and can also reflect the efficacy of drugs indirectly, which can be converted to EQ-5D scores using the transfer to utility (TTU) technique. After reviewing, the NICE OA model supposed that the difference in efficacy between the NSAIDs/COX-2 drugs was not significant, therefore, the efficacies of imrecoxib and celecoxib included in this study were equal (17). Considering the suggestions from the guideline development group, after 3 months, the patients with HF were reverted to the no-complications utility score (8,17).

Update with Chinese costs

Cost data in the NICE OA model was based on UK medical expenses, and in this study, cost was updated with Chinese costs after collecting real-world data and relevant literature. The real-world data was extracted from the Su-Value database (Shanghai Su-Value Health Scientific Ltd., Shanghai, China) (21). The Su-Value database encompasses information from the hospital information systems (HIS) of 170 hospitals in 20 provinces across China. Based on the ICD-10 categories, patients with OA, GI discomfort, symptomatic ulcer, complicated GI events, stroke, MI, and HF were recognized, and diagnostic information, medical expenses, and basic social characteristics were extracted from 2016 to 2018. For the state of "OA patients without any AEs", cost was calculated by drug cost and other outpatient expenses extracted from the Su-Value database, and drug cost was extracted from the Beijing Medicine Sunshine Purchasing system (14) and adjusted by the recommended dosage in each cycle by the doctors. For the state of patients with 6 initial AEs, the costs were calculated directly from the Su-Value database. There was no maintenance cost, however, there was a higher risk of suffering from GI events for patients in the post complicated GI events state and the post symptomatic ulcer state according to the NICE OA model. Therefore, costs for post complicated GI events and post symptomatic ulcer were obtained by combining the recurrence rates and the cost of corresponding initial AE states (17). Maintenance costs were considered for post CV states, and the cost of post CV was extracted from the literature which reported the cost of Chinese patients. For

Table 1 Model inputs

Items	Values	Distribution	Sources
Drug price in each cycle ($)			
Imrecoxib	19.89	Gamma	Medicine Purchasing System (14)
Celecoxib	9.32	Gamma	Medicine Purchasing System (14)
Topical diclofenac	20.30	Gamma	Su-Value database
Clinic cost for managing OA and AEs			
OA management without drug	26.50	Gamma	Su-Value database
GI discomfort	10.66	Gamma	Su-Value database
Symptomatic ulcer	34.57	Gamma	Su-Value database
Complicated GI events	1,354.15	Gamma	Su-Value database
Stroke	1,289.92	Gamma	Su-Value database
MI	5,190.93	Gamma	Su-Value database
HF	1,182.33	Gamma	Su-Value database
Post symptomatic ulcer	0.81	Gamma	Yani P (19)
Post complicated GI events	21.54	Gamma	Xingjing W (20)
Post stroke	619.56	Gamma	Wang C (21)
Post MI	948.47	Gamma	Wang C (21)
Post HF	451.29	Gamma	Wang C (21)
Incidence of AEs, celecoxib (%)			
GI discomfort	12.45	Beta	Nasef SA (15)
Symptomatic ulcer	0.09	Beta	Nasef SA (15)
Complicated GI events	0.05	Beta	Nasef SA (15)
Stroke	0.02	Beta	Nasef SA (15)
MI	0.15	Beta	Nasef SA (15)
HF	0.04	Beta	Nasef SA (15)
Relative incidence of AEs (imrecoxib *vs.* celecoxib)			
GI discomfort	0.49	Lognormal	Jianlin Huang (12)
Symptomatic ulcer	1.34	Lognormal	Dong Xu (13)
Complicated GI events	0.50	Lognormal	Dong Xu (13)
Stroke	1.00	Lognormal	Jianlin Huang and Dong Xu (12,13)
MI	1.00	Lognormal	Jianlin Huang and Dong Xu (12,13)
HF	1.00	Lognormal	Jianlin Huang and Dong Xu (12,13)
Mortality rates in the Chinese population (%)			
55–64	0.37	Uniform	Chinese Health Yearbook 2019 (22)
65–74	0.94	Uniform	Chinese Health Yearbook 2019 (22)
75–80	2.67	Uniform	Chinese Health Yearbook 2019 (22)

Table 1 (*continued*)

Table 1 (*continued*)

