Cost-Effectiveness Analysis of Atrial Fibrillation Screening for Stroke Prevention in China: A Markov Model

Lihui Zhou

Tianjin Medical University

Ye Cao

Tianjin Medical University

Bei Gao

Tianjin Medical University

Wenli Lu

Tianjin Medical University

Yuan Wang (✉ gw_928@163.com)

Tianjin Medical University

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Abstract

Objectives: To evaluate the cost-effectiveness of community-based Atrial fibrillation (AF) screening by 12-lead electrocardiogram (ECG) in Chinese healthcare setting.

Methods: A Markov state transition model was used to simulate the costs and effects on a 55/65/75-year-old cohort under routine care and AF screening by 12-lead ECG. The circle length was 1 year, and people were simulated until 90 years old. The cost-effectiveness analysis was performed using a societal perspective. Transition probability, costs, and utility data were derived from open dataset and published literature. One-way and probabilistic sensitivity analyses were performed to examine the uncertainty of the results.

Results: Annual AF screening in 65/75-year-old cohort was highly cost-effective with the incremental cost-effectiveness ratio (ICER) Chinese Yuan Renminbi (CNY) 64147/49736 per quality-adjusted life year (QALY) gained. Annual AF screening in 65/75-year-old cohort was associated with 535/492 prevented ischemic strokes and 174/163 more intracerebral hemorrhages, and the anticoagulation rate increased from the assumed 10% on routine care to 61.5%. Probabilistic sensitivity analysis indicated that these two strategies have 55% and 78% chances of being cost-effective at a willingness-to-pay (WTP) threshold of 1× gross domestic product per capita of China in 2019, US \$10635 QALY.

Conclusion: Annual community-based screening of population aged 65 years and older in China is likely to be cost-effective at conventional willingness-to-pay thresholds to reduce the unnecessary burden of strokes.

Introduction

Atrial fibrillation (AF) is the most common arrhythmia in clinical practice, with prevalence increased sharply with age[1]. The mean age of patients with AF is 64.4 ± 12.1 years old[2]. And the lifetime risk of AF was approximately one in five among Chinese adults[3]. AF is associated with an increased risk of stroke, congestive heart failure, cognitive dysfunction, reduced quality of life and all-cause mortality[4]. AF-related stroke patients tend to be more severe and would cost a lot more than non-AF-related stroke[5]. However, studies had shown that AF-induced strokes can be highly prevented by taking anticoagulation medications. And evidences had proved that anticoagulation therapy can reduce approximately 64% of ischemic stroke risk and 26% of all-cause mortality risk, with the side effect of increased risk of bleeding[6]. Guidelines on prevention and treatment of cardiogenic stroke has recommended long-term prophylactic anticoagulation therapy for AF patients with CHA₂DS₂-VASc (congestive heart failure, hypertension, age ≥ 75 years, diabetes mellitus, stroke, vascular disease, age 65–74 years, sex category; scores range from 0 to 9) score ≥ 2 in China and many other countries[7–9].

Some people with AF may experience palpitations, chest pain, dizziness or, in severe cases, loss of consciousness, while 30%–40% of AF patients were without symptoms and therefore lack of awareness and treatment, ischemic stroke was often the first sign of these patients[10]. It has been pointed out previously that screening for AF meets many of the Wilson-Jungner criteria[11, 12]. Several studies had proved that AF screening using both pulse palpation and 12-lead electrocardiogram (ECG), 12-lead ECG only and other types of ECG can detect more new cases as well as be cost-effective[13–17].

In China, atrial fibrillation healthcare centers have been established since 2016. Government has taken more and more emphasis on AF treatment and stroke prevention. However, the anticoagulation rate in AF patients was significantly lower than developed countries, which might cause unnecessary stroke burden[18]. AF screening programs should be launched to identify asymptomatic AF and increase anticoagulation rate. The aim of this study was to perform a cost-effectiveness analysis of community-based AF screening by 12-lead ECG in Chinese healthcare setting.

