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中風相關的個人化高血壓預防之成本效益分析

Cost-effectiveness analysis of personalized prevention for hypertension associated with stroke

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本論文係 郭書帆君（學號 P06849005）在國立臺灣大學流行病學與預防醫學研究所完成之碩士學位論文，於民國 108 年 7 月 15 日承下列考試委員審查通過及口試及格，特此證明

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Contents

doi:10.6342/NTU201903838

doi:10.6342/NTU201903838

Tables

doi:10.6342/NTU201903838

Chapter 4

doi:10.6342/NTU201903838

Figures

Chapter 3

Chapter 4

doi:10.6342/NTU201903838

doi:10.6342/NTU201903838

中文摘要

<研究背景> 雖然控制高血壓已廣被接受為預防中風之必要措施，但不同階段的血壓控制對於發生中風所造成之影響不同，使得對於不同高血壓防治方法之實證效益難以進行評估。此外，近年來對於運用初段預防進行高血壓防治受到重視，然而此一介入措施對於減少後續發生中風之效益卻甚少被提及。如何於民眾運用前述以族群為基礎之初段預防措施，結合以個人高血壓進展風險分數為導向之篩檢與預防性投藥之次段預防措施，在現有之研究仍付之闕如。本論文因此希望能針對前述對結合初段與次段預防之中風防治措施所能預防中風發生的比例、介入後所增加之人年，以及調整生活品質後進行成本效益分析。

<研究目的>

(1) 以具不同危險因子之社區世代為基礎，預測其多階段多因子高血壓進展及後續中風發生；

(2) 利用(1)，進一步發展個人化高血壓防治措施在中風防治的介入分析模型；

(3) 評估彰化社區世代個人化高血壓防治措施之成本效益分析。

<材料與方法> 我們採用以基隆社區世代所發展的多階段多因子高血壓預測模式，配合不同血壓階段的中風發生率，套用於彰化社區世代具不同危險因子的族群。以馬可夫決策模型，考量中風後功能狀態，進行個人化高血壓防治相對於控制組之成本效益分析，並以機率性成本效益分析處理參數不確定性問題。主要結

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果呈現包括中風的減少、生活品質調整人年的增加，及增加成本效用比，並以成本效益散佈圖及接受曲線呈現。

<結果> 以彰化社區世代個人的危險因子進行的模擬分析，預測其中風的年發生率約為每千人年 13 例，包括 3.59 及 9.48 例的出血性和缺血性中風，個人化高血壓防治策略可降低 17%中風發生(95%信賴區間：15-18%)。考慮中風的減少及其後續殘障等級的變化之後，個人化高血壓防治策略對個人平均可增加 0.17 個生活品質調整人年，且平均每人整體花費較控制組減少新台幣 161,170 元。在考量參數的變異之下，個人化高血壓防治策略的成本效益優勢仍然存在。

<結論> 本研究建立評估個人化高血壓及中風防治的架構，在考量高血壓狀態的動態轉移之下，對以全民為基礎的初段預防及高危險群者之預防性投藥及次段預防措施進行評估，結果發現個人化高血壓防治就成本效益的角度而言是一項節省成本的優勢策略，除了可增加生活品質調整人年之外，累積花費成本亦較低。本研究的結果預期可以做為個人化高血壓防治策略之參考。

關鍵詞：高血壓、中風、馬可夫決策模型、成本效益分析

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Abstract

Background Although the control for hypertension have widely been accepted as a necessary component for stoke prevention, the heterogeneity regarding the evolution of hypertension in associated with the occurrence of stoke render the elucidation of the effectiveness of each components of prevention strategies intractable. As the primary prevention have gained great attention in current strategies of hypertension management, its contribution to stoke prevention remain not fully addressed. The effectiveness on the application of multiple prevention strategies including the population-based primary prevention and risk-oriented carotid ultrasound screening followed by a series of treatment and therapy for stoke prevention also has not been elaborated. The cost incurred by the multi-step prevention strategies and the attributes of its effectiveness including stroke averted, life-year gained, and quality adjusted life-years gained motivate our research by applying a cost-effectiveness analysis to evaluate the decision on the proposed personalized stroke prevention strategies.

Aims This thesis aims

doi:10.6342/NTU201903838

(1) to explore the dynamic of stoke embedded in the evolution of hypertension defined by multiple disease status including normal, prehypertension, stage I hypertension, and stage II hypertension;

(2) to develop a risk-guided individual-tailored stoke prevention strategy incorporating primary and secondary prevention based on (1); and

(3) to assess the cost-effectiveness of (2) applied to Changhua population following the principle of decision analysis.

Materials and Methods We calculated the personalized risk score with 4-state hypertension Markov model underpinning in light of definition from JNC 7, normal, pre-hypertension, stage 1 hypertension, stage 2 hypertension. The clinical weights of the risk score were borrowed from literature with Keelung Community-based Screening (KCIS) cohort, and applied to the Changhua Community-based Screening (CHCIS) cohort to stratify the cohort into different risk groups. A Markov decision tree, incorporating the 4-state hypertension model, hemorrhagic stroke, ischemic stroke, three functional outcomes after stroke, and death was built. Finally, the probabilistic cost-effectiveness analysis of personalized prevention of hypertension compared with control group was conducted. The main outcome measures include stroke avoided and quality-adjusted life-year prolonged, incremental cost-utility ratio, and the acceptability curve for personalized prevention against control.

doi:10.6342/NTU201903838

Results Among the Changhua population, the incidence of stroke is 16 per 1,000 with 4.2 and 11.8 per 1,000 for hemorrhagic and ischemic type, respectively. The personalized prevention strategy results in stroke risk reduction by 17% (95% CI: 15-18%). Taking into account the stroke events reduction and the functional status after stroke, the personalized prevention program not only results in 0.17 QALY gained per person in a 20-year time horizon, but also leads to an average NTD 161,170 less expenditure per person. Considering the distribution of parameters, the benefit of personalized prevention program over control is still dominant even under the worst case of parameters.

Conclusion We developed a framework for the evaluation of individual-tailored hypertension and stroke prevention, which incorporated primary and secondary prevention. As the personalized prevention is cost-effective against control in terms of quality-adjusted life year gained, our results support the personalized prevention as a promising policy for hypertension associated stroke.

Key words: hypertension, stroke, Markov decision model, cost-effectiveness analysis

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Chapter 1. Introduction

1.1 The importance of hypertension prevention

Hypertension has long been the most common chronic disease in the world. According to the statistics, the prevalence of hypertension in the past 20 years was 30% or so in American adults [1] and 26% in Taiwan [2]. In other words, there is one in every four adult nationals suffering from hypertension.

Although high blood pressure rarely causes a direct life threat, it is still closely related to many chronic comorbidities. These include heart disease, cerebrovascular disease and renal disease, the 2nd, the 4th and the 9th of the top ten causes of death in Taiwan, respectively. A meta-analysis study showed for every 20 mmHg raise in systolic blood pressure, the risk of death from ischemic heart disease and stroke doubled [3]. That is why hypertension was so called “a silent killer” and was often ignored. According to the 2015 National Nutrition and Health Examination Survey of Taiwan, as many as 65% young adults and 25% middle-aged and elderly people do not realize that they have high blood pressure. In fact, 36% of stroke, 43% of heart failure, and 16% of coronary heart disease would be avoided if hypertension could be controlled in the early stage [4]. Therefore, blood pressure control has always been a priority in health promotion all over the world.

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1.2 Relationship between hypertension and stroke

Stroke is a leading cause of disability and mortality. It is also the number 4th cause of death in Taiwan, which took 11,000 lives in 2016. There are two types of stroke, hemorrhagic and ischemic stroke. The ratio of hemorrhagic to ischemic stroke is about 1:3 to 1:4. Both strokes cause permanent damage to brain and result in handicap and impaired quality of life among survivors. They share a common risk factor, hypertension. High systolic pressure is associated with hemorrhagic stroke including intracerebral hemorrhage and subarachnoid hemorrhagic (HR=1.44, CI=1.32-1.58)[5], mainly by causing the cerebral vessel or aneurysm rupture. High blood pressure is also associated with ischemic stroke (HR=1.19, CI=1.08-1.30)[6] by several different mechanism, such as carotid artery atherosclerosis and small vessel hyalinosis. It is generally considered the higher the blood pressure, the more risk of stroke will be. Therefore, control the blood pressure, at the same time lower the stroke incidence.

1.3 Personalized hypertension prevention strategy

In the past, disease screening was usually implemented to general population that referred as population-based prevention strategy, such as breast cancer screening using mammography or cervical cancer screening using Pap smear. However, it is

doi:10.6342/NTU201903838

cost-consuming to screen nation-wide and might have the problem of false positive. An alternative strategy of individualized screening evolved. If we can formulate a risk stratification person by person, we can make tailored prevention strategy. In the case of hypertension prevention, patients with higher risk (such as old age, male gender, obesity, positive family history) may need regular screening, medication control and non-pharmacological intervention in the earlier stage of hypertension. With multistate Markov model, we can estimate the effect of respective risk factor modification on disease progression. In this thesis, we conduct a risk score oriented personalized preventing program in reducing hypertension and stroke incidence.

1.4 Cost-effectiveness analysis of hypertension associated with stroke

In the past 10 years, the national health expenditure in Taiwan kept raising from 814 billion NTD in 2007 to 1,127 billion NTD in 2017. While the resource is limited, economic appraisal is fundamental to help health authority to decide how health care resource are used. The outcome could be measured in quality-adjusted life year (QALY), benefit measure (lives saved or events avoided), and how much money saved.

Adverse effects of hypertension on cardiovascular system got attention in the past decades. After the hypertension treatment guideline had been developed in the

doi:10.6342/NTU201903838

1980s, researchers has been working on hypertension prevention strategy, screening program and treatment medication invention. Not surprisingly, cost-effectiveness analysis has also been a big issue contrary to different preventive and treating strategy. However, most of these cost-effectiveness analysis use composite cardiovascular disease (CVD), including coronary heart disease and stroke, as effectiveness endpoint. Though both events caused impact on the patient's health condition and quality of life, stroke leads to direct neurological damage and handicap. It is reasonable to assume that patients with coronary heart disease and stroke have different outcome and deserves separate studies.

In this thesis, we explore the transition probability of both hemorrhagic and ischemic stroke in different hypertension stage by applying the multistate Markov exponential regression model regarding the dynamic change of blood pressure status with different risk profiles from a community-based cohort in the mid-west Taiwan. We also review literatures pertaining to the quality of life for patients after stroke. All parameters are fitted in into a Markov decision model for the cost-effectiveness analysis for hypertension prevention associated with quality of life after stroke. Different functional outcome after stroke is considered. The main outcome measures include stroke avoided and quality-adjusted life-year prolonged. We anticipate the

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results of this study can provide insightful reference for policy of tailored hypertension prevention.