Items	Values	Distribution	Sources
Utility weights (1= OA, no complications)			
GI discomforts	0.733	Lognormal	NICE OA model (17)
Withdraw due to GI	0.989	Lognormal	NICE OA model (17)
Symptomatic ulcer	0.552	Lognormal	NICE OA model (17)
Complicated GI events	0.459	Lognormal	NICE OA model (17)
Stroke	0.348	Lognormal	NICE OA model (17)
MI	0.374	Lognormal	NICE OA model (17)
HF	0.710	Lognormal	NICE OA model (17)
Post symptomatic ulcer	0.980	Lognormal	NICE OA model (17)
Post complicated GI events	0.980	Lognormal	NICE OA model (17)
Post stroke	0.706	Lognormal	NICE OA model (17)
Post MI	0.880	Lognormal	NICE OA model (17)
Post HF	1.000	Lognormal	NICE OA model (17)
Post treatment	0.989	Lognormal	NICE OA model (17)

The maintenance costs of symptomatic ulcer and complicated GI events were calculated by multiplying the cost of the initial state by the recurrence rate. The recurrence rates were 2.33% (23) and 1.59% (24) for symptomatic ulcer and complicated GI events in each cycle, respectively. OA, osteoarthritis; AEs, adverse events; GI, gastrointestinal; MI, myocardial infarction; HF, heart failure; NICE, National Institute for Health and Care Excellence.

patients taking topical diclofenac to manage OA due to AEs, the cost of topical diclofenac was considered. The RMB exchange rate against the USD was 100:689.85 in 2019 (25), and all costs were adjusted to 2019 based on the exchange rate.

Update with Chinese transition probabilities

The incidence of AEs with celecoxib was extracted from the NICE OA model. Because imrecoxib is a new drug which was not included in the guidelines, the relative incidences of AEs with imrecoxib and celecoxib were extracted from the literature. The doses for celecoxib and imrecoxib were reported to be 200 mg once a day (200 mg QD) and 100 mg two times a day (100 mg BID) (14), respectively. The incidence rates of AEs of the drugs were adjusted, and it was assumed that the AE rate reduction had a relative incidence of half the dose reduction (16). The mortality rates were updated with data from the Chinese population. The observation period of the rate in the literature might not have been completely consistent with the period divided in the model, therefore, the probability was obtained by adjusting the instantaneous rate, and the formula was as follows: $r=-[\ln(1-P1)]/t1$, $P2=1-\exp(-rt2)$, where r represents the instantaneous rate, P1 represents the rate observed in the literature during the specific period, P2 is the probability needed in the model, t1 is the time of observation in the literature, and t2 is the time of each cycle set in the study (t2=3 months in this study) (26).

Statistical analysis

In the base-case analysis, the simulation was carried out for 100 cycles with 3 months in each cycle. Cohort simulation with 10,000 patients per cycle was performed. In the sensitivity analysis, both deterministic sensitivity analysis (DSA) and probability sensitivity analysis (PSA) were performed to validate the robustness of the model. In the DSA, discount rate was performed according to its preset range: 0–8% (18). Cost, utility, and transition probabilities were set up ±50% for sensitivity analysis. In order to study the robustness of model outputs when multiple research variables changed simultaneously according to their corresponding distributions, PSA was

Table 2 Incremental cost-effectiveness ratio

Items	Imrecoxib	Celecoxib
Total costs ($)	1,169.40	1,116.34
Total QALYs	5.62	5.60
Cost per QALY gained (imrecoxib *vs.* celecoxib)	3,041.14	

QALYs, quality-adjusted life years.

carried out using a Monte Carlo approach with 10,000 iterations (16). Beta distribution was applied for utilities and transition probabilities, gamma distribution was applied for costs, lognormal distribution was applied for relative risk, and uniform distribution was applied for mortality rate. Estimates for which distributional information was unavailable were assumed to have lower and upper bounds of 95% confidence intervals equal to 50–150% of base case values (27) (*Table S1*).

TreeAge Pro Healthcare software was used to build and analysis the simulation model.

The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. This study was approved by the institutional review board of Zhejiang University School of Public Health (No. 20180923). Participants were given informed consent before taking part. All procedures performed in this study involving human participants were in accordance with the Declaration of Helsinki (as revised in 2013).