Methods

Model design

Cost-effectiveness analysis and sensitivity analysis were performed using Markov model, with TreeAge Software (TreeAge Software, Inc., Williamstown, United States of America). The base-case model of this study was a Markov simulation of a hypothetical cohort of 100000 55/65/75-year-old residents underwent annual AF screening by 12-lead ECG compared to routine healthcare. In this study, the model length was 35/25/15 years (1 year circles) for 55/65/75-year-old cohort, respectively, until reaching 90 years old. The half-cycle correction was conducted for quality of life and cost every step in this model.

The base case scenario of this model was as following. A 55/65/75-year-old cohort of 100 000 was assigned to no screen or screen cohort. People at no screening cohort would have a certain group diagnosed with AF when they had symptoms and seek doctor's help or went to hospital for other disease and diagnosed accidentally. People at screening cohort would be diagnosed with AF through screening method, and people who did not participate screening in the screening cohort would have the same chance to be diagnosed AF as people at no screening cohort. Furthermore, biennial and triennial 12-lead ECG screening in 55/65/75-year-old cohort were simulated to see the effect of screen intervals. The parameters used in these models were listed in table 1.

There were 5 independent health states in this model (Fig 1): no event, AF (with treatment & without treatment), ischemic stroke (IS) (with different severity rank), intracerebral hemorrhage (ICH) (disabled and fatal) and death. In one stage, there would be none or one and only clinical event happens. The clinical states could only progress forward and would not improve. AF, IS and ICH were assumed to be chronic diseases and could persist for a long time.

Some assumptions were made in this model. The anticoagulation therapy was warfarin prescription. Studies had proved that warfarin did a great job in IS risk reduction, minimizing the risk of bleeding with better persistence and can be cost effective than new oral anticoagulants (NOACs) [19, 20]. In this model, AF patients who was on warfarin was assumed to be adherence to it. And the AF patients who rejected anticoagulation therapy at diagnosis would never take the medication. Anticoagulation treatment with warfarin need relative frequently international normalized ratio (INR) monitoring in the first month and then INR monitoring monthly in the following long-term treatment. Patients developed with IS would be simulated to be at different disabled states in the acute phase:

mild (modified Rankin Scale [mRS] score, 0–1), moderate (mRS score, 2–3), severe (mRS score, 4–5) and fatal (mRS score, 6), and would die of other causes and stroke after acute phase. And ICH patients were simulated the same way but without severity ranks.

The benefits in this model were risk reduction of ischemic stroke and all-cause mortality, increasing life years and life quality in patients of AF due to early detection and anticoagulation treatment. The costs in this model were expenses on treatment of AF, IS, ICH and screening. According to the Commission on Macroeconomics and Health of the World Health Organization, if the incremental cost-effectiveness ratio (ICER) was less than Chinese Yuan Renminbi (CNY) 70892 (1 gross domestic product [GDP] per capita of China in 2019, US \$10635) per QALY gained, then the screening was considered highly cost-effective, and if the ICER was less than CNY 212676 (3 GDP per capita of China in 2019, US \$31905) per QALY gained, then the screening was cost-effective.

Probabilities and rate

The resources of disease morbidity in this model was from the results of Global Burden of Diseases (GBD) 2019 study, including the incidence of AF, IS, ICH, the prevalence and mortality of AF and all-cause mortality in China. The GBD 2019 is the world's most comprehensive catalog of surveys, vital statistics and other health-related data by the institute for health metrics and evaluation[21, 22]. The age-related IS risk ratio (RR) of AF patients were derived from the Framingham study[23]. The IS incidence of people with and without AF was calculated using attributable risk formula:

$$I_1 = \frac{I \times RR}{f(RR - 1) + 1}$$

$$I_0 = \frac{I}{f(RR - 1) + 1}$$

In the equations above, I_1 , I_0 and I were the IS incidence of AF patients, people without AF, and general population, respectively. f was the AF prevalence of general population. RR was the relative risk of IS in AF patients.

