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A Cost-Effectiveness Analysis between Amlodipine and Angiotensin II Receptor Blockers in Stroke and Myocardial Infarction Prevention among Hypertension Patients in China

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ABSTRACT

Objective: Uncontrolled hypertension (HTN) results in strokes, myocardial infarction (MI), and other complications, which are the leading cause of disability, death, and severe economic consequence. We conducted an economic evaluation to determine the costs and quality-adjusted life-years (QALYs) associated with amlodipine (Norvasc) and the angiotensin II receptor blockers (ARBs) in preventing stroke and MI among Chinese HTN patients. **Methods:** A cost-utility analysis was conducted from the third-party payer perspective. A Markov model was constructed to estimate 5-year costs and health consequences of amlodipine and valsartan. Effectiveness data were based on a published meta-analysis. Utility data were retrieved from the published literature. Costs of MI were retrieved from China Health Statistics Yearbook. Costs of stroke were obtained from retrospective chart review and follow-up interviews in Chinese tertiary hospitals. Costs included costs of drugs, direct medical costs of HTN management, stroke/MI treatment, and follow-up management. Discounting rate used for costs and QALYs was 3%. **Results:** Total direct medical and drug costs of amlodipine and valsartan (ARB) users were ¥111,731,716 and ¥132,058,611, respectively; total QALYs of amlodipine and valsartan users were 30,648.5 and 30,520.8, respectively. Amlodipine is dominant with lower costs and higher QALYs. This demonstrated that compared with valsartan, amlodipine is a cost-saving therapy with better QALY outcome. When irbesartan data were used in the comparison, the magnitude of cost saving changed but the overall conclusion remained the same. **Conclusion:** Amlodipine is a cost-saving therapy compared with ARBs in preventing stroke and MI for Chinese HTN patients.

Keywords: amlodipine, angiotensin II receptor blockers, China, cost-effectiveness, hypertension, irbesartan.

Introduction

Hypertension (HTN), or high blood pressure, now defined as systolic blood pressure of more than 140 mm Hg and diastolic blood pressure of more than 90 mm Hg, is attributed as the leading cause of cardiovascular mortality by the World Health Organization. In 2000, it was estimated that 972 million adults or 26.4% of the adult population had HTN worldwide [1]. The number of adults with HTN in 2025 is predicted to increase by 60% to 1.56 billion [2]. In China, there were approximately 153 million people with HTN in 2005, leading to 1.27 million premature deaths from cardiovascular diseases and more than 2 million deaths in total [2]. Among Chinese people with HTN, approximately 19% received pharmacological treatment, but only about 25% of the treated patients had their blood pressure well controlled [3]. The direct medical cost of HTN was ¥20.2 billion, according to 2003 National Health Services Survey [4].

Uncontrolled HTN may result in various complications (e.g., strokes, heart failure, myocardial infarction [MI], and peripheral vascular disease), which are the major causes of morbidity and mortality. About 54% of stroke, 47% of ischemic heart disease, and 25% of other cardiovascular diseases worldwide were caused by elevated blood pressure [5]. In East Asia and the Pacific, deaths and disability-adjusted life-years of hypertensive patients attributed to stroke were the highest among all cardiovascular end points [5]. The incidence of stroke increases in proportion to both systolic and diastolic blood pressures. Most ischemic strokes occur in individuals with pre-HTN or stage 1 HTN [6]. The incidence of ischemic or hemorrhagic stroke is reduced substantially by adequate treatment of HTN [6]. A slight reduction in blood pressure over a time period of 3 to 4 years among moderately complicated hypertensive patients lowers the incidence of all cardiac events by 35% [7].

Conflict of Interest: The authors have indicated that they have no conflicts of interest with regard to the content of this article.

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Across the world, stroke is considered the second leading cause of death, responsible for 4.4 million (9%) of the total 50.5 million deaths each year [8]. In China, recent epidemiologic studies confirmed that stroke was the leading cause of adult disability, and the second commonest cause of death, with an incidence more than fivefold that of MI [9]. The direct medical cost of stroke was ¥24.3 billion, according to 2003 National Health Services Survey [4]. HTN is the single most important risk factor for all types of strokes including both ischemic and hemorrhagic [10]. The association between high blood pressure and stroke has been evident for many years. Meta-analysis of randomized controlled trials showed that lowering of blood pressure was associated with a 30% to 40% reduction in stroke risk [11]. To prevent the future occurrence of stroke among hypertensive patients, it is critical to keep blood pressure under good control with effective pharmacological treatments.