Results

Incremental cost-effectiveness ratio (ICER)

In the base case analysis, a 6-month treatment duration and patients aged 55 years old and above were applied. A lifetime time horizon was adopted, and it was demonstrated that treatment with imrecoxib resulted in costs of $1,169.40 and benefits of 5.62 QALYs, while celecoxib resulted in costs of $1,116.34 and benefits of 5.60 QALYs. Compared to treatment with celecoxib, treatment with imrecoxib was associated with an increase in costs of $53.06 and an increase in benefits of 0.02 QALYs, resulting in an ICER of $3,041.14 (*Table 2*).

Parameters influencing the ICER

After performing DSA, the results showed that the relative risk of MI, the cost of imrecoxib, and the utility of OA patients without any AEs were the main factors influencing the ICER of imrecoxib compared with celecoxib (*Figure S1*). All ICERs of imrecoxib *vs.* celecoxib were below $25,000, and most of them were below $10,000 (*Figure S1*). A further one-way sensitivity analysis was carried out, varying drug costs and relative incidence rates of AEs with imrecoxib and celecoxib (*Figures 1*,*2*). Different scenarios were carried out by varying the start age from 55 to 65 years old, and treatment duration from 6 to 24 months. It was found that ICERs were similar to the base case results, and the ICERs of imrecoxib *vs.* celecoxib varied from $2,814.97 to $3,918.35 (*Table 3*).

Probabilistic representation of uncertainty

PSA showed that there were more plots to the right of the threshold of $30,000 (*Figure 3*). The cost-effectiveness acceptability curve also demonstrated the dominance of imrecoxib, as there was a 59.87% and 59.02% probability of imrecoxib as the more cost-effective drug, at a willingness-to-pay (WTP) of $10,000 and $30,000 per QALY, respectively (*Figure 4*).

Discussion

This analysis assessed the cost-effectiveness of imrecoxib and celecoxib based on the OA model built by the NICE, and an update with Chinese real-world data. Although there was a higher cost of treatment with imrecoxib, a gain in benefit was found when compared to treatment with celecoxib. Treatment with imrecoxib was supposed to be a more cost-effective option compared with celecoxib with the ICER of imrecoxib compared with celecoxib far lower than 1.0 GDP. The relative risk of MI, the cost of imrecoxib, and the utility of OA patients without any AEs were the main drivers of the results of the ICER, which was similar to Brereton *et al.*'s findings (8), while the main driver in the NICE model was the risk of stroke (16). The increased

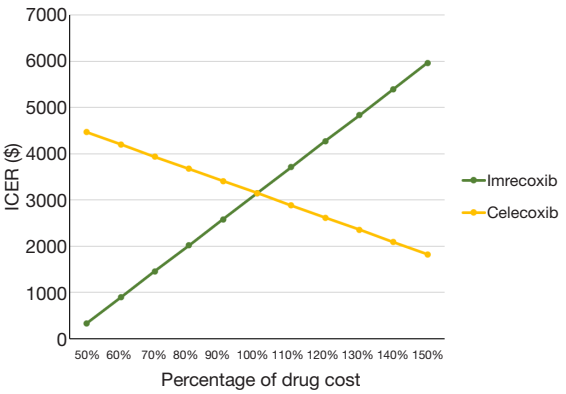

Figure 1 Sensitivity analysis varying drug cost. ICER, incremental cost-effectiveness ratio.

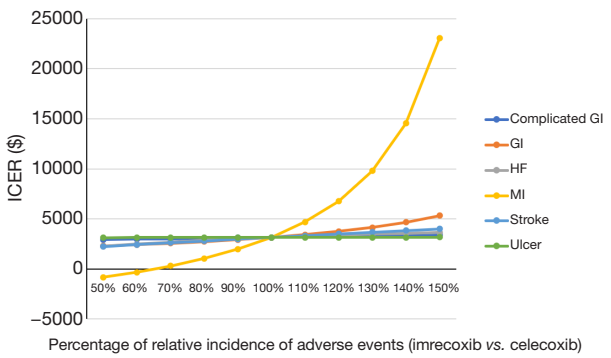

Figure 2 Sensitivity analysis varying the relative incidence of adverse events. ICER, incremental cost-effectiveness ratio; GI, gastrointestinal; HF, heart failure; MI, myocardial infarction; ICER, incremental cost-effectiveness ratio.