The case-fatality of AF was estimated as quotient of AF mortality divided by AF prevalence. The distribution of stroke severity under different conditions was derived from the studies of Hart *et al*, Sorensen *et al* and Gabet *et al*. The case fatality of stroke after the acute phase were assumed based on a two-year retrospective analysis of Chinese population[24]. The risk reduction of IS and risk increase of ICH due to warfarin anticoagulation therapy were from the RELY study[25], and the all-cause mortality decrease data was obtained from a meta-analysis[20]. The anticoagulation rates and their ranges of no screen and screen cohort were assumed based on published literatures[18, 26].

Utility

The utility values used to calculate the quality-adjusted life year (QALY) were based on the EQ-5D scale. The baseline health state utility values of no event people were from pooled health surveys for England, to avoid overestimating the life qualities of no event population by simply defining the utility as 1[27]. The utility values of AF, IS with different severity status, disabled ICH were derived from the studies of Sullivan *et al* and Gage *et al* [28, 29].

Costs

This study was conducted from the societal perspective, and only direct healthcare cost was included, consisting of the expenses on screening program and anticoagulation medication, the economic burden of IS, ICH. The cost of 12-lead ECG screening was calculated as the average outpatient ECG examination fee in China, which was supposed to cover the depreciation charge of electrocardiogram machines and the salary of nurses or general practitioners for reading results. And the screening program management expenses, including questionnaires inquiry, staff training, expert literature, consulting, material design, printing, screening invitation, on site epidemiological research and so on, were from the handbook of stroke screening program of China pressed by government. The anticoagulation treatment fee of warfarin included medication cost and INR test expense[25, 30, 31]. The expenses due to IS and ICH were divided into first year acute hospital treatment and annual long-term stroke rehabilitation and healthcare. The data used in this model was from Chinese published literatures[5, 32].

Discount rate

All costs parameters used in this model were expressed in 2019 CNY with the discount rate of 5%. The values of utility and costs in this model were discounted 5% per year, with the sensitivity analysis range of 3% to 8%.

Uncertainty and sensitivity analysis

To analyze the uncertainty of some important parameters, deterministic 1-way sensitivity analysis was performed with parameters of plausible ranges. A probabilistic sensitivity analysis was also adopted in this model to study the variability of all variables. The proportion and utility variable were assumed to be beta distributions. The ratio risk (RR) variables were assumed to be lognormal distributions. Stroke severity ranks were assumed to be dirichlet distributions. Cost parameters were assumed to be normal distributions. All the variables above were varied simultaneously and 10000 estimates of costs and effects were obtained by sampling from the distributions.

Results

Table 2 shows the results of cost-effectiveness analysis on different age cohort and screening interval scenarios. All strategies in this model could be considered cost-effective at the WTP threshold of 3 times GDP per capita of China in 2019 per QALY gained. Strategies of annual AF screening in 65-year-old

cohort and annual, biennial, triennial AF screening in 75-year-old were highly cost-effective (the ICER were less than 1 GDP per capita of China in 2019 per QALY gained). In 65-year-old cohort, annual AF screening gained 0.061 life year and 0.027 quality-adjusted life year per people attending the screening program, the incremental cost-effectiveness ratio (ICER) for any gained QALY was CNY 64147. Compared to no screen strategy in 65-year-old cohort, annual AF screen would have 3891 more treated AF, prevent 535 ISs and induce 174 more ICHs. Much lower ICER was seen in 75-year-old cohort. In 75-year-old cohort, the ICER for any gained QALY was CNY 49736, CNY 52293 and CNY 53155 for annual, biennial and triennial screening, respectively, while the ICER for any gained life year (LY) was CNY 31922, CNY 35632 and CNY 34183. According to the results, screening strategies with a wider screen interval would achieve less effect than annual screening, means less QALYs and LYs gained per individual, lower anticoagulation rate among AF, less prevented IS cases, and the ICER was higher.