There are many classes of antihypertensive drugs in the market with different mechanisms of action. Among the most important and most widely used are the thiazide diuretics, the angiotensin-converting enzyme inhibitors , the calcium channel blockers (CCBs), the beta blockers, and the angiotensin II receptor blockers (ARBs). ARBs, such as losartan and valsartan, are a newer and safer class of antihypertensive agents. They are primarily used for the treatment of HTN when the patient is intolerant of angiotensin-converting enzyme inhibitor therapy, because of their affirmative efficacy and better tolerance. Clinical trial data showed that ARBs did not adversely affect kidney function, even in the presence of chronic renal insufficiency [12]. Because of their short half-lives, however, many of the ARBs may require twice-daily dosing in some patients to keep the blood pressure under control, which would substantially increase the cost [12].

CCBs is another widely used type of antihypertensive. They account for approximately 60%, with an upward trend of all antihypertensive drugs prescribed by clinicians [13–15]. Dihydropyridine CCBs, for example, amlodipine (Norvasc) and aranidipine, make up more than 85% of all CCBs prescribed [16]. Their advantages over other types of antihypertensive drugs include good tolerance and lack of withdrawal syndrome. They can also be taken together with drugs from other groups such as antibiotics, nonsteroidal anti-inflammatory drugs, and glucose-lowering drugs. CCBs are especially suitable for the treatment of senior hypertensive patients with stable angina pectoris or diabetes mellitus. By using CCBs, the risk of fatal stroke can be reduced by 44% to 55% and the risk of stroke-related dementia can be reduced by 50% [17]. Compared with all the other antihypertensive drugs, CCBs have the lowest drug discontinuation and switching [14].

Norvasc (amlodipine besylate), the besylate salt of amlodipine, is a long-acting CCB of the third generation. It is the most frequently prescribed drug in the CCB group, because of a number of its favorable pharmacodynamic and pharmacokinetic properties: high bioavailability, long half-life, and longer duration of action, which allows patients to take the medication once daily. During treatment with Norvasc in hypertensive patients of different degrees of severity, the risk of cardiovascular events, including the development of cerebral circulatory disorders, gradually decreases [18].

In a meta-analysis, Wang et al. [19] demonstrated that Norvasc is superior to ARBs in the prevention of stroke and MI in HTN patients. On the basis of the results from that analysis, we conducted an economic evaluation to determine the long-term cost-effectiveness of Norvasc from the payer perspective given its association with the reduction in stroke events and associated averted costs when compared with ARBs. In addition, the quality-adjusted life-years (QALYs) gained under each therapeutic strategy was estimated over a 5-year period.

Methods

Overview

Using Excel, a Markov model was constructed to conduct the cost-effectiveness analysis comparing Norvasc and the ARBs. The model evaluated a population of HTN patients in the Chinese setting.

We conducted a thorough review on inpatient cost, cost of home health care, rehabilitation costs after discharge, and indirect cost associated with stroke and MI treatment. Given the limited cost data available in the literature, a retrospective chart review of patients with stroke in three tertiary Chinese hospitals and a follow-up telephone interview on the patients after discharge were carried out to determine the acute hospitalization costs associated with stroke and 1-year follow-up costs poststroke hospitalization discharge.

Clinical data were obtained from the meta-analysis study by Wang et al. [19], studies cited by Wang et al., and the retrospective chart review in the three tertiary Chinese hospitals.

The analysis was conducted from the perspective of the third-party health care payer, with costs expressed in 2011-2012 prices. Costs and outcomes were discounted at 3% per year.

Model Structure

A cost-effectiveness analysis based on Markov model was constructed to explore the economic benefits and QALY gained

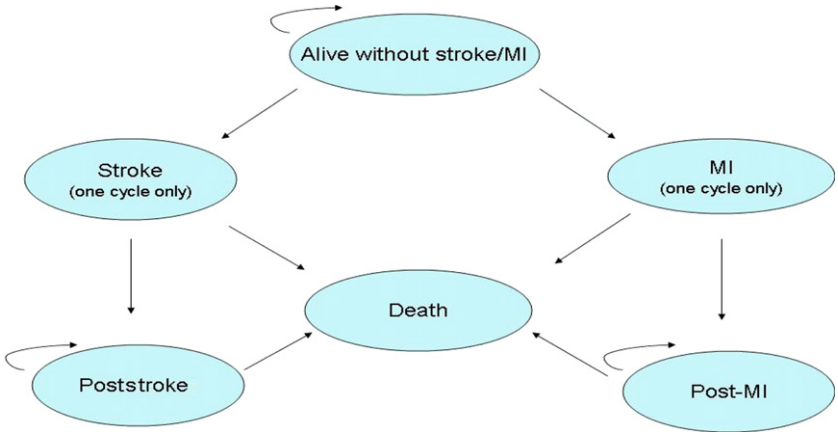

Fig. 1 – Structure of the Markov model. MI, myocardial infarction.