cost of imrecoxib drives the advantage of treatment with celecoxib, and vice versa. After varying the costs of the 2 drugs, the result was unchanged in that imrecoxib was the more cost-effective drug. In regards to the relative incidence of AEs with imrecoxib and celecoxib, the relative incidence of complicated GI events, ulcer, GI discomfort, stroke, and HF did not affect the results significantly, while the relative incidence of MI did affect the results significantly. In most cases, the results stayed robust, and all the ICERs were below $30,000. The decrease in the relative incidence of MI favored treatment with imrecoxib. In addition to DSA, PSA was also performed to validate the robustness of the model, which is part of the reference case for technology submissions to the NICE (26,28). The results of PSA also showed that imrecoxib was the more cost-effective drug when the parameters varied according to preset distributions, with the threshold of $10,000. This was lower than the WHO-recommended ICER acceptability threshold of 1-time per capita GDP (which was $10,276.44 in 2019) (25). The results of PSA validate the conclusions of this study, and should be paid attention to when adopting the conclusions.

Imrecoxib was first developed in 1997, and during development, the withdrawal of rofecoxib reminded developers that the value of IC_{50} COX-1/IC_{50} COX-2 should remain under control (10). Because a higher risk would have been brought by over-inhibition, moderate inhibition was advised, and the value of IC_{50} COX-1/IC_{50} COX-2 was limited to 2–30 (10). In addition to safety, similar efficacy to celecoxib was also required when developing the new COX-2 inhibitor. From the perspectives of both safety and efficacy, imrecoxib was finally selected among several choices. The value of IC_{50} COX-1/IC_{50} COX-2 of imrecoxib was 6.39, which was 77% of that of celecoxib, demonstrating that imrecoxib was more likely to have a lower incidence of AEs compared with celecoxib (11,29), which could have also accounted for the lower relative incidence of several AEs adopted in this study. Nowadays, according to the list of national basic insurance drugs, imrecoxib is a second-line drug for managing OA (30), which challenges its wider application. Although there were uncertainties in the results of this study, considering the long-term cost-effectiveness of imrecoxib as a definite possibility, relevant departments can also take imrecoxib into consideration.

As with other economic models, as well as the original NICE OA model, there are some limitations. First, the relative incidences of several AEs of different treatments were extracted from randomized controlled trials (RCTs), and there was a lack of pooling of observational data, which was also a limitation in the original model. Given this uncertainty, sensitivity analysis varying the relative incidence of AEs was performed in this study to validate the robustness of the model. Second, utility data was extracted from the original model due to a lack of utility data in the Chinese population. There is uncertainty regarding whether the values represent the Chinese population entirely, which also suggests that the Chinese local utilities system of these diseases can be built into further studies, and this can be useful for the development of pharmacoeconomic in China. Lastly, as in the original model, there were also some assumptions in the model which might have increased

Table 3 Sensitivity results varying age and treatment duration

Start age	Treatment duration (months)	ICER (imrecoxib *vs.* celecoxib, $)
55	12	3,759.13
	24	2,814.97
65	6	3,164.79
	12	3,918.35
	24	3,373.14

ICER, incremental cost-effectiveness ratio.

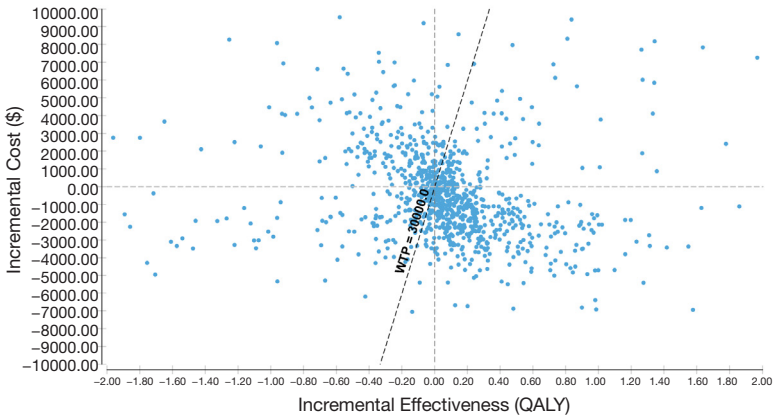

Figure 3 Cost-effectiveness plane. QALYs, quality-adjusted life years.