Sensitivity analysis

Fig 2 shows the results of one-way sensitivity analysis (only top 10 most influential factors included) of annual AF screening in 75-year-old cohort. The most influential factor was relative risk reduction of all-cause mortality of AF on anticoagulation. If this value lower than 13%, the corresponding ICER in 75-year-old annual screening cohort would be higher than GDP per capita in China in 2019, however, even if this value was 0.0%, the ICER would still no more than 3 times GDP per capita in China in 2019. Higher first year cost of hospitalization and treatment of ICH, higher AF detection and anticoagulation rate among people under routine care, lower anticoagulation rate among screen-detected AF, lower sensitivity of screen method, and poorer IS risk reduction effect of anticoagulant therapy would affect the ICER of 75-year-old annual screening cohort, but the ICERs were all below 3 times GDP per capita in China in 2019.

The results of probability sensitivity analysis were consistently with the main results. The cost-effectiveness acceptability curves (Fig 3.) showed that at the WTP threshold of GDP per capita in China in 2019 the probabilities of annual AF screening in 55/65/75-year-old cohort being cost-effective were 32%, 55% and 78% respectively. And at the WTP threshold of 3 times GDP per capita in China in 2019 the probabilities of annual AF screening in all cohorts being cost-effective were almost 100%.

Discussion

In this modelling cost-effectiveness analysis, a community-based AF screening program by a 12-lead ECG is cost-effective in different strategies with start-age of 55, 65, and 75 years old. And AF screening is highly cost-effective in annual screening from 65 and 75 years old, and in biennial and triennial screening from 75 years old. AF screening was associated with increasing anticoagulation rate among AF patients, therefore reducing strokes in 55/65/75-year-old cohort. The results proved to be robust in the sensitivity analyses when we varied the estimates for effectiveness of screening, utility scores and costs.

Uncertainty about this study arises from the anticoagulation rate in routine care. Hospital-based study have showed that a low rate of OAC use among AF patients in China, with the rate varying from 21.4% to 36.5%[18]. However, most AF patients have not been diagnosed under routine healthcare[39]. So, a proportion of 10% and sensitivity range up to 30% was assumed to be the rate of AF patients have awareness of the condition and start anticoagulation treatment under routine care. And the results for AF screening is supportive. Another main uncertainty is the effect of anticoagulants. The corresponding parameter in this model was derived from RE-LY (randomized evaluation of long-term anticoagulant therapy) study, a multi-center trial conducted in 951 clinical centers of 44 countries, including China[40]. Therefore, the base-case value is reliable. Further, a wide sensitivity range was used in these parameters, and the results was still unchanged.

Recently, evidence about AF screening strategies in different countries accumulated to prove it a cost-effective method for preventing strokes by increase anticoagulation rate among screen-identified AF patients[13-16, 41]. A cost-effectiveness analysis of community-based annual ECG or pulse palpation AF screening programs compared with no screening for people older than 65 years in Japan also concluded that screening would be cost-effective, with the ICER of annual ECG US\$ 7830/QALY for men and US\$ 10220/QALY for women[14]. Although, the sensitivity of ECG, uptake of screen, anticoagulants prescription rate in this study all set to 100%, and these parameters were not all tested in sensitivity analysis. A cost-effectiveness analysis study was conducted on a national opportunistic screening program for AF in Ireland, by 12-lead ECG if an irregular pulse detected in patients aged 65 years above who went to general practitioner for consultations. The conclusion was proved AF screening to be cost-effective with the ICER €23,004/QALY[15]. To our best knowledge, our study was the first cost-effectiveness analysis of AF screening in Chinese setting. Our study also used 12-lead ECG as screening method, and the results were consistent with the studies above, and had further proved systematic annual AF screening by 12-lead ECG in China might be a cost-effective way to reduce unnecessary stroke burden induced by untreated AF.

This study had some limitations. First, as other modelling analysis, this study was based on assumptions defined by authors, and the parameters were extracted from published studies, which might affect the validity of the results. Even though the sensitivity analysis supported the main results. Second, due to the principal of Markov transition model, AF patients could not recover to sinus rhythm in the natural history, and other AF-related clinical events were not included, such as systemic embolism, heart failure and so on, to simplify model structure. And the prognosis and progression after stroke would be more complex than this model. Third, the effect of screening rounds might be underestimated because of the assumption that if the one who did not be diagnosed in first screen or developed AF on no screen year, would never be detected by screening. Fourth, the anticoagulants in this study only used warfarin, in real-world data, due to allergy and socioeconomic status, some AF patients might choose other anticoagulation medication, such as novel oral anticoagulants and antiplatelet therapy. However, compared to other anticoagulants, warfarin was considered to be cost-effective in China[30]. Thus, further pilot trial of AF screening is needed to test the true effect and get more reliable data for cost-effectiveness analysis.