Table 1 – Summary of input parameters applied in the base-case model.

Variables	Value	Source
Baseline patient characteristics		
Age (y)	65	Assumption
Sex	50% men	Assumption
Stroke risk		
Male ARB users	11.3/1,000 PY	[22] (Estimated on the basis of the incidence rate and gender distribution in the VALUE trial, and gender-specific risk ratio in the Chinese population)
Female ARB users	8.2/1,000 PY	[22] (Estimated on the basis of the incidence rate and gender distribution in the VALUE trial, and gender-specific risk ratio in the Chinese population)
Relative risk for stroke (amlodipine vs. ARBs)	0.84	[19]
MI risk		
Male ARB users	15.1/1,000 PY	[22] (Estimated on the basis of the incidence rate and gender distribution in the VALUE trial, and gender-specific risk ratio in the Chinese population)
Female ARB users	6.1/1000 PY	[22] (Estimated on the basis of the incidence rate and gender distribution in the VALUE trial, and gender-specific risk ratio in the Chinese population)
Relative risk for MI (amlodipine vs. ARBs)	0.83	[19]
Mortality risk		
Among stroke events	27.2%	[20]
Among MI events	6.3%	[21]
Stroke survivors vs. general population	2.3	[20]
MI survivors vs. general population	2.3	[21]
Annual cost of each health state		
Alive without MI/stroke	¥100.00	Based on the telephone follow-up on patients discharged from x tertiary hospitals
Fatal stroke	¥11,836.30	Based on the telephone follow-up on patients discharged from x tertiary hospitals
Nonfatal stroke (year 1)	¥35,479.50	Based on the telephone follow-up on patients discharged from x tertiary hospitals
Poststroke (year 2+)	¥3,547.95	Assume 10% of year 1 cost
MI (year 1, fatal or nonfatal)	¥26,422.35	[23] (assuming 50% surgery and 50% nonsurgery treatment)
Post-MI (year 2+)	¥2,642.24	Assume 10% of year 1 cost
ARBs annual cost (valsartan)	¥2,388.00	[24]
Amlodipine annual cost	¥1,987.00	[24]
Other-cause death	¥1,000.00	Estimation
Quality of life of each health state		
Alive without MI/stroke (55–59 y, male)	0.77	[25]
Alive without MI/stroke (55–59 y, female)	0.75	[25]
Alive without MI/stroke (60–64 y, male)	0.75	[25]
Alive without MI/stroke (60–64 y, female)	0.73	[25]
Alive without MI/stroke (65–69 y, male)	0.73	[25]
Alive without MI/stroke (65–69 y, female)	0.70	[25]
Alive without MI/stroke (70–74 y, male)	0.70	[25]
Alive without MI/stroke (70–74 y, female)	0.69	[25]
Nonfatal stroke (year 1)	0.50	[26]
Poststroke (year 2+)	0.63	[26]
Nonfatal MI (year 1)	0.70	[26]
Post-MI (year 2+)	0.80	[26]
Annual discount rate		
On costs	3%	
On QALYs	3%	

ARB, angiotensin II receptor blocker; MI, myocardial infarction; PY, person year; QALY, quality-adjusted life-year.

Table 2 – Age-specific mortality rate in general Chinese population [21].

Age (y)	Mortality	
	Men (%)	Women (%)
55–59	1.06	0.66
60–64	1.79	1.14
65–69	2.96	1.91
70–74	5.10	3.41

Table 3 – Results of base-case analysis comparing ARBs and amlodipine over 5-y time horizon.