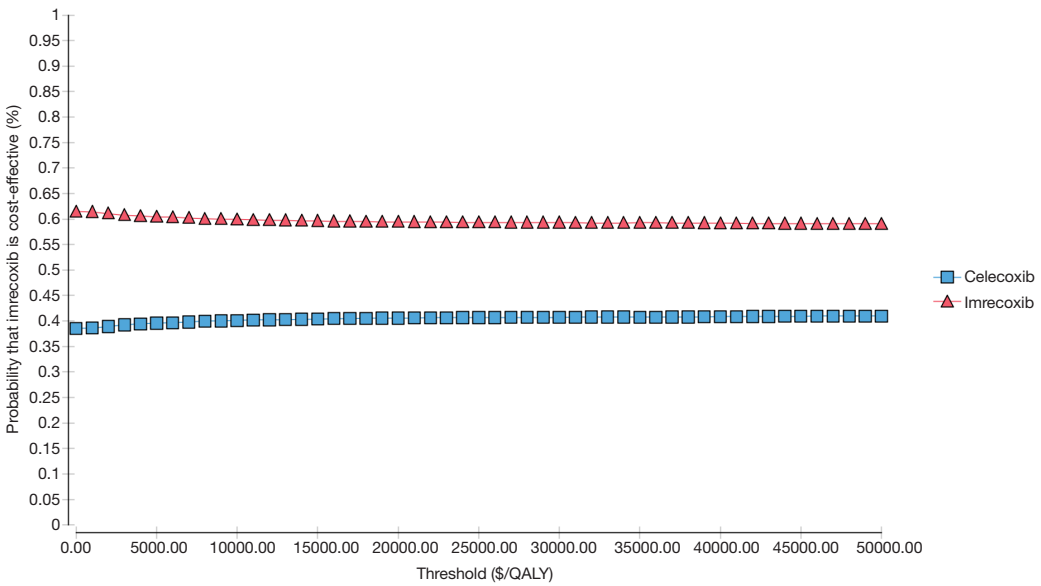

Figure 4 Cost-effectiveness acceptability curve. QALYs, quality-adjusted life years.

uncertainties in this study. In order to decrease the potential uncertainties caused by these assumptions, both DSA and PSA were carried out.

Conclusions

Our results showed that, over a lifetime time horizon, although there were uncertainties in this model, treatment with imrecoxib was more cost-effective compared to celecoxib. The key drivers of the model were the relative risk of MI, the cost of imrecoxib, and the utility of OA patients without any AEs. To our knowledge, this study was the first analysis based on real-world data to assess the cost-effectiveness of imrecoxib and celecoxib. These results provide a good reference for relevant stakeholders when managing OA.

Acknowledgments

We would like to thank Shanghai Su-Value Health Scientific Ltd., Shanghai, China, for their great support with the Su-Value Database. We gratefully acknowledge the significant efforts of Shiming Sun and Shaofeng Xue. We also thank Shuyan Gu, Can Zhao, Qilong Gao, and Kaijie Liu for their great help.
Funding: None.

Footnote

Reporting Checklist: The authors have completed the CHEERS reporting checklist. Available at http://dx.doi.org/10.21037/atm-21-290

Data Sharing Statement: Available at http://dx.doi.org/10.21037/atm-21-290

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/atm-21-290). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. This study was approved by the institutional review board of Zhejiang University School of Public Health (No. 20180923). Participants were given informed consent before taking part. All procedures performed in this study involving human participants were in accordance with the Declaration of Helsinki (as revised in 2013).