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Chapter 2. Literature review

2.1 Stages of hypertension

Before the publication of the 7th Joint National Committee report (JNC 7, 2003), the hypertension was defined as systolic pressure >140mmHg or diastolic pressure >90mmHg. However, more and more evidence showed a positive correlation between hypertension and cardiovascular disease. One study using Framingham Heart Study revealed the relative risk of myocardial infarction and coronary heart disease was 3.5 and 1.7 respectively in pre-hypertensive population with systolic blood pressure of 120-139 mmHg, compared to the population with systolic blood pressure less than 120 mmHg [7]. Therefore, JNC 7 [8] introduced a new stage of "pre-hypertension" with systolic pressure between 120-139mmHg and diastolic pressure between 80-89mmHg (Table 2.1) to allow early intervention in this high-risk group, such as life-style modification and diet control, to avoid progressing to true hypertension and even return to normal blood pressure.

In the past, pre-hypertension stage represented a warning area before progressing to real hypertension. Generally anti-hypertensive medicine is not applied in this stage (except for patients with diabetes, coronary heart disease and chronic kidney disease, the target blood pressure is <130/80mmHg). Even though, the odds ratio of becoming

doi:10.6342/NTU201903838

true hypertension and cardiovascular events is 1.7 in pre-hypertensive population compared to that with normal blood pressure. Eighty percent of the pre-hypertensive population will become true hypertension in 6 years [9]. Therefore non-pharmacological therapy is emphasized now in pre-hypertension stage, such as weight loss, DASH diet, low fat, low salt intake, exercise and decrease alcohol consumption, to avoid stage progression[10]. In 2017 American Heart Association Guideline for hypertension management, they modified the definition of stage 1 hypertension as “SBP 130~139mmHg or DBP 80~89mmHg”. The rationale for this categorization is based on observational data related to the association between blood pressure and cardiovascular risk, and clinical trials of treatment with antihypertensive medication to prevent cardiovascular disease in this range of blood pressure. However, European Society of Cardiology and Taiwan Society of Cardiology still keep hypertension as JNC7 definition. Whether to give anti-hypertensive medicine in this “high-normal” blood pressure range is under debating.

2.2 Risk score of hypertension progression

In a previous study using a community based screening program in Keelung had introduced the application of risk score of hypertension progression to evaluate the effect of risk modification (Tseng et al, 2012)[11]. They used a exponential form of

doi:10.6342/NTU201903838

regression model to recognize the weight of each risk factors of hypertension. The hypertension risk factors are:

- ***Obesity***

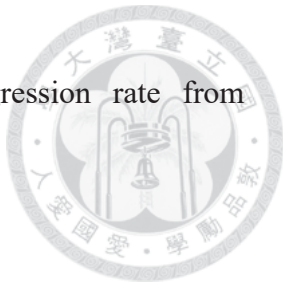
Obesity is a strong predictor for hypertension progression. Body mass index (BMI) is generally taken as a surrogate measurement of obesity, as more than 25 is considered overweight and obesity if more than 30. A Japanese cohort study [12] shows that BMI ≥23 was the strongest determinant of pre-hypertension (OR=1.47 in male and 1.67 in female).

- ***Age***

Advancing age is associated with increased blood pressure. In another study using community-based integrated screen data in Keelung (Chiu et al , 2006)[13], the author described the annual transition rate between each hypertension stages in different age groups. The transition rate of normal to pre-hypertension, pre-hypertension to stage 1 hypertension were increasing with age in both male and female. However, transition rates from stage 1 to stage 2 hypertension were constant across age groups which might be interfered by medical treatment. It also showed the treatment rate was higher in the elder than in the young patients, which may explain the reason transition rate from stage

doi:10.6342/NTU201903838

1 to stage 2 didn't grow with age. On the other hand, regression rate from pre-hypertension to normal decreased with age.



- ***Gender***

Male has higher risk of hypertension than female does. It is believed the key is the protective effect of estrogen on cardiovascular system. In another study using community-based integrated screen data in Keelung (Yen et al , 2011)[14], the author calculated the annual transition rate between each hypertension stages in different age groups stratified by gender. Male has higher transition rate from normal to pre-hypertension and pre-hypertension to stage 1 hypertension. At the same time, female has higher regression rate from pre-hypertension to normal. However, this trend diminished after age 50, which probably contribute to menopause at this period.

- ***Education***

Education is associated with better health awareness and understanding of the disease such as diabetes and hypertension. The governments are working on public education for these chronic disease. According to the American National Health and Nutrition Examination Survey, the hypertension control rate was raising through 1999 to

doi:10.6342/NTU201903838

2010 and remained steady after 2010. In the study of Tseng et al, high education level (senior high or above) is inversely associated with the risk of hypertension progression.

- ***Blood sugar***

Diabetes coexists with hypertension very commonly and both of them contribute to cardiovascular event, stroke and renal impairment. They share many factors in etiology, such as genetics, oxidative stress, insulin resistance, obesity [15]. The significance of hypertension progression with high fasting blood sugar was revealed in the Tseng's study, which elucidate the positive relationship between blood sugar and blood pressure.

- ***Cholesterol***

Hyperlipidemia is also a common chronic health problem along with diabetes and hypertension. Positive evidence showed elevated cholesterol, especially low-density lipoprotein(LDL), lead to an increase risk for cardiovascular event. Hypercholesterol also had linked to progression in hypertension stage. In the Tseng's study, high total cholesterol level (≥200mg/dl) is associated with significant higher risk for pre-hypertension in both gender.

doi:10.6342/NTU201903838

- ***Uric acid***

Hyperuricemia had been found to associated with hypertension for a long time but it still a debate that is the hyperuricemia a cause or an effect of hypertension [16]. Some assumed that uric acid changes hydrostatic pressure of the serum causing the renal blood flow decrease and then elevate systemic blood pressure. The others supposed the uric acid increase secondary to hypertension by decreasing the urate excretion in the kidney. Obviously, uric acid level is important in predicting hypertension development. Tseng's study showed hyperuricemia (≥7mg/dl in men and ≥6mg/dl in women) is associated with hypertension progression in both gender.

- ***Smoking***

Cigarette smoking may cause elevated blood pressure by the mechanism of sympathetic system stimulation by nicotine and increase the arterial stiffness. However, there are many studies showed the opposite result of smoking effect on blood pressure. The hypothesis is that smokers usually have lower body weight than non-smokers and the metabolite of nicotine has vasodilation effect, that causes lower blood pressure. In the Tseng's study also revealed the protective effect of smoking on hypertension suggesting the cigarette smoking might lower the blood pressure.

doi:10.6342/NTU201903838

- ***Alcohol***

Excessive alcohol consumption is linked to elevated blood pressure and some kinds of cancer, while light to moderate alcohol intake maybe beneficial in reducing hypertension and cardiovascular risk[17]. The mechanism of excessive alcohol intake may explained by hyper-sympathetic activity, stimulation of the renin-angiotensin-aldosterone system, damaged to the endothelium and impairment to the nitric oxide production[18]. In Tseng's study, alcohol consumption increase the risk of hypertension progression in men but not in women.

- ***Betel nut chewing***

Betel nut chewing is common in southeast Asia. It is estimated about 11% Taiwan population have this habit in 1997. It brings some health problem like oral cancer, diabetes mellitus, and hypertension. It contains the tannins arecatannin and gallic acid, oil gum, a little terpineol, lignin, and three main alkaloids—arecoline, arecaidine, and guvacine—all of which have vasoconstricting properties that may cause hypertension. A study showed the odds ratio of hypertension in diabetic male betel nut chewer is 1.067 (95%CI:1.007-1.131) [19]. In Tseng's study also showed significant association between betel nut chewing and hypertension progression.

doi:10.6342/NTU201903838

2.3 Quality of life after stroke

Stroke can be a catastrophic disease causing death or handicap even survived, which brings many issues more than the disease itself. In society aspect, stroke result in increased long term care expenditure and lose of labor manpower. In the personal aspect, patients suffer from psychosocial impairment and lost their financial ability. They may have to give up their job, hobbies and sometimes dignity. When we evaluate the impact of stroke, we should not only focus on the mortality but also the disability which may impair the quality of life.

One study in Taiwan used a hospital-based stroke mortality data, revealed a stroke patient may lose 9.5 QALY (quality-adjusted life-year) in life-long follow up. In other words, stroke cause a person lose 9.5 healthy years in average[20]. The result suggested the loss of QALY is similar in large and small volume ischemic stroke but significantly greater loss in hemorrhagic stroke (14.1 QALY) because of younger onset age.

Another study from Oxford Vascular study, a population-based study in UK[21], reported the 5–year quality-adjusted life-year after stroke(including hemorrhagic and ischemic type) is 2.21, in other words, 55% discount QALY after stroke.

Other studies had used various measurement to evaluate the utility of specific stroke treatments (e.g. tissue plasminogen activator and intra-arterial thrombolysis in

doi:10.6342/NTU201903838

acute stroke) or preventive programs (e.g. anti-coagulant in preventing stroke). Among these studies, quality-adjusted life year (QALY) is the most widely used measurement. One QALY equals to one year in perfect health and 0 represented death, so it's a compound index of survival function adjusted by quality of life.

The first step to estimate the QALY is to evaluate the patient's daily activity function and independence after stroke. There are many ways to help developing a quantified scale for this purpose. We will take an example of modified Rankin Scale (mRS) in the next section.

2.4 Modified Rankin Scale (mRS)

Modified Rankin Scale is a widely used grading system for neurological impaired patient, separated the patients into 7 categories, which 0 indicated no symptoms at all, 1 and 2 indicated mild symptoms and slight disability, 4 and 5 indicated moderate to severe disability and 6 indicated death (Table 2.2).

The scale was originally introduced in 1957 by Dr. John Rankin of Stobhill Hospital, Glasgow, Scotland, and had been modified to its current version in 1980s. Researchers could use mRS as an endpoint to assess the efficacy of a new drug or treatment. It provides a standardized grading basis with inter-rater reliability. It also has convergent validity with other disability scales, such as Barthel index[22]. To

doi:10.6342/NTU201903838

minimized the inter-rater variation, training of the grader and developing structural questionnaire are essential. A simple 9-question “yes/no” check list for grading mRS had been tested for its reliability[23]. Now, it is much easier to follow up the patient’s functional status via internet or postal mRS questionnaire.

2.5 Applying modified Rankin Scale to quality of life analysis

As an ordinal scale, some researchers use dichotomous approach, separating the outcome into good and poor. The cut-off point of good and poor outcome varies between studies, some defined good outcome as mRS 0-1 and some defined as mRS 0-2 or 0-3. Multivariable logistic regression and odds ratio are often applied in dichotomous approach of mRS.

In order to translate the mRS level into quality of life after stroke, utility value is getting more attention recently. A utility of 1 represented excellent health and 0 represented death. Some utility scales even have minus value that indicated “worse than death”.

There are many ways to transform the mRS level into a utility value. Some investigators mapped the responses from EQ-5D onto the mRS in patients with stroke to synthesis the utility value. EQ-5D is a questionnaire for measuring health performance with 5 dimensions (mobility, self-care, usual activities, pain, and anxiety) and each with

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3 levels (no problem, some problems, and extreme problems), so there would be 243 (3^5) possible status. In the previous studies, each result of EQ-5D was assigned a value using different "tariff" by time-trading off method, which are different in each county (e.g. UK utility value, US utility value). One study used Ordinary least squares regression to predict UK EQ-5D tariffs from mRS scores and use the tariff as utility value [24]. Another study calculate the utility weight for each mRS grades by averaging the EQ-5D utility value of all patients in the same mRS level[25].