	Total cost (¥)	Total QALY
Amlodipine (Norvasc)	105,757,181.9	29,019.4
ARBs	125,021,803.2	28,900.7
Difference	−19,264,622.3	118.7

ARBs, angiotensin II receptor blockers; QALY, quality-adjusted life-year.

associated with the stroke and MI prevention when Norvasc was used in comparison with ARBs. The Markov model considered costs and outcomes within 5 years by using annual cycles. We chose the time span of 5 years given that social security authorities at provincial or municipal governments in China use that as their frame for budget planning. Six health states were defined in the model: alive without stroke/MI, stroke, poststroke, MI, post-MI, and death (Fig. 1). The model was based on 10,000 patients in the amlodipine and ARBs arms, respectively.

The model was populated with the following data: 1) incidence of stroke and MI in the general HTN population, amlodipine-treated population, and ARBs-treated population; 2) costs of clinical management of HTN and its associated outcomes; 3) costs of drugs and drug-associated side effects; 4) unit costs of stroke and MI acute treatment and the costs of long-term follow-up; and 5) other relevant data required for the model.

Model Inputs

Baseline event rates

A meta-analysis study by Wang et al. [19] examined the effects of amlodipine or ARBs in the prevention of stroke and MI in patients with HTN, coronary artery disease, or diabetic nephropathy. The study included 12 trials of 94,338 patients. Compared with ARBs, amlodipine reduced the incidence of stroke and MI by 16% and 17%, respectively, with better blood pressure control. Mortality risk in stroke or MI survivors is 2.3 times higher than that in the general population [20,21]. The rates are presented in Table 1. Mortality risk in the general Chinese population by age group is presented in Table 2 [27]. It is assumed that the risk of stroke or MI and the mortality risk in each year of the 5-year time period will be the same.

Resource use and costs

Costs of managing MI hospitalization and follow-up medical care cost during year 1 were obtained from China Health Statistics Yearbook 2010, assuming 50% surgery and 50% nonsurgery treatment (Table 1). For the costs of stroke management, we identified 80 recent patients with stroke in three Chinese tertiary hospitals to conduct a retrospective chart review project to document the costs associated with the clinical management of stroke during hospitalization. A detailed data exaction form was designed to retrieve the data. In addition, telephone interviews were conducted to identify the follow-up costs associated with stroke management and recovery following hospital discharge during year 1. The costs of managing MI or stroke survivors from years 2 to 5 were assumed to be 10% of that of year 1.

Quality-of-life adjustment

To estimate QALYs, it was necessary to apply utility value to adjust the quality for the average period of time of survival within the time span of the model, using an appropriate utility or preference score. We used the utility measured in a 2008 survey in China for elderly population living without stroke or MI (Table 1) [25]. Utility scores of poststroke or post-MI patients were based on the values provided in a review study by Ara et al. (Table 1) [26]. As shown in Table 1, different utility scores were used for different age groups without stroke or MI; different utility scores were used for the first year of a stroke or MI event and the years after that.

Table 4 – Total discounted cost, quality-adjusted life-years (QALYs), and incremental cost-effectiveness ratios (ICERs) for the sensitivity analyses in 2011–2012 Chinese yuan.

	Total cost (¥)		Total QALYs		ICER
	Amlodipine	ARBs	Amlodipine	ARBs	
Base case	105,757,180.9	125,021,803.2	29,019.4	28,900.7	Dominant
ARB irbesartan (¥1950)	105,757,180.9	107,837,911.9	29,019.4	28,900.6	Dominant
Gender males 30%	104,192,276.6	123,062,115.9	29,069.8	28,944.9	Dominant
Gender males 40%	104,992,424.7	124,039,783.0	29,039.4	28,929.3	Dominant
Gender males 60%	106,625,875.8	125,996,463.8	28,995.5	28,870.4	Dominant
Gender males 70%	107,439,945.0	126,847,406.7	28,910.1	28,838.8	Dominant
Cohort age at 55 y	109,838,524.0	129,859,467.0	32,485.5	32,353.9	Dominant
Cohort age at 60 y	108,270,116.4	127,983,091.7	30,930.2	30,803.7	Dominant
Cohort age at 70 y	101,297,725.0	119,685,447.8	26,721.9	26,623.6	Dominant
Discount 1%	113,798,954.4	134,493,297.9	30,084.3	29,959.7	Dominant
Discount 2%	109,642,802.1	129,598,341.9	29,541.6	29,420.0	Dominant
Discount 4%	102,120,670.3	120,738,479.1	28,516.6	28,400.5	Dominant
Discount 5%	98,713,797.6	116,725,458.3	28,032.2	27,918.9	Dominant
Discount 6%	95,518,840.8	112,961,888.7	27,565.5	27,454.7	Dominant
Discount 7%	92,519,652.9	109,428,770.9	27,115.5	27,007.2	Dominant
Discount 8%	89,701,505.4	106,108,774.5	26,681.5	26,575.6	Dominant

Analytical Methods

The base-case analyses were undertaken for a cohort at the age of 65 years, and 50% were men, using valsartan's cost (¥2388 annually) as the ARB comparator.