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Cite this article as: Sun X, Zhen X, Hu X, Li Y, Gu S, Gu Y, Zhao Z, Yang W, Dong H. Cost-utility analysis of imrecoxib compared with celecoxib for patients with osteoarthritis. Ann Transl Med 2021;9(7):575. doi: 10.21037/atm-21-290

Supplementary

Table S1 Distributional information for model inputs

Variables name	Distribution	Estimate	a	b	SE	95% CI	
						Lower	Upper
Cost-imrecoxib	Gamma	19.8900			5.0740	9.9450	29.8350
Cost-celecoxib	Gamma	9.3200			2.3776	4.6600	13.9800
Cost-topical diclofenac	Gamma	20.3000			5.1786	10.1500	30.4500
Cost-managing OA without any drugs	Gamma	26.5000			6.7602	13.2500	39.7500
Cost-GI	Gamma	10.5200			2.6837	5.2600	15.7800
Cost-ulcer	Gamma	34.5700			8.8189	17.2850	51.8550
Cost-complicated GI events	Gamma	1,354.1500			345.4464	677.0750	2031.2250
Cost-stroke	Gamma	1,289.9200			329.0612	644.9600	1934.8800
Cost-MI	Gamma	5,190.9300			1324.2168	2595.4650	7786.3950
Cost-HF	Gamma	1,182.3300			301.6148	591.1650	1773.4950
Cost-post ulcer	Gamma	0.8100			0.2066	0.4050	1.2150
Cost-post complicated GI events	Gamma	21.5400			5.4949	10.7700	32.3100
Cost-post stroke	Gamma	619.5900			158.0587	309.7950	929.3850
Cost-post MI	Gamma	948.4700			241.9566	474.2350	1422.7050
Cost-post HF	Normal	451.2900			115.1250	225.6450	676.9350
Probability-celecoxib-GI	Beta	0.1245	775.0125	3,466.9875		0.0623	0.1868
Probability-celecoxib-ulcer	Beta	0.0009	5.6025	4,236.3975		0.0005	0.0014
Probability-celecoxib-complicated GI events	Beta	0.0005	3.1125	4,238.8875		0.0003	0.0008
Probability-celecoxib-stroke	Beta	0.0002	1.2450	4,240.7550		0.0001	0.0003
Probability-celecoxib-MI	Beta	0.0015	9.3375	4,232.6625		0.0008	0.0023
Probability-celecoxib-HF	Beta	0.0004	2.4900	4,239.5100		0.0002	0.0006
Probability-general-death (age years=55-64)	Uniform	0.0037				0.0019	0.0056
Probability-general-death (age years=65-74)	Uniform	0.0094				0.0047	0.0141
Probability-general-death (age years=75-80)	Uniform	0.0267				0.0134	0.0401
Probability-complicated GI events-death	Uniform	0.0951				0.0476	0.1427
Probability-post complicated GI events-death	Uniform	0.0277				0.0139	0.0416
Probability-stroke-death	Uniform	0.0323				0.0162	0.0485
Probability-post stroke-death	Uniform	0.0046				0.0023	0.0069
Probability-HF-death	Uniform	0.0495				0.0248	0.0743
Probability-post HF-death	Uniform	0.0017				0.0009	0.0026
Probability-MI-death	Uniform	0.0428				0.0214	0.0642
Probability-post MI-death	Uniform	0.0045				0.0023	0.0068
Probability-COX-2-withdraw	Beta	0.1120	446.5440	3,540.4560		0.0560	0.1680
Utility-OA patients with treatment of COX-2	Beta	0.1806			0.0461	0.0903	0.2709
Relative risk-GI-imrecoxib *vs.* celecoxib	Lognormal	0.4900				0.2450	0.7350
Relative risk-ulcer-imrecoxib *vs.* celecoxib	Lognormal	1.3400				0.6700	2.0100
Relative risk-complicated GI events-imrecoxib *vs.* celecoxib	Lognormal	0.5000				0.2500	0.7500
Relative risk-stroke-imrecoxib *vs.* celecoxib	Lognormal	1.0000				0.5000	1.5000
Relative risk-MI-imrecoxib *vs.* celecoxib	Lognormal	1.0000				0.5000	1.5000
Relative risk-HF-imrecoxib *vs.* celecoxib	Lognormal	1.0000				0.5000	1.5000
Relative risk-utility-GI	Lognormal	0.7330				0.3665	1.0995
Relative risk-utility-withdraw due to GI	Lognormal	0.9890				0.4945	1.4835
Relative risk-utility-ulcer	Lognormal	0.5520				0.2760	0.8280
Relative risk-utility-post ulcer	Lognormal	0.9800				0.4900	1.4700
Relative risk-utility-complicated GI events	Lognormal	0.4590				0.2295	0.6885
Relative risk-utility-post complicated GI events	Lognormal	0.9800				0.4900	1.4700
Relative risk-utility-stroke	Lognormal	0.3480				0.1740	0.5220
Relative risk-utility-post stroke	Lognormal	0.7060				0.3530	1.0590
Relative risk-utility-MI	Lognormal	0.3740				0.1870	0.5610
Relative risk-utility-post MI	Lognormal	0.8800				0.4400	1.3200
Relative risk-utility-HF	Lognormal	0.7100				0.3550	1.0650
Relative risk-utility-post HF	Lognormal	1.0000				0.5000	1.5000
Relative risk-utility-post treatment	Lognormal	0.9890				0.4945	1.4835
Relative risk-risk of bleeding/ulcer (aged 65) *vs.* (aged 55)	Lognormal	2.9600				1.4800	4.4400
Relative risk-risk of CV (aged 65) *vs.* (aged 55)	Lognormal	1.9400				0.9700	2.9100