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Availability of data and materials

Datasets and model are available through the corresponding author upon request.

Competing interests

The authors declare that they have no competing interests

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Authors' contributions

Wenli Lu and Yuan Wang conceptualize the study. All authors made substantial contributions to the study implementation. Lihui Zhou analyzed the simulation model for the study and wrote the manuscript. Ye Cao collected the data and Bei Gao reviewed literature for available published data. All authors have read and approved the manuscript.

Corresponding author

Correspondence to Yuan Wang.

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Tables

Table 1

Main parameters in the Markov model.

Variables	Base-case scenario (range for sensitivity analysis)				Reference
Clinical parameters					
Atrial fibrillation (AF)					
prevalence at 64/54/74 years (/100 thousands)	1996.33/636.13/4940.69				GBD 2019 (http://ghdx.healthdata.org/gbd-results-tool)
Incidence, by age	Table 1 in Supplemental Materials				
Mortality, by age	Table 1 in Supplemental Materials				
Ischemic stroke (IS) incidence, by age	Table 1 in Supplemental Materials				
Intracerebral hemorrhage (ICH) incidence, by age	Table 1 in Supplemental Materials				
All-cause mortality, by age	Table 1 in Supplemental Materials				
Risk ratio (RR) of ischemic stroke risk among AF patients, by age	50-59 years: 4.0 / 60-69 years: 2.6 / 70-79 years: 3.3 / 80-89 years: 4.5				(23)
Proportion of fatal ICH in acute phase year	46.2% (30.0-50.0)				(33)
Stroke severity distribution by different condition in acute phase year					
	Mild (mRS=0/1)	Moderate (mRS=2/3)	Severe (mRS=4/5)	Fatal (mRS=6)	
No AF	49.54%	19.35%	8.51%	22.60%	(25, 33-35)
AF without anticoagulation therapy	40.88%	19.06%	8.02%	32.04%	
AF with warfarin	53.70%	20.37%	3.70%	22.23%	
IS annual fatality after acute phase year	8.71% (5.00-10.00)				(24)
ICH annual fatality after acute phase year	5.31% (2.00- 6.00)				(24)
Anticoagulation (Warfarin)					
RR of ischemic stroke risk reduction	0.22 (0.20-0.50)				(25)
RR of intracerebral hemorrhage risk increase	2.78 (1.50-3.50)				(25)
Relative risk reduction of all-cause mortality	0.26 (0.00-0.30)				(20)
Rate of AF detection and anticoagulation treatment under routine care	0.10 (0.05-0.30)				(18, 26)
Rate of anticoagulation treatment for screen-detected AF	0.80 (0.60-1.00)				Assumption
Utility					
Sinus rhythm, by age	Table 1 in Supplemental Materials				(27)
AF	0.81 (0.68-0.91)				(29)
ICH	0.75 (0.68,0.83)				(28)
	Mild	Moderate	Severe		
IS	0.75(0.68-0.83)	0.39(0.35-0.43)	0.11(0.10-0.12)		(28)
Cost (CNY)					
Screening management cost	40(30-50)				a
Cost of 12-lead ECG examination	30(20-40)				b
First year cost of warfarin treatment (including INR tests)	982(763-1220)				(25, 30, 31)
Sequent annual year cost of warfarin treatment (including INR tests)	572(427- 716)				
First year cost of hospitalization and treatment by condition					
Mild IS	24303 (18227- 30379)				(5, 36)
Moderate IS	66046 (49535- 82558)				
Severe IS	95318 (71488-119147)				

ICH	32825 (24619- 41031)	
Sequent annual cost of rehabilitation treatment by condition		
Mild IS	10522 (7891-13152)	(5, 36)
Moderate IS	21487 (16116-26859)	
Severe IS	40586 (30439-50732)	
ICH	10522 (7891-13152)	
Sensitivity of 12-lead ECG read by general practitioner with aid of interpretative software	0.92 (0.67-0.97)	(37)
Attendance rate of screening	0.80 (0.60-1.00)	Assumption
Discount rate	0.05 (0.03-0.08)	(38)

a: The handbook of stroke screening program in China; b: Outpatients 12-lead ECG examination fee in primary healthcare institutions of China.