After knowing the utility value of each mRS level, QALY can be derived by multiplying the live year with utility value (QALY= live year x utility value). For example, 5 year in mRS level 2 (e.g. utility =0.83 in Dijkland's study) equivalent to 4.15 QALY. Because the lacking of Taiwan local utility value, we reviewed some of previous literature that had described the utility value corresponding to mRS (Table 2.3)[26].

2.6 Modified Rankin scale distribution after stroke

Disability severity after stroke is related to the patient's age, comorbidity, stroke mechanism, involved artery territory, stroke volume, location of the lesion, and the rehabilitation program after acute phase. In a study developed the disability-weights scale for mRS, they provided a review of frequency of each mRS level[27]. Six trials

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and data base were analyzed, 2 for ischemic stroke, 2 for intracranial hemorrhage and 2 for subarachnoid hemorrhage. The frequency of each mRS grades are listed in Table 2.4.

doi:10.6342/NTU201903838

Tables of chapter 2

Table 2.1 JNC 7 stages of hypertension

Stage	SBP(mmHg)	DBP(mmHg)
Normotensive	<120	and <80
Pre-hypertension	120-139	or 80-89
Stage 1 hypertension	140-159	or 90-99
Stage 2 hypertension	≥ 160	or ≥ 100

doi:10.6342/NTU201903838

Table 2.2 Definition of modified Rankin scale

mRS	Clinical presentation
0	No symptoms.
1	No significant disability despite some symptoms. Able to carry out all usual activities.
2	Slight disability. Able to look after own affairs without assistance, but unable to carry out all previous activities.
3	Moderate disability. Requires some help, but able to walk unassisted.
4	Moderately severe disability. Unable to attend to own bodily needs without assistance, and unable to walk unassisted.
5	Severe disability. Requires constant nursing care and attention, bedridden, incontinent.
6	Dead.

doi:10.6342/NTU201903838

Table 2.3 Utility value of mRS in other studies.

mRS	0	1	2	3	4	5
Dijkland et al (2018) [25]	0.95	0.93	0.83	0.62	0.42	0.11
Rivero-Arias et al (2010) [24]	1.00	0.87	0.73	0.60	0.28	-0.1
Ali et al (2017)[28]	0.92	0.84	0.73	0.58	0.37	0.15

Table 2.4 mRS distribution after stroke, reference from Hong and Saver[27]

mRS	Ischemic stroke (%)	Hemorrhagic stroke (%)
0	26.7	20.4
1	27.2	27.6
2	16.7	23.4
3	11.2	14.6
4	11.6	6.6
5	6.6	7.3

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Chapter 3. Materials and Methods

3.1 Study Design

Figure 3.1 illustrates the framework of this thesis. We start from calculating the personalized risk score with 4-state hypertension Markov model underpinning in light of definition from JNC 7, normal, pre-hypertension, stage 1 hypertension, stage 2 hypertension (Table 3.1). The clinical weights of the risk score are borrowed from Tseng's study [11] with Keelung Community-based Screening (KCIS) cohort, and applied to the Changhua Community-based Screening (CHCIS) cohort to stratify the cohort into different risk groups.

Next, we build up a Markov decision tree, incorporating the 4-state hypertension model, incidence of hemorrhagic and ischemic stroke, three functional outcomes after stroke, and death. The parameters of incidence and prognosis of hemorrhagic and ischemic stroke were estimated from KCIS. Functional outcome transition after stroke and quality-adjusted life-years are borrowed from literatures (See below).

The final step is to conduct the cost-effectiveness analysis of personalized prevention of hypertension compared with control group. Probabilistic cost-effectiveness analysis with Monte Carlo simulation with 1st order simulation trials of 24000 study subjects and 2nd order parameter samples of 1000 sampling is applied.

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3.2 Study population

3.2.1 Keelung Community-based Screening (KCIS)

The first study population is from a prospective cohort in a community-based integrated screen program in Keelung (KCIS), Taiwan. This program started in 1999 and targeted on five cancer (breast, cervical, oral, colon and liver cancer) and three chronic disease (hypertension, diabetes mellitus and hyperlipidemia). Participant's baseline demographics, life style, diet habits and disease history were also recorded. The eligible residents in Keelung were invited annually to enter the screening program and different screen intervals for different diseases after their first visit. The clinical weights of risk factor for the four-state hypertension progression and regression, the incidence of hemorrhagic and ischemic stroke, and stage-specific death rate are derived from this cohort.

3.2.1 Changhua Community-based Screening (CHCIS)

The second population is from a community-based integrated screening program in Changhua (CHCIS). This program has been launched since 2005 and is similar to the KCIS program, which screens for liver cancer, breast cancer, colorectal cancer, oral cancer, cervical cancer, and also non-neoplastic diseases such as hyperlipidemia,

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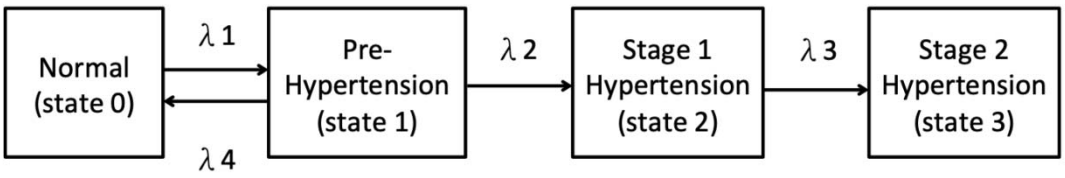
hypertension, and hyperglycemia. We use data from residents who participate this program between 2005 and 2014 as the empirical cohort. The abovementioned multi-state and multifactorial prediction model for hypertension is applied to this cohort for the prediction of incident stoke, and the consequence after taking personalized prevention strategy.

3.3 Four-state Markov model of hypertension considering personal risk profiles

The 4-state discrete state, continuous time, homogenous Markov model, including normal blood pressure, pre-hypertension, stage 1, and stage 2 hypertension is depicted below.



Hypertension stage is classified according to JNC 7 published in 2003: normal (< 120 and < 80 mmHg), pre-hypertension (120 – 139 and/or 80 – 89 mmHg), stage 1 hypertension (140 – 159 and/or 90 – 99 mmHg), and stage 2 hypertension (≥160

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and/or 100 mmHg above). Transition between normal and pre-hypertension is allowed bi-directional, whereas the others are not reversible assuming the hypertension would not be “cured” once stage 1 hypertension is diagnosed. The stage 2 hypertension (state 3) is the absorbing state.

The transition rates of λ_1, λ_2, λ_3, λ_4 are different with age, gender, and individual risk factors for hypertension. An exponential form for the abovementioned transition rates is applied with the following expression:

$$\lambda_i = \lambda_{i0} \times \exp(\alpha+\beta_1 X_1+\beta_2 X_2+\ldots+\beta_k X_k) , \quad i=1,2,3,4$$

The X represents the risk factors, such as BMI, fasting glucose, total cholesterol, uric acid, cigarette smoking, betel quids chewing, and alcohol consumption. The coefficients of covariates and whether the covariates are statistically significant are obtained from Tseng’s study [11]. The author came to a final model for multivariate analysis by keeping the covariates that reach significant level ($\alpha<0.05$).

The risk score of net force for pre-hypertension, stage 1 and stage 2 hypertension are computed by the summation of the values of each factor weighted by regression coefficients, in other words, $(\alpha+\beta_1 X_1+\beta_2 X_2+\ldots+\beta_k X_k)$.

Note that Tseng et al derived risk scores for male and female separately. In order

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to obtain a general score for the entire population, we use the logarithm transformed rate ratio of different transitions by sex and age groups in KCIS [32] to compensate the difference between male and female.

Risk score for men

Net risk score (1) for pre-hypertension

= [(0.028)x(if 40≤ age ≤49)+ (0.3524)x(if 50≤ age ≤59)+ (0.5969)x(if 60≤ age ≤69)+ (0.8)x(if 70≤ age ≤79)+ (0.0431)x(if education above high school)+ (0.5747)x(if BMI≥25)+ (0.2629)x(if fasting glucose≥110)+ (0.1832)x(if cholesterol≥200)+ (0.3232)x(if uric acid≥7)+ (-0.3694)x(if smoking) +(0.2273)x(if betel nut chewing) +(0.2838)x(if alcohol drinking)]

Net risk score (2) for stage 1 hypertension

= [(-0.0382)x(if 40≤ age ≤49)+ (0.6124)x(if 50≤ age ≤59)+ (0.9107)x(if 60≤ age ≤69)+ (1.4042)x(if 70≤ age ≤79)+ (0.0534)x(if education above high school)+ (0.6757)x(if BMI≥25)+ (0.6445)x(if uric acid≥7)+ (-0.3673)x(if smoking) +(0.4746)x(if betel nut chewing) +(0.2578)x(if alcohol drinking)]

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Net risk score (3) for stage 2 hypertension

= [(-0.3471)x(if 40≤ age ≤49)+ (0.3449)x(if 50≤ age ≤59)+ (0.2948)x(if 60≤ age ≤69)+ (0.8989)x(if 70≤ age ≤79)+ (-0.7305)x(if education above high school)+ (0.6088)x(if uric acid≥7)+ (-0.7642)x(if smoking) +(0.882)x(if alcohol drinking)]

Risk score for women

Net risk score (1) for pre-hypertension

= [(0.4345)x(if 40≤ age ≤49)+ (0.9597)x(if 50≤ age ≤59)+ (1.1896)x(if 60≤ age ≤69)+ (1.3606)x(if 70≤ age ≤79)+ (-0.196)x(if education above high school)+(0.5247)x(if BMI≥25)+ (0.3279)x(if waist ≥ 80cm)+(0.3532)x(if fasting glucose≥110)+ (0.1827)x(if cholesterol≥200)+ (0.3784)x(if uric acid≥7)+ (-0.3726)x(if smoking) +(0.3691)x(if positive family history)]

Net risk score (2) for stage 1 hypertension

= [(0.8651)x(if 40≤ age ≤49)+ (1.7573)x(if 50≤ age ≤59)+ (2.1587)x(if 60≤ age ≤69)+ (2.4969)x(if 70≤ age ≤79)+ (-0.2837)x(if education above high school)+ (0.6447)x(if BMI≥25) + (0.2956)x(if waist ≥ 80cm) +(0.5796)x(if fasting glucose≥110)+ (0.6861)x(if uric acid≥7)+ (-0.6524)x(if smoking) +(0.6985)x(if positive family history)]

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Net risk score (3) for stage 2 hypertension

= [(1.6346)x(if 40≤ age ≤49)+ (2.1999)x(if 50≤ age ≤59)+ (2.6665)x(if 60≤ age ≤69)+ (3.5783)x(if 70≤ age ≤79)+ (0.9171)x(if uric acid≥7) +(0.598)x(if positive family history)]

The total net force of hypertension progression is the summation of the three net risk scores = Score (1) + Score (2) + Score (3). The applied results to the CHCIS cohort are used to classify the entire cohort into 10 risk groups by their total net force risk score.