OA, osteoarthritis; COX-2, cyclooxygenase; GI, gastrointestinal; HF, heart failure; MI, myocardial infarction; CV, cardiovascular diseases.

http://dx.doi.org/10.21037/atm-21-290

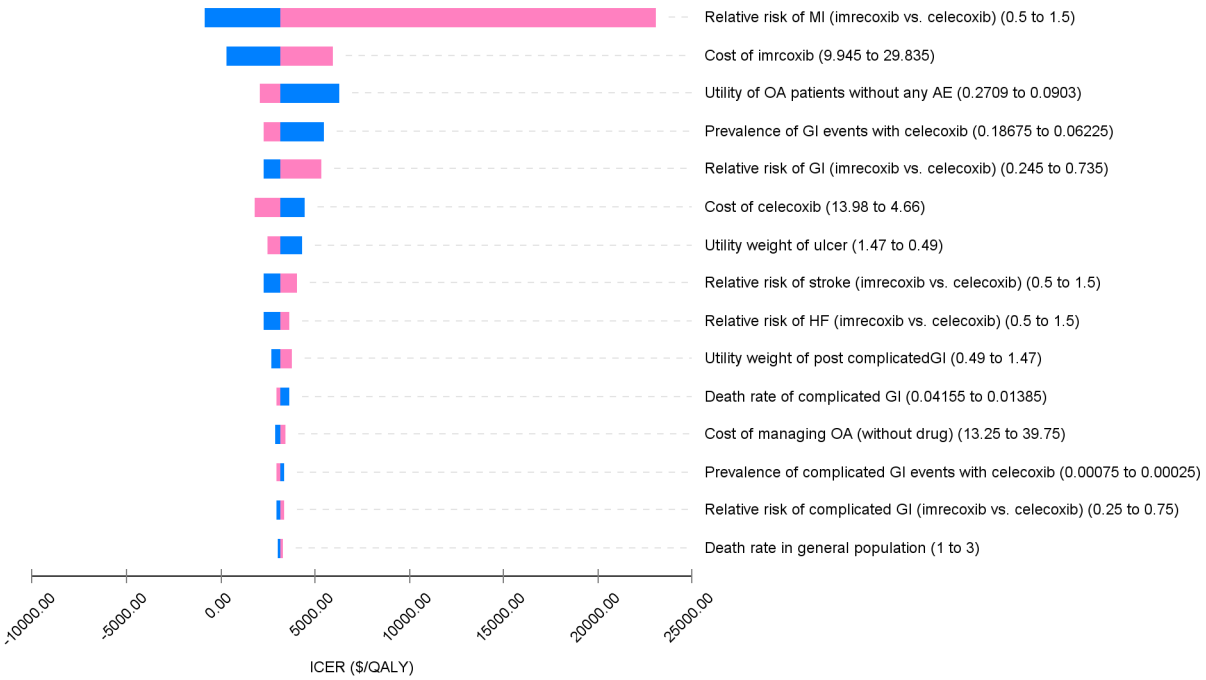

Figure S1 The tornado diagram (imrecoxib versus celecoxib). OA, osteoarthritis; GI, gastrointestinal; HF, heart failure; MI, myocardial infarction.

http://dx.doi.org/10.21037/atm-21-290