Table 2

Main results of cost-effectiveness analysis.											
Strategies	Lifetime cost	Incremental cost *	QALYs	Incremental	ICER	LYs	Incremental LYs *	ICER	No. of AF with treatment	Anticoagulation rate among AF patients	No. of AF-related IS
	(CNY)	(CNY)		QALYs *	(CNY /QALY)			(CNY /LY)	(/100 thousands)	(%)	(/100 thousand
55-year-old cohort											
No screen	17619	-	12.002	-	-	23.184	-	-	742	10.0	1490
Annual	19496	1877	12.023	0.021	91052	23.255	0.071	26431	4567	61.5	935
Biennial	19237	1618	12.014	0.012	134649	23.225	0.041	39876	2810	37.9	1185
Triennial	19150	1531	12.011	0.009	167505	23.214	0.030	50380	2214	29.8	1268
65-year-old cohort											
No screen	17784	-	9.176	-	-	15.444	-	-	755	10.0	1425
Annual	19496	1712	9.202	0.027	64147	15.505	0.061	28204	4646	61.5	891
Biennial	19317	1534	9.194	0.019	81954	15.486	0.042	36655	3182	42.1	1076
Triennial	19258	1475	9.192	0.016	91842	15.480	0.036	41477	2693	35.7	1138
75-year-old cohort											
No screen	11499	-	5.979	-	-	8.845	-	-	835	10.0	1285
Annual	12855	1355	6.007	0.027	49736	8.888	0.042	31922	5140	61.5	794
Biennial	12717	1218	6.003	0.023	52293	8.879	0.034	35632	4189	50.1	882
Triennial	12667	1168	6.001	0.022	53155	8.879	0.034	34183	3839	46.0	911

* Compared with no screening strategies in the corresponding age cohort. QALY, quality-adjusted life-year. LY, life-year. ICER, Incremental cost-effectiveness ratio. AF, atrial fibrillation. IS, ischemic stroke. ICH, intracranial hemorrhage.

the numbers of non AF-related IS were 12288, 10323 and 6477 per 100 000 people in 55 / 65 / 75-year-old cohort respectively.

Figures

Figure 1

Model structure. AF, atrial fibrillation. IS, ischemic stroke. ICH, intracerebral hemorrhage. Part a. refers to the possible treatment status of AF and IS, ICH severity distribution after acute phase (first year). Part b. refers to the Markov model structure.

Figure 2

Tornado diagram for annual AF screening in 75-year-old cohort. The graph indicated changes in the incremental cost-effectiveness ratio (ICER; per quality adjusted life year [QALY]) caused by plausible variations in the respective parameter (sensitivity analysis). For example, if the assumed relative risk reduction of all-cause mortality of AF on anticoagulants decreased to 0%, other than the base-case value 26%, then the ICER would be increase from CNY49736/QALY to CNY 118000/QALY. The vertical dotted grey and black lines represent the parameters' value in the base case scenario and the value when the ICER was GDP per capita in China in 2019 respectively. Parameters are ordered hierarchically, with the topmost parameters having the most effect on ICER outcome, arranged

in declining order from the top to the bottom of graph. Only top 10 most influential factors were included in this graph, other uncertainties of variables' influence were rather small and had been listed in the supplemental figure.

Figure 3

Acceptability curves of probability sensitivity analysis. The three dotted black lines in this graph represented the 1, 2 and 3 times of GDP per capita in China in 2019 from left to right.

Supplementary Files

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- [Supplementalmaterials.docx](#)
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