3.4 Incidence of stroke

All participants in KCIS between January, 1999 and December, 2004 are checked with the claimed data in National Health Insurance (NHI) program for the diagnosis of stroke by International Classification of Disease version 9 (ICD 9). Subjects with ICD9 of 430, 431 and 432 are classified as hemorrhagic stroke; those with ICD9 of 433, 434 are classified as ischemic stroke. To maximize the case ascertainment, only subjects with at least two ambulatory visits in one year was considered as stroke. Because the ICD9 of 436-438 is coding for unspecified cerebrovascular disease, it is difficult to determine the stroke type of these patients. We

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used missing complete at random principle to assign unspecific stroke into hemorrhagic or ischemic stroke according to the four states of blood pressure. Those with stroke history recognized by NHI database before they entered the screening program are excluded. The stroke index date is the first visit day with stroke ICD 9 coding obtained from NHI database.

3.5 Time-variant transition probability of the functional outcome after stroke

In order to estimate the quality-adjusted life after stroke more precisely, we incorporate the function outcome after stroke. Modified Rankin scale (mRS) is a commonly used measure to evaluate the functional level of the stroke patients.

Some studies assume the functional level after stroke is constant for analytic convenience; however, in practice, functional state usually change in the first few months then become stable thereafter. Pan et al studied the dynamic functional outcome after ischemic stroke assuming the transition probability is variant with time[29, 30]. They gave a 3-state Markov model, classified the survivors of ischemic stroke into 3 categories according to the Barthel index (poor functional state: 0-40; moderate functional state: 45-80; good functional state: 85-100).

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The transition intensity ν is modeled time-varying by a power function of time:

$\nu_{ij}(t) = \nu_{ij}t^r$

The r is power parameter and the unit of time is month. The result of transition intensity ν and r is listed in Table3.2.

We assumed this classification of the functional outcome also fit the mRS if we define the poor functional state as mRS 4-5, moderate functional state as mRS 2-3, and good functional state as mRS 0-1. We can use the transition intensity to calculate the time-dependent transition probability between function outcome after stoke.

3.6 Utility of the functional outcome after stroke

Because our data did not include the disabled degree after stroke, we extracted the mRS distribution from the study of Hong and Saver, 2009 [27] (Table 2.4). To convert the ordinal scale of mRS into utility value, we also use the referential utility in the study of Dijkland et al[25] (Table 2.3).

The utility value in Dijkland's study is correlated to each mRS level. In this study, we combine mRS 0 and 1 into the good functional state. The utility of good

doi:10.6342/NTU201903838

functional state is then weighted by case number. Utility values of moderate functional state and poor functional state are calculated with the same method, as shown in Table 3.2. mRS 6 is refer to death with a utility value of 0.

3.7 Mortality of patients with and without stroke

The KCIS cohort were followed up to the end of 2010. We firstly depict the cumulative survival curve by states of blood pressure and stoke with life-table method. For subjects without stroke, the survival time is calculated since the entry to the KCIS program up to the endpoint, death or the end of 2010, whichever comes first. For those with stroke ascertained, the survival time is calculated since diagnosis of stroke to the endpoint. Deaths from all causes are treated as event.

Because we only have 12-year empirical data, the projection of survival with longer follow-up is needed. We fit the data with parametric method. Considering that the hazard rate of death vary with time, we use the accelerated failure time model assuming Weibull distribution for the survival time. The predicted survival function is expressed as follows,

$$S(t) = exp\left[-\left(\frac{t}{\lambda}\right)^{\gamma}\right]$$

where λ and γ are scale and shape parameters. The larger the λ, the lower the risk of death. $\gamma > 1$ refers to an increasing hazard rate with time, $\gamma < 1$ indicates a

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decreasing hazard rate with time, and $\gamma = 1$ stands for constant hazard rate regardless of time.

3.8 Personalized intervention to prevent stroke

Personalized intervention strategy is different from population-intervention that we focus on selecting the high risk subjects to give specific, usually more intensive, intervention to avoid the complication occurrence.

The personalized prevention programs for hypertension included three intervention programs. One is applied in the subjects with top 20% risk score in the stage 1 and 2 hypertension to identify the carotid artery stenosis by using one-time carotid ultrasound screen. People with >70% carotid stenosis will undergo intra-arterial stenting and long-term medical follow up. The second program is designed to give blood pressure-lowering medicine to highest 30% risk score group in pre-hypertension state. The third one is population-based primary prevention approach.

Program 1. Carotid stenosis screen and treat

One-time screening with carotid ultrasound would be applied in the top 20% high risk score subjects if they reach stage 1 or 2 hypertension. The sensitivity of using ultrasound as a tool to diagnose carotid stenosis is high, ranging from 90-98%[31].

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After the carotid ultrasound, the patient will receive carotid stenting if they have severe stenosis (70%-99% stenosis). These patients have to be hospitalized and confirmed diagnosis by cerebral angiography before carotid stenting. After carotid stenting, they have to take dual antiplatelet, usually aspirin plus clopidogrel, for 3 months and then aspirin for life long.

The prevalence of carotid stenosis is based on a meta-analysis by Weerd et al[32]. They collected 4 population-based studies with total 23,706 participants underwent carotid ultrasound screen. The prevalence of severe carotid stenosis (≥ 70%) was depicted by gender and age in decile as in Table 3.3. In another meta-analysis published by de Weerd et al[33], they reported the pooled prevalence of severe asymptomatic carotid stenosis in general population was 1.7% (95% CI, 0.7% to 3.9%). In this thesis, we assume the top 5% highest risk group in the general population with stage 2 hypertension at entry of screening have severe carotid stenosis because they possess most risk factors. These population make up 1.25% of all sampled CHCIS participants, which is close to the pooled prevalence reported by de Weerd et al.

The cost of carotid ultrasound is based on Taiwan National Health Insurance reimbursement price in 2019, which is 2,040 NTD. The cost of hospitalized for cerebral angiography and carotid stenting is calculated by an empiric data of averaged fee from a Medical center in north Taiwan, which is 172,273.5 NTD (SD 28,101,

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95%CI: 163,094 – 181,453). The annual cost of medicine and outpatient clinic follow up is about 6,404 ~ 6,504 NTD in the first year and 3,164 ~ 3,264 NTD in the subsequent years, calculating from each antiplatelet price and outpatient clinic fee.

The efficacy of carotid stenting is assumed the same as endarterectomy, which is an older fashion of carotid stenosis treatment in the 1990s. According to the Asymptomatic Carotid Surgery Trial (ACST)[34], an international randomized clinical trial conducted in 1993-2003, the stroke incidence rate decreased by 46% (RR=0.54, 95% CI: 0.43-0.68) after endarterectomy in asymptomatic carotid stenosis. The Carotid Revascularization Endarterectomy versus Stenting Trial (CREST) is a randomized trial with patients randomized to endarterectomy or carotid stenting[35]. There was no significant difference in the rates of stroke in asymptomatic carotid stenosis for stenting and endarterectomy (2.5% VS 1.4%, HR=1.88, 95% CI: 0.79-4.42).

Program 2. Blood pressure lowering medicine in pre-hypertension

This specific treatment is designed to give anti-hypertensive medicine to the subjects with high risk score (top 30%) for hypertension progression if they reach the pre-hypertension state. We assumed the blood pressure is relative easy to control by using single-drug therapy in pre-hypertensive subjects. In a Taiwan study, they sampled 200,000 person during 1997-2004 for NHI database. They found the most

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frequent used anti-hypertensive medicine was calcium channel blocker (51.8% of total medicine prescribed). Therefore we choose a commonly used calcium channel blocker, Amlodipine(@Norvasc) as the prescribed medicine. The cost is based on Taiwan National Health Insurance reimbursement price in 2019 in standard dosage (5-10mg per day). It takes 1,668 NTD every year. The patient need to be followed up at outpatient clinic every 3 months, which cost 2,416~2,516 NTD every year. The total estimate cost is 4284~ 4,384 NTD per year. One study had simulated a cohort of Chinese adult in the high-ranged pre-hypertension (blood pressure 130-139/85-89 mmHg) to analyze the cost-effectiveness of anti-hypertensive and the cost of annual anti-hypertension medicine is $ 161.4[36], which is similar to our estimation. The effect of the anti-hypertensive medication use in pre-hypertensive group had been reported in literature. Julius et al conducted a randomized control trial (Trial of preventing hypertension, TROPHY) on 722 high-normal pre-hypertensive participants and separated them into two group[37]. One group took an anti-hypertensive agent, candesartan, which is a kind of angiotensin receptor blocker, and the control group took placebo. The result showed the relative risk of developing hypertension is 0.34(95%CI: 0.25-0.44) at 2 years.

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Program 3. Population-based primary prevention strategy

The population-based primary hypertension prevention strategy was also applied to all participants at the same time. This primary prevention is composed of approaches to promote public health, such as encourage exercise by building convenient and cheap sport environment, encourage low salt diet, DASH diet, body weight control, and supportive program for quitting smoking or drinking. A study published by Cook et al (1995) examined the impact of a population-based strategy aimed to reduce diastolic blood pressure by an average of 2 mmHg. They reported a 15% reduction in risk of stroke. We cited the result of Cook's study as the effectiveness of primary hypertension prevention in general population.

We borrow the expenditure from Pay for Performance Program for Diabetes under Taiwan National Health Insurance as our cost for primary prevention. This program assigned the reimbursement price of the clinic visit of a diabetic patient. It costs 600 NTD each year to cover evaluation for patient's drug adherence, lifestyle modification, psychosocial status, nutrition therapy, tobacco and alcohol use, physical examination and laboratory tests. All these items are similar to that in primary prevention.

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3.9 The cost of stroke

We obtain the cost after stroke by referring the data published by Taiwan National Health Insurance Administration (https://www1.nhi.gov.tw/mqinfo/Map_1.aspx?Type=Stroke&DAID=2259&List=4#). The average medical cost, including the acute phase hospitalization and subacute rehabilitation facility, within 180 days after stroke during 2016-2018 is listed in Table 3.3.

The long-term care cost after stroke is depending on the functional performance. According to the Report of Disabled People's Living Condition and Demand Survey 2016, published by Taiwan Ministry of Health and Welfare, the average medical and nursing expenditure in each disability degree is listed in Table 3.4.

We consider the functional performance after stroke by mRS level in our thesis. Usually, patients with good outcome (mRS 0-1) have no or minimal disability. Therefore the cost in good functional group just counts the medical cost (2,034 NTD) per month. In the patients with moderate functional outcome (mRS 2-3), we assume their disability level is correspond to mild to moderate disability, so the monthly cost would be the average of total cost of mild to moderate disability (24,126 NTD). Similarly, the cost of poor functional outcome (mRS 4-5) would be the average of total

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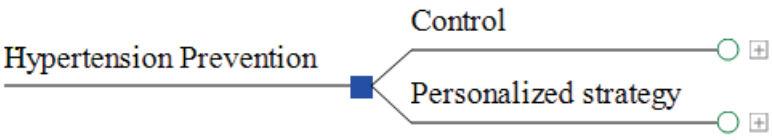
cost of severe to very severe disability (25,846 NTD) per month. We summed up the annual direct cost after the stroke, separated by functional level in Table 3.5.

We also considered the indirect cost made by income loss from carotid ultrasound exam (0.5 day), hospitalized for carotid stenting (7 days), and working ability impairment after stroke (per year). We assumed the patients with mRS 0-1 could maintain their working ability as before, therefore the indirect loss from lose job just count those with mRS 2-5. The income loss is calculated by Taiwan GDP in 2017 multiplied by the days.

3.10 Markov decision tree

We depicted a flow chart of our model in Figure 3.2 , including a 4-state hypertension stage, hemorrhagic or ischemic stroke, and a 3-state functional outcome after stroke. The patient might die whenever they are free of stroke, immediate after stroke, or a period after stroke. Taken together, we constructed a Markov decision tree to conduct the cost-effectiveness.

1. The first decision node represents the decision for a subject receiving a personalized intervention program or in the control group.



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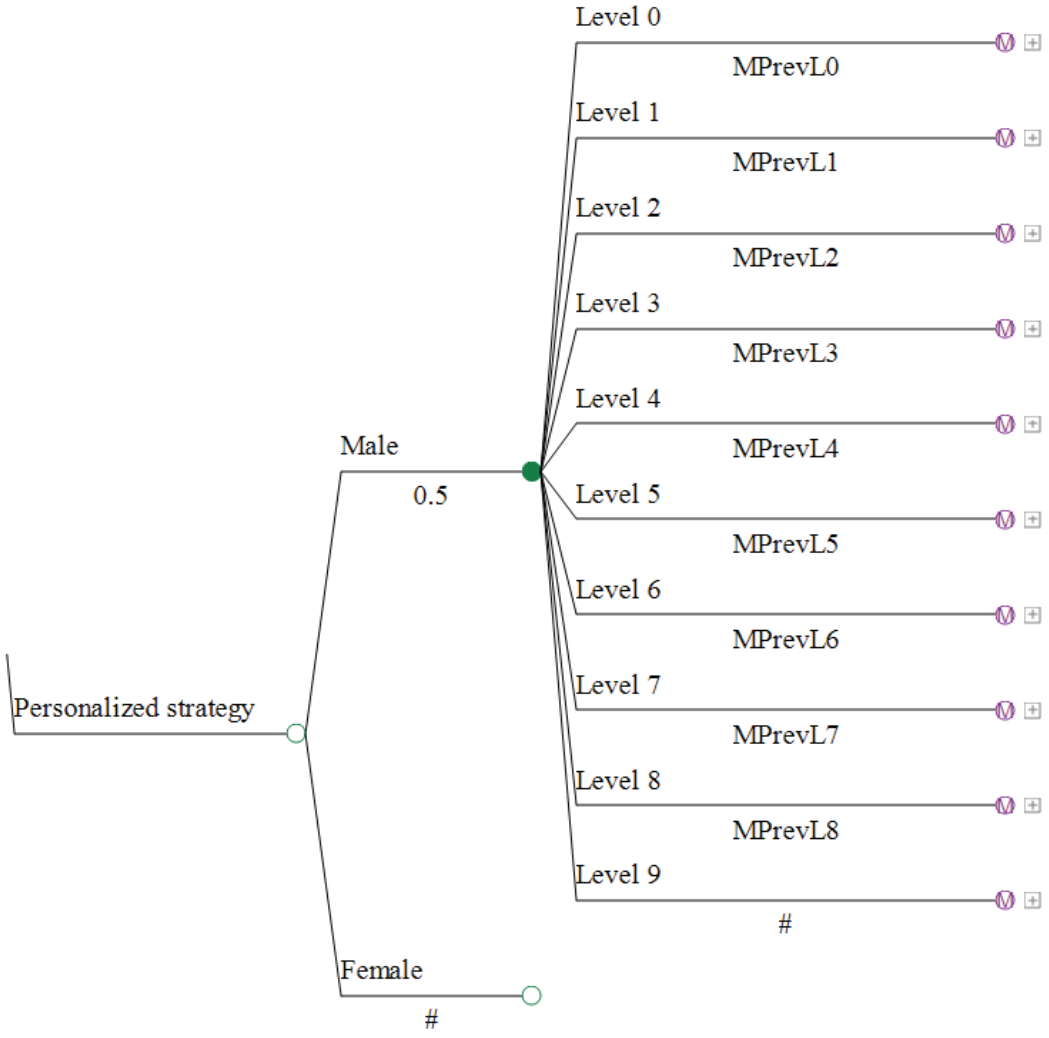
2. Under each decision, one subjects could be assigned to any risk level (Level 1 to Level 10) according to proportions of all risk levels by sex.



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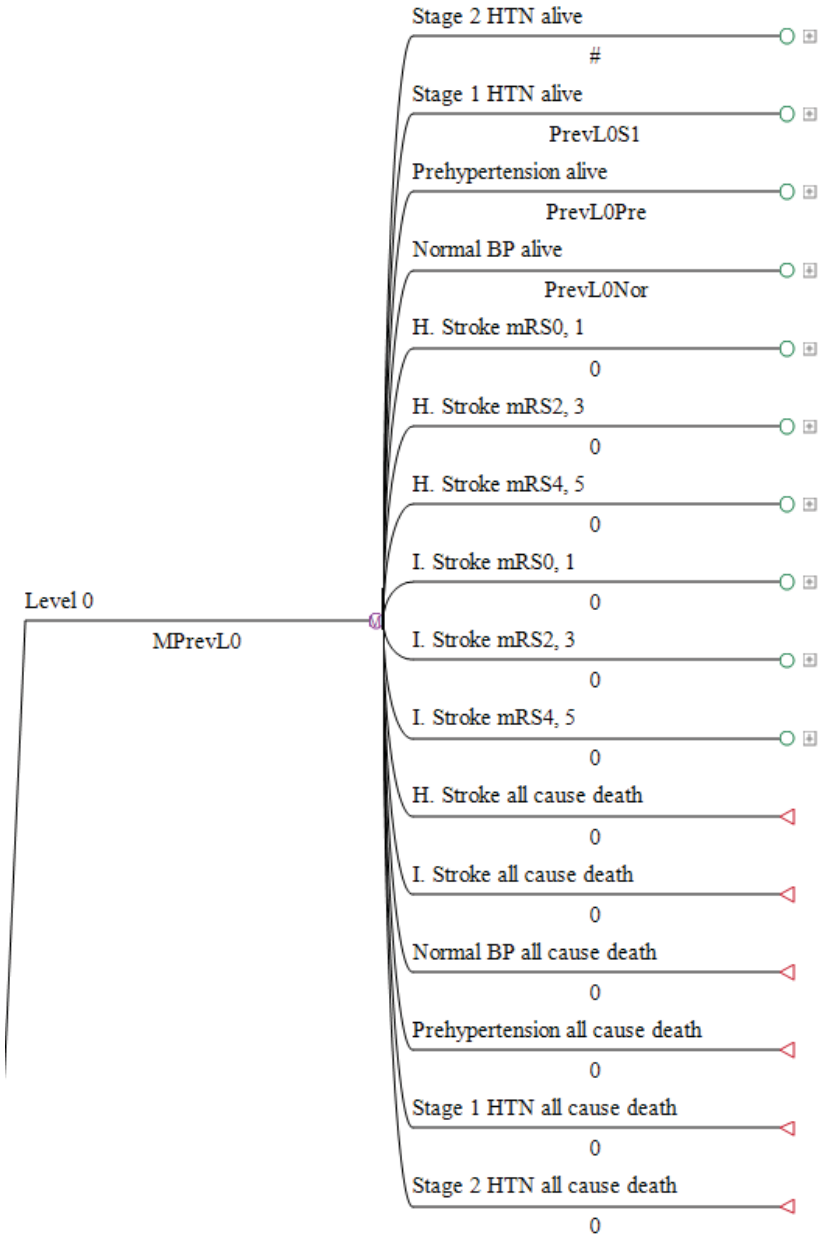
3. Each node of different risk level would be followed by a Markov node for the repetition with time. The first cycle begins with allocating the cohort into one of the hypertension stage according to the prevalence we observed from CHCIS population using the first visit blood pressure record in each group by gender. In addition, all the possible states of future events, including incidence stroke by subtypes and the associated deaths are defined in this level.



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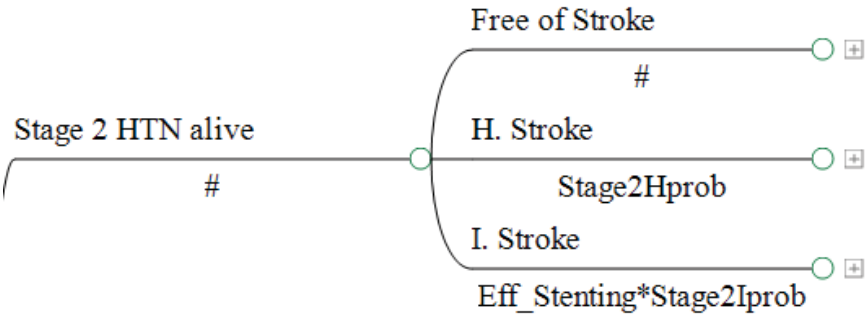
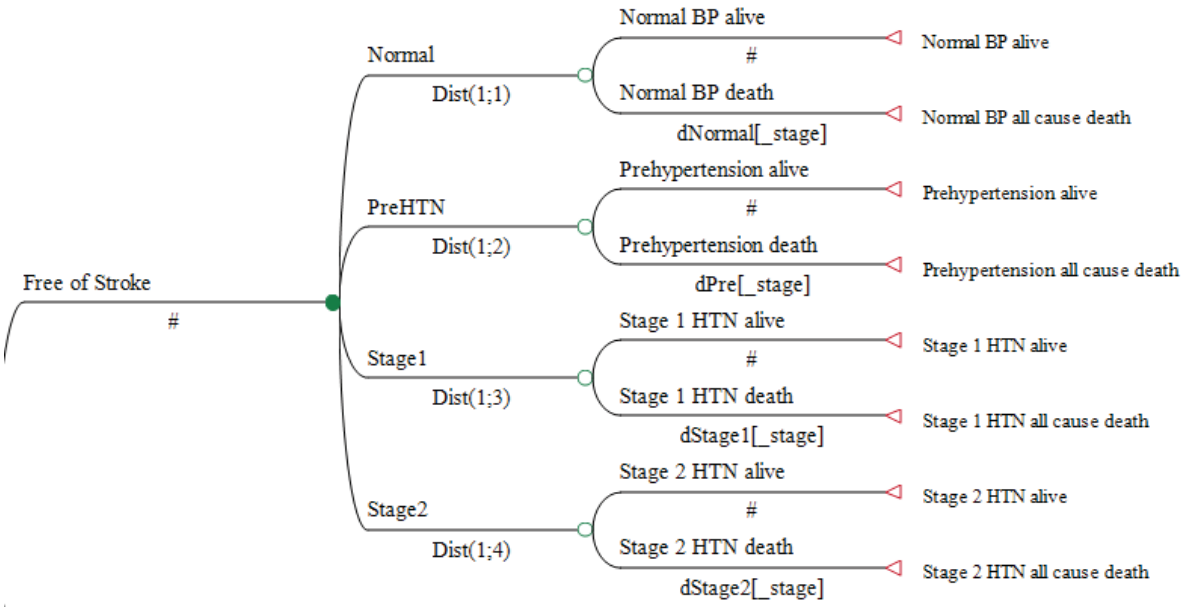
4. The subjects free of stroke come to a chance node of having a stroke (by subtype) or not, depending on the transition rate of hemorrhagic and ischemic stroke by risk group (Section 4.2). The efficacy of prevention program is assigned if applicable.



5. If the subject is free of stroke, he/she will be assign to one of the hypertension state (Section 4.1). The transition of the blood pressure state is according to the risk level (Section 4.1). Given each stage, the subject can stay alive or death according to the stage-specific mortality rate (Section 4.4).



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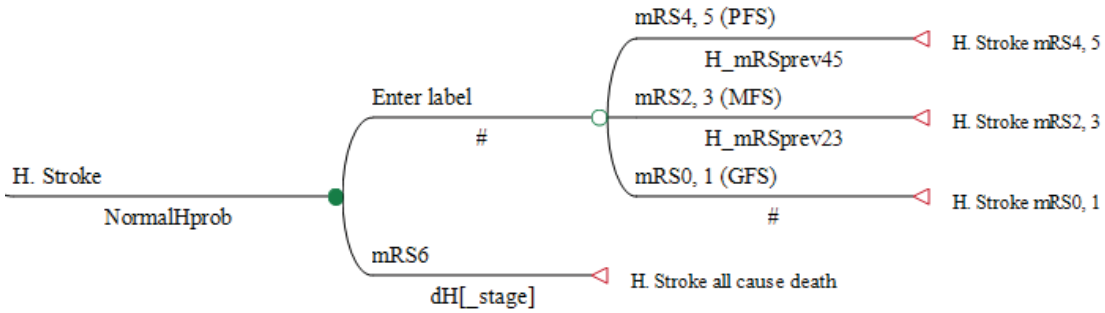
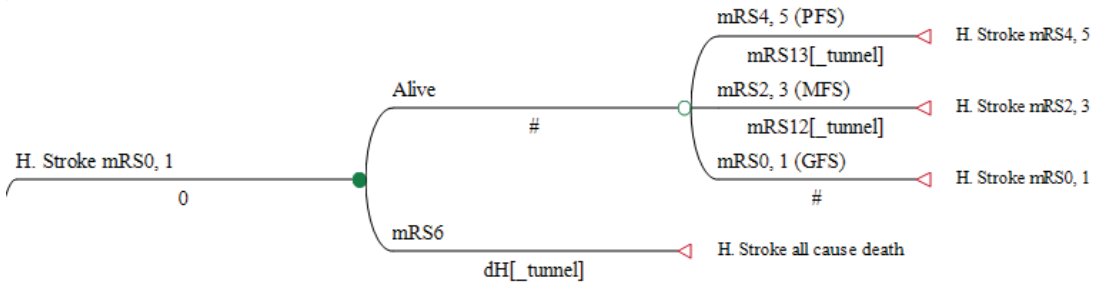
6. If the subject has either incident hemorrhagic or ischemic stroke, he/she will enter a chance node to determine the functional state after stroke, good functional state(mRS 0-1), moderate functional state(mRS 2-3), poor functional state(mRS 4-5), and dead from stroke(mRS=6). The distribution of the mRS state is extracted from literature (Section 3.6). If the patient survives form stroke, he/she will enter the next cycle start from the corresponding functional state after hemorrhagic or ischemic stroke.



7. The patient then comes to a chance node of staying alive or die from any cause. The patient would have functional state transition if they are alive, according to the time-varying transition probability (Section 4.3), and enter the next Markov cycle.



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The parameters of natural history, effectiveness, and cost used in our Markov decision tree were listed in Table 3.6 and Table 3.7. In addition to the values assigned for the base case, the distributions corresponding to different parameters are also shown in tables in order to consider the uncertainty from parameters in the probabilistic cost-effectiveness analysis (see below). Our Markov decision tree has 1 year for each cycle. The time horizon is 20 years. We set 3% discount for both measures of cost and effectiveness. A societal viewpoint is taken in this thesis.

3.11 Cost-effectiveness Analysis

The endpoints of this analysis are the number of stroke adverted and the long-term quality-adjusted life-year (QALY) gained in the personalized preventive strategy. The incremental cost-utility ratio (ICUR) are calculated in probabilistic analysis model which applied Monte Carlo simulation to select values at random from specific distributions for the relevant parameters in each Markov cycle.

To assess whether the interventional program is more cost-effective than no intervention is affected by the effect of uncertainty of parameters. We perform a series of 1000 replicates of simulation by using Monte Carlo simulation. The results of ICUR from the 1000 replicates are plotted in four quadrants of incremental cost-effectiveness plane. Besides, the probability of being cost-effective for the personalized intervention

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against the ceiling ratio was delineated by using acceptability curve. The sooner the curve of acceptability curve reaching 1 the more likely to be cost-effective.

doi:10.6342/NTU201903838

Tables of chapter 3

Table 3.1 Transition intensity of functional states from Pan's study[30].

ν12	ν23	ν32	ν21	r
0.8181	0.1024	0.0764	0.0290	-1.0620

Table 3.2 Combined utility of functional states from Dijkland's study[25].

mRS	**0**	**1**	**2**	**3**	**4**	**5**	**6**
Utility	0.95	0.93	0.83	0.62	0.42	0.11	0
Case number	7	36	84	87	133	45	108
Combined utility	0.93		0.72		0.34		0

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Table 3.3. The average medical cost within 180 days after stroke during 2016-2018

Period	Cost (NTD)	Period	Cost (NTD)
2016 Q1	178,700	2017 Q2	170,491
2016 Q2	171,258	2017 Q3	169,221
2016 Q3	172,964	2017 Q4	189,254
2016 Q4	173,836	2018 Q1	187,417
2017 Q1	181,428	2018 Q2	182,023

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Table 3.4 The average medical and nursing expenditure of each disability degree

Disability degree	Medical Cost (NTD)/ month	Nursing cost (NTD)/ month	Total cost (NTD)/ month
Mild	2,034	23,118	25,152
Moderate	1,928	21,173	23,101
Severe	2,773	21,916	24,689
Very severe	3,909	23,093	27,002

Table 3.5 The annual direct cost after stroke by functional level

Functional level	Cost of first year after stroke (NTD)	Cost of subsequent years (NTD/year)
Good function	First 6 month cost +12,204	24,408
Moderate function	First 6 month cost +144,756	289,512
Poor function	First 6 month cost +155,076	310,152

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Table 3.6 Parameter of natural history for hypertension progression and regression by different risk group

	Parameters of Dirichlet distribution			
From Normal to Normal, Prehypertension, Stage I, and Stage II Hypertension ~ Dirichlet $(\alpha_1, \alpha_2, \alpha_3, \alpha_4)$				
Risk Group	α_1	α_2	α_3	α_4
1	1035.6	317.1	37.7	3.6
2	580.1	279.7	45.6	3.6
3	442.7	246.6	41.6	3.1
4	382.5	245.9	48.6	4.0
5	320.0	223.2	44.8	4.0
6	282.4	220.7	46.4	4.5
7	209.4	195.6	44.9	4.1
8	153.1	171.4	41.2	4.3
9	126.9	159.2	43.0	4.9
10	81.1	127.8	41.5	5.6
From Prehypertension to Normal, Prehypertension, Stage I, and Stage II Hypertension ~ Dirichlet $(\alpha_1, \alpha_2, \alpha_3, \alpha_4)$				
Risk Group	α_1	α_2	α_3	α_4
1	391.5	346.2	94.9	14.4
2	355.2	474.8	162.3	19.7
3	294.2	517.3	176.4	20.1
4	283.6	587.9	230.5	28.0
5	240.0	551.8	211.8	28.4
6	214.6	562.9	225.8	33.7
7	193.0	582.4	251.7	34.9
8	177.4	587.9	256.3	38.4
9	148.2	577.8	283.7	46.3
10	114.2	554.0	318.3	59.5

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From Stage I Hypertension to Stage I, and Stage II Hypertension ~ Dirichlet (α_1, α_2)				
Risk Group	α_1	α_2		
1	94.7	27.3		
2	210.7	49.3		
3	222.9	49.1		
4	272.8	64.2		
5	310.5	81.5		
6	301.3	89.7		
7	364.2	99.8		
8	366.1	109.9		
9	376.6	123.4		
10	356.9	135.1		

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Table 3.7 Parameters of effectiveness of intervention and cost

Parameter		95% CI/ Distribution	Reference
Effectiveness	RR		
Efficacy of primary prevention on stroke	0.85		Nancy, Cook et al
Efficacy of carotid stenting on stroke	0.54	0.43-0.68 Beta(33.66, 28.67)	ACST, Halliday et al
Efficacy of anti-hypertensive medicine on hypertension	0.34	0.25-0.44 Beta(33.14, 64.33)	TROPHY, Julius et al
Direct cost	**Mean(NTD)**		
Cost of primary prevention	600		Pay for Performance Program for Diabetes
Cost of carotid ultrasound	2,040		Taiwan NHI price
Cost of hospitalization for carotid stenting	172,274	Triangular(115,050, 254,242)	One Medical center data in Taiwan
Cost of follow up after stenting in first year	6,454	Triangular(6,404, 6,504)	Taiwan NHI price
Cost of follow up after stenting in subsequent year (per year)	3,224	Triangular(3,164, 3,264)	Taiwan NHI price
Cost of anti-hypertensive medicine (per year)	4,334	Triangular(4284, 4,384)	Taiwan NHI price
Cost of stroke in first year	177,659	Triangular(169,221, 189,254)	Taiwan National Health Insurance Administration, Report of Disabled People's Living Condition and Demand Survey, 2016
mRS 0-1	+12,204		
mRS 2-3	+144,756		
mRS 4-5	+155,076		
Cost of stoke in subsequent year (per year)			
mRS 0-1	24,408		

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Parameter		95% CI/ Distribution	Reference
mRS 2-3	289,512		
mRS 4-5	310,152		
Indirect cost	**Mean(NTD)**		
Work lost for stroke case (per year)	737,310		Using Taiwan GDP in 2017
Work loss for carotid ultrasound	1,009		
Work loss for hospitalization for carotid stenting	14,130		

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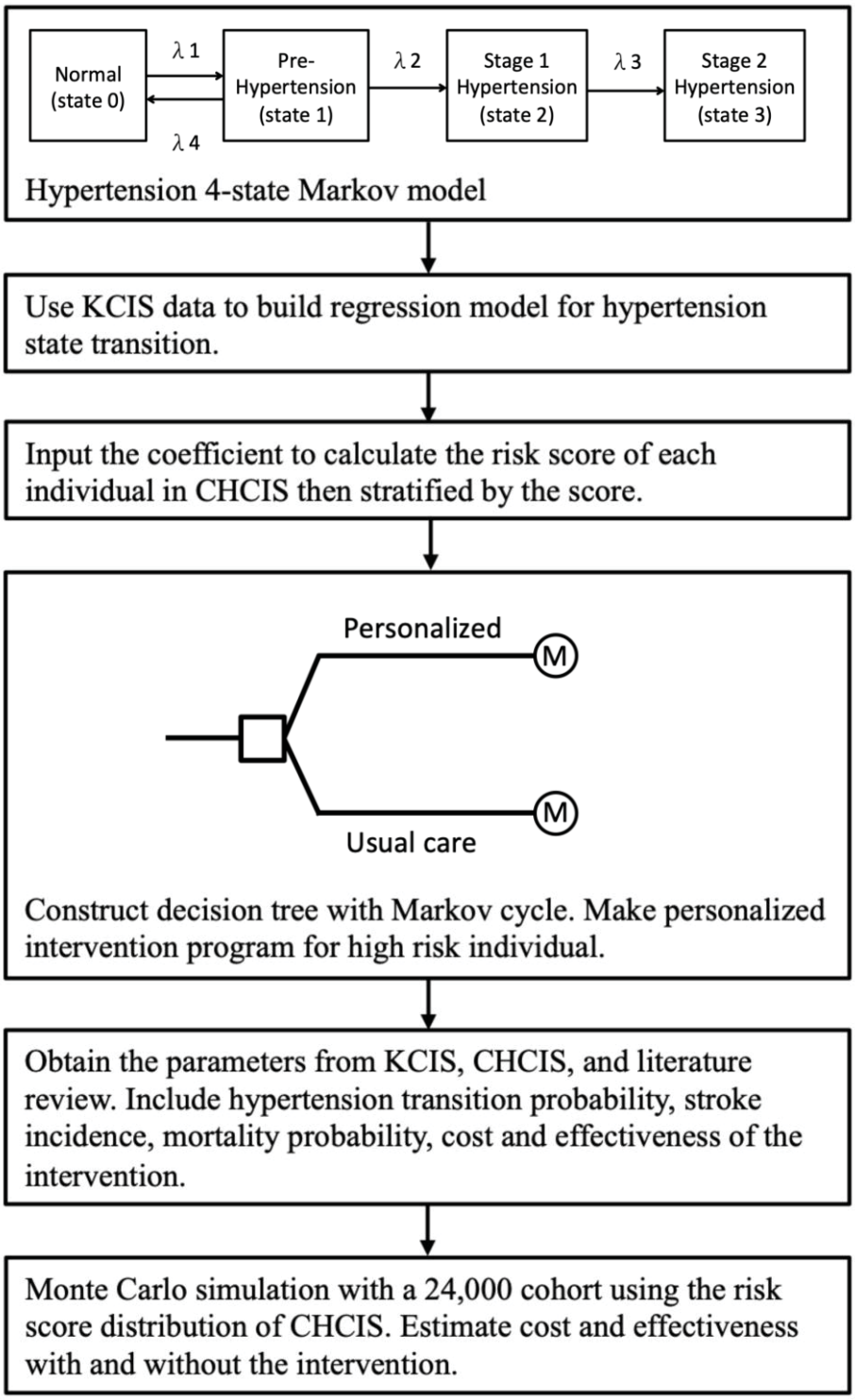
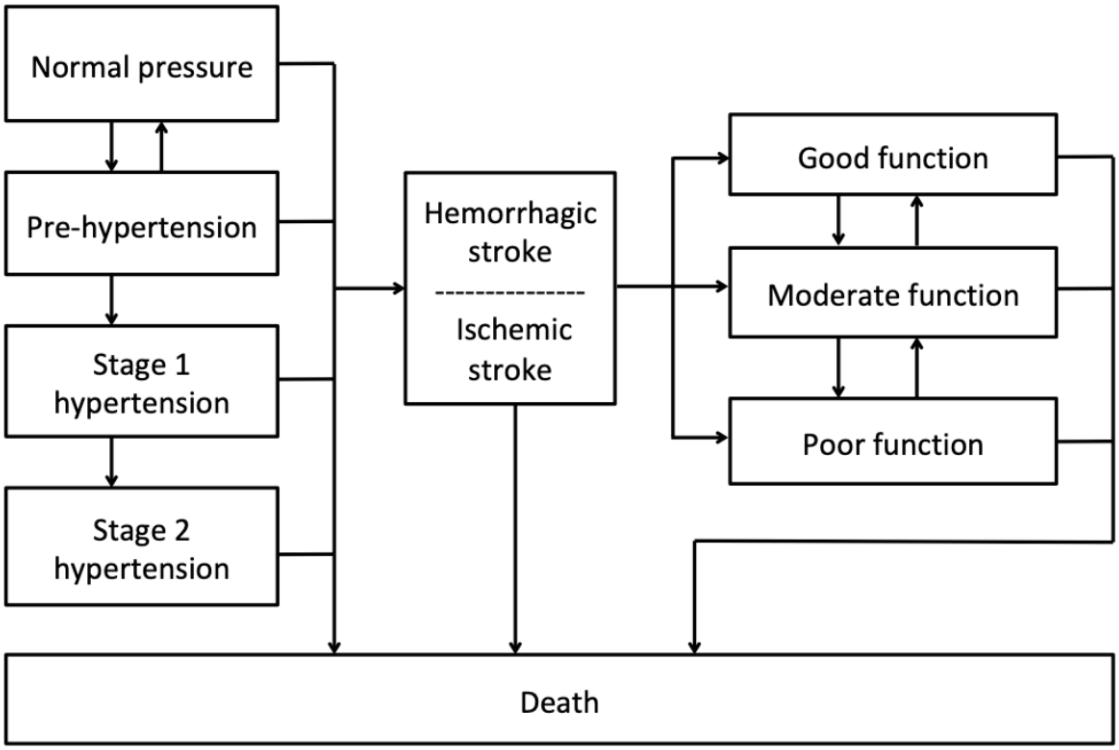
Figures of chapter 3

Figure 3.1. Framework of study design



doi:10.6342/NTU201903838

Figure 3.2 Schematic diagram of the Markov process of stroke.



doi:10.6342/NTU201903838

Chapter 4. Results

4.1 Personalized risk profiles in the CHCIS cohort

The risk profiles of our simulated cohort are borrowed from the participants in the CHCIS program in 2005-2014. However, in the original screening cohort, male participants (n=32498) are outnumber by female participants (n=12122). We therefore randomly sample 12,000 men and 12,000 women from the CHCIS cohort. The distributions of risk factors of these samples are shown in Table 4.1 separated by gender. Male has higher prevalence of hypertension than female. The prevalence of prehypertension, stage 1, and stage 2 hypertension are 43.5%, 17.4%, and 18.3%, respectively, for men, and 41.9%, 13.7%, and 12.6% for women. In male participants, hypertension is associated with elder age, lower education level, higher BMI and waist circumference, higher fasting glucose, higher cholesterol, alcohol drinking, elevated uric acid, and family history of hypertension, but negatively associated with smoking. There is no statistically significant association between betel quid chewing and hypertension. Regular exercise is more common in those with stage 1 and stage 2 hypertension. The trends of association between these risk factors in female are similar to those in male, except regular exercise and family history of hypertension are not related to hypertension in female, and alcohol drinking shows inverse association with

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hypertension.

We apply the prediction model for hypertension and the trained clinical weights from Tseng's study [11] to the CHCIS sampled cohort and calculated the risk scores for the CHCIS cohort. The distribution of score for pre-hypertension, stage 1, and stage 2 hypertension in male and female for the CHCIS cohort is shown in Figure 4.1. The scores roughly follow normal distribution. It can be seen that men have higher score for pre-hypertension (43.75 ± 6.11), stage 1 (49.52 ± 8.27), and stage 2 hypertension (57.94 ± 12.1) than female [pre-hypertension (27.63 ± 9.51), stage 1 (45.26 ± 13.83), and stage 2 hypertension (53.97 ± 13.91)]. We further categorized our population into 10 risk groups according to the deciles of the total risk score. Higher risk level was associated with elder age, and larger proportion of male (Table 4.2). Female predominate the lowest risk group (98% in Risk group 1). The proportion of female decrease with higher risk groups.

In the lowest risk group, the prevalence of stage 1 and stage 2 hypertension are both 5%. It increase with risk profile to 22% and 25% for stage 1 and stage 2 hypertension, respectively, in the higher risk group (Table 4.3). We also found the higher transition probabilities of progression to severe hypertension states in the higher risk groups (Table 4.4).

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4.2 Incidence of stroke

The cumulative incidence of hemorrhagic and ischemic stroke are depicted in Figure 4.2. The risk of hemorrhagic stroke increase with severity of hypertension. The 5-year cumulative incidence rates are 2.7, 7.8, 10.8, and 20.6 for subjects with normal blood pressure, pre-hypertension, stage 1 and stage 2 hypertension, respectively. Given the same hypertension level, incidence of ischemic stroke is higher than its counterpart of hemorrhagic stroke. For the ischemic stroke, the incidence is similar in subjects with normal blood pressure and prehypertension. Those with stage 1 and stage 2 hypertension have higher incidence rate, but not differ between each other. The 5-year cumulative incidence rates are 10.9, 13.1, 43.6, and 54.3 for subjects with normal blood pressure, pre-hypertension, stage 1 and stage 2 hypertension, respectively. The incidence of unspecific stroke is closed to ischemic stroke, except for stage 1 hypertension.

If we redistribute unspecific stroke into hemorrhagic and ischemic stroke, we can have the 5-year cumulative incidence rates of hemorrhagic stroke as 4.3, 12.6, 14.2, 31.3 per 1000 in normal blood pressure, pre-hypertension, stage 1 and stage 2 hypertension, respectively. The corresponding figures for ischemic stroke were 17.3, 21.4, 57.3, and 82.6 per 1000, respectively (Figure 4.2).

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4.3 Annual transition probability of functional states depending on time

Figure 4.4 shows the annual transition probability of function states by time after stroke according to the state in the initial of the year. As indicated in Pan's study [30], the estimated power to time (r=-1.0620) on transition rate from poor to moderate implies that the recovery rate from poor would decrease by time. The annual transition probability from poor to good are 41.5% in year 1, 39% in year 2, 12.7% in year 3, 7.6% in year 4, 5.4% in year 5, and decrease to less than 3% after year 8. It also shows that one-year transition probabilities of staying in poor function are 13% in the initial year, 19% in year 2, 67% in year 3, 80% in year 5, and increased to 90% in year 7 after (Figure 4.4 (A)).

For those in moderate function, transition to good function is (43%) stable across time. The probability of progression to poor function is about 12% in year 1, and increase gradually to about 20% after year 5 (Figure 4.4 (B)). If patients have good function, they have quite stable chance to staying in good function (60%) and progressing to moderate (32%) or poor function (8%) in each year (Figure 4.4 (C)). This finding elucidates the fact that the initial function level after stroke has great influence on the subsequent functional shifting.

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4.4 Mortality of subjects with and without stroke

The cumulative survival for subjects with and without stroke using life-table method is depicted in Figure 4.5. The 10-year survival is 95.9%, 93.1%, 88.6%, and 85.0% for subjects without stroke but of normal blood pressure, pre-hypertension, stage 1, and stage 2 hypertension, respectively. The corresponding figures for hemorrhagic and ischemic stroke are 66.5% and 64.2%, respectively.

In order to have survival data for our 20-year long decision tree, we model the survival with parametric model. Table 4.5 shows the estimated results of AFT model assuming Weibull distributed survival by blood pressure and stroke. The scale parameters decrease with severity of blood pressure for subjects without stroke, which implies that the death rate increased with severity of hypertension. Patients with stroke have higher risk of death than those without stroke. The shape parameters is statistically significantly larger than one for the four types of subjects without stroke, suggesting increasing death rate by time, which can be explained by the aging effect. Such an aging effect is not shown in patients with stroke. The cumulative survival is depicted in Figure 4.5. The 10-year survival by level of blood pressure and stroke is close to their counterparts from the life-table method.

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4.5 Cost-effectiveness of personalized prevention of hypertension

Table 4.6 shows the simulated incident stroke cases by sex and risk group in a simulated cohort size of 24,000 subjects under the two strategies, personalized prevention program and control. Among the Changhua population, the incidence of stoke is 16 per 1,000 with 4.2 and 11.8 per 1,000 for hemorrhagic and ischemic type in the control group. The personalized prevention can reduce risk of stroke by 17% (95% CI: 15-18%). The reduction in preventing ischemic stroke (17%, 95% CI: 16-19%) is larger than that in hemorrhagic stroke(15%, 95% CI: 11-18%), possible due to the extra benefit from carotid stenosis screening.

Table 4.7 shows the results of cost-effectiveness analysis for the personalized prevention for hypertension compared with control and the incremental cost-utility ratio in the light of outcomes defined as accumulative utility in 20 years. The average quality-adjusted life year (QALY) gained per subject as a result of personalized strategy is 0.17 years compared to control. The accumulative cost of personalized strategy is less than control by NTD 161,170, which suggests personalized prevention dominates over control from societal perspective because personalized prevention not only prolongs life bus also saves cost.

After taking the uncertainty into account, Figure 4.6 shows the simulated results of 1000 replicates of ICURs plotted on the scatter C-E plane. As the majority of points lie

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in the quadrant IV (less cost and more effectiveness) the dominance of personalized prevention program over control is almost certain even taking the worst case of parameters. This is also supported by the results of acceptability curve in Figure 4.7 that shows the probability of being cost-effective is almost certain even in the low value of the maximum amount of willingness to pay (ceiling ratio).

4.5.1 Sensitivity Analysis

In order to test the influence of re-distribution of unspecific stroke into hemorrhagic and ischemic stroke, we perform another set of cost-effectiveness analysis with incidence of stroke without inclusion of unspecific stroke. Namely, the incidence of hemorrhagic stroke for normal blood pressure, stage 1, and stage 2 hypertension are 0.5, 1.6, 2.2, and 4.2 per 1000 person-years, respectively. The corresponding figures for ischemic stroke are 2.2, 2.6, 8.9, and 11.2 per 1000 person-years, which are about two-thirds risk of the basecase estimate. The results show that the QALY gained of personalized prevention became smaller (0.14). The magnitude of cost saving also shrinks than the basecase estimate. Nonetheless, the results still suggest that personalized prevention is a dominate strategy against control (Table 4.8). Taking the uncertainty into account, the scatter incremental cost-effectiveness plot (Figure 4.8) and acceptability curve (Figure 4.9) also support the finding.

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Tables of chapter 4

Table 4.1 Descriptive statistics for sampling population in CHICS during 2005 to 2014

	Normal	Prehypertension	Stage1 Hypertension	Stage2 Hypertension	P-value[a]	P-value[b]
Male (n =12,000)	2493	5221	2090	2196		
Prevalence, %	20.78	43.51	17.42	18.30		
Age(years), mean(s.d.)	54.87 (10.54)	55.95 (10.35)	57.89 (10.61)	57.09 (10.41)	<0.0001	<0.0001
Higher education, %	44.56	41.91	37.99	36.89	<0.0001	<0.0001
BMI ≥25 kg/m2, %	27.12	43.77	51.96	56.06	<0.0001	<0.0001
Waist (90cm+), %	16.89	27.91	37.94	40.80	<0.0001	<0.0001
Fasting glucose (110 mg/dl+), %	9.99	14.38	19.14	19.67	<0.0001	<0.0001
Total cholesterol (200 mg/dl+), %	33.81	39.51	41.91	44.95	<0.0001	<0.0001
Smoker, %	60.85	55.77	52.49	51.23	<0.0001	<0.0001
Betel quid chewer, %	30.45	29.42	30.72	29.55	0.6326	0.8259
Alcohol drinker, %	52.95	56.29	57.13	57.42	0.0059	<0.0001
Regular exerciser, %	53.67	58.74	61.82	60.38	<0.0001	<0.0001
Uric acid (7+ mg/dl), %	22.10	28.39	29.67	31.24	<0.0001	<0.0001
Family history of hypertension, %	19.53	20.95	21.87	23.68	0.0051	0.0004

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	Normal	Prehypertension	Stage1 Hypertension	Stage2 Hypertension	P-value[a]	P-value[b]
Female (n =12,000)	3823	5027	1638	1512		
Prevalence, %	31.86	41.89	13.65	12.60		
Age(years), mean(s.d.)	51.55 (8.40)	54.66 (8.78)	56.73 (8.75)	56.68 (9.31)	<0.0001	<0.0001
Higher education, %	44.68	30.93	22.34	22.88	<0.0001	<0.0001
BMI ≥25 kg/m2, %	23.72	40.96	53.85	54.43	<0.0001	<0.0001
Waist (80cm+), %	24.20	42.07	54.21	54.70	<0.0001	<0.0001
Fasting glucose (110 mg/dl+), %	6.91	13.87	18.56	19.78	<0.0001	<0.0001
Total cholesterol (200 mg/dl+), %	39.71	49.95	56.11	55.09	<0.0001	<0.0001
Smoker, %	2.62	1.87	1.59	1.65	0.0197	0.0066
Betel quid chewer, %	0.31	0.24	0.31	0.13	0.6581	0.3414
Alcohol drinker, %	17.21	12.37	10.74	10.65	<0.0001	<0.0001
Regular exerciser, %	56.89	57.41	58.30	57.54	0.8111	0.4663
Uric acid (6+ mg/dl), %	11.93	17.94	21.92	22.49	<0.0001	<0.0001
Family history of hypertension, %	23.28	23.71	23.57	24.80	0.7046	0.2993

P-value[a] with chi-square test. P-value[b] with Cochran–Armitage trend test.

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Table 4.2 The distribution of score, age, and sex by risk group in CHCIS

Risk Group	Total Score		Age		Sex	
	Mean	Std	Mean	Std	Male	Female
0	76.96	11.21	45.16	3.86	2%	98%
1	104.08	4.92	51.75	7.64	14%	86%
2	116.86	3.59	52.57	9.52	53%	47%
3	127.32	2.57	57.49	9.30	45%	55%
4	135.92	2.56	55.18	10.31	66%	34%
5	144.46	2.72	56.90	9.71	66%	34%
6	153.08	2.80	58.35	9.05	63%	37%
7	163.07	2.96	57.17	10.05	67%	33%
8	174.78	3.84	58.47	9.13	68%	32%
9	195.18	11.03	59.78	9.17	60%	40%

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Table 4.3 Prevalence of hypertension by risk group in CHCIS

Risk Group	Prevalence (%)			
	Normal	Pre hypertension	Stage 1 Hypertension	Stage 2 Hypertension
0	56%	35%	5%	5%
1	39%	41%	9%	10%
2	33%	44%	12%	11%
3	27%	46%	14%	13%
4	25%	44%	17%	14%
5	23%	44%	17%	16%
6	19%	44%	19%	18%
7	15%	44%	20%	22%
8	14%	43%	21%	22%
9	11%	43%	22%	25%

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Table 4.4 The calculated annual transition probability by risk groups

Risk Group	Transition probability	*Destination state*			
		Normal	Pre hypertension	Stage 1 Hypertension	Stage 2 Hypertension
	Departing state				
0	Normal	74.3%	22.7%	2.7%	0.3%
	Pre hypertension	46.2%	40.9%	11.2%	1.7%
	Stage 1 Hypertension			77.6%	22.4%
1	Normal	63.8%	30.8%	5.0%	0.4%
	Pre hypertension	35.1%	46.9%	16.0%	2.0%
	Stage 1 Hypertension			81.0%	19.0%
2	Normal	60.3%	33.6%	5.7%	0.4%
	Pre hypertension	29.2%	51.3%	17.5%	2.0%
	Stage 1 Hypertension			82.0%	18.0%
3	Normal	56.2%	36.1%	7.1%	0.6%
	Pre hypertension	25.1%	52.0%	20.4%	2.5%
	Stage 1 Hypertension			81.0%	19.0%
4	Normal	52.6%	38.9%	7.8%	0.7%
	Pre hypertension	23.3%	53.5%	20.5%	2.7%
	Stage 1 Hypertension			79.2%	20.8%
5	Normal	51.0%	39.8%	8.4%	0.8%
	Pre hypertension	20.7%	54.3%	21.8%	3.2%
	Stage 1 Hypertension			77.0%	23.0%
6	Normal	46.1%	43.1%	9.9%	0.9%
	Pre hypertension	18.2%	54.8%	23.7%	3.3%
	Stage 1 Hypertension			78.5%	21.5%
7	Normal	41.4%	46.3%	11.1%	1.1%
	Pre hypertension	16.7%	55.5%	24.2%	3.6%
	Stage 1 Hypertension			76.9%	23.1%
8	Normal	38.0%	47.7%	12.9%	1.4%
	Pre hypertension	14.0%	54.7%	26.9%	4.4%
	Stage 1 Hypertension			75.3%	24.7%
9	Normal	31.7%	49.9%	16.2%	2.1%
	Pre hypertension	10.9%	53.0%	30.4%	5.7%
	Stage 1 Hypertension			72.5%	27.5%

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Table 4.5 Estimated results of scale and shape parameters of Weibull distribution in the AFT model for all cause of death by level of blood pressure and stroke

Level of blood pressure/ Stroke	Parameter	Estimate	Standard Error	95% Confidence Interval
Free of stroke				
Normal blood pressure				
	Scale	140.41	13.10	116.94, 168.59
	Shape	1.17	0.04	1.10, 1.25
Prehypertension				
	Scale	76.78	4.74	68.03, 86.66
	Shape	1.26	0.03	1.20, 1.33
Stage I hypertension				
	Scale	47.11	2.93	41.71, 53.21
	Shape	1.33	0.04	1.25, 1.42
Stage II hypertension				
	Scale	37.72	2.83	32.57, 43.70
	Shape	1