A deterministic model was run with the value inputs of all necessary parameters. The total costs in the ARB and amlodipine arms during the 5-year time period were calculated and compared. Separately, QALYs in the ARB and amlodipine arms during the 5-year time period were calculated and compared.

Results

Base-Case Analysis

Table 3 presents the base-case results for the duration of 5 years. Amlodipine is dominant compared with ARBs. Total costs of the amlodipine arm are ¥20,326,895.3 lower than those of the ARBs arm, which is ¥2,032.7 lower per patient. QALYs of the amlodipine arm are 127.8 (QALY) higher than those of the ARBs arm.

Alternative Scenarios

A series of sensitivity analyses was conducted to explore the impact of alternative assumptions on the incremental cost-effectiveness ratios for the values of key input parameters. The following parameters and ranges were tested:

1. Comparator in the ARB group: Irbesartan's cost (¥1950), which is lower than that of valsartan, is used to replace valsartan;
2. Percentage of male patients: The assumption of 50% was changed to 30%, 40%, 60%, and 70%;
3. Discount rate for cost and QALY: The base-case rate of 3% was changed to 1%, 2%, 4%, 5%, 6%, 7%, and 8%.

The results of these analyses are shown in Table 4, which demonstrates that the results are robust to the variables tested, with the most sensitive parameter being the ARB comparator. When irbesartan was used to replace valsartan in the comparison, the cost difference between amlodipine and ARB changed from ¥−19,264,622.3 to ¥−80,731.0. It should also be noted that the total cost was more sensitive than total QALYs to the sensitivity test. For example, when the discount rate was set at 1%, the total cost of the amlodipine arm changed from ¥105,757,180.9 to ¥113,798,954.4 while the total QALYs changed from 29,019.4 to 30,084.3. In conclusion, the cost saved by amlodipine was sensitive to the various ARB comparators; the total cost of both amlodipine and ARB is somewhat sensitive to the change in the discount rate. But in all cases, amlodipine is consistently dominant in all the scenarios, demonstrating the robustness of the results.

Discussion

Recent clinical evidence shows that new CCBs such as amlodipine provide additional benefit than ARBs [19]. No published studies have attempted to formally evaluate the relative cost-effectiveness of amlodipine and ARBs in the Chinese setting. The present study provides the first cost-effectiveness analysis comparing these two most popular classes of antihypertensive medications currently available in the Chinese market.

The study showed that amlodipine is a cost-saving therapy compared with ARBs for the management of HTN with lower long-term cost and higher QALY gained.

This is mainly due to the greater clinical effectiveness of amlodipine compared with ARBs in terms of stroke and MI events. Patients using amlodipine have fewer hospitalizations and invasive surgical procedures in both short and long term. It is noted that the total cost was more sensitive than total QALYs during sensitivity analyses. Although the cost saved by amlodipine varied when compared with different ARB comparators and with different discount rates, amlodipine is dominant in all the scenarios. If more expensive ARB comparators (e.g., losartan) are included in the model, amlodipine will still be dominant and the cost saved with amlodipine will be even higher. Our findings in the Chinese setting are consistent with pharmacoeconomics studies in the US and European settings [28]. The review of those studies suggests that amlodipine had better clinical outcome with cost savings in the long term [28].

Some limitations of this study have been identified. Caution should be taken to extrapolate our findings to the time period longer than 5 years. The above results are subject to the price change of amlodipine and/or ARBs. It should be noted that the cost estimation of stroke management was based on patients from the Chinese tertiary hospitals. The generalizability of the findings to lower-tier hospitals should be examined in future studies. Last, we did not include patients with both MI and stroke in the model because of the lack of risk data; this may limit the generalizability of this study. Given the complexity and higher cost in managing such patients, however, the inclusion of such patients is likely to show more cost saved by amlodipine.

Conclusions

The present study found that compared with ARBs, amlodipine provides better quality of life over the 5-year time period projected. From a Chinese payer perspective, amlodipine is a cost-saving therapy when compared with ARBs by lowering the costs needed to manage acute stroke and MI episodes and related long-term recovery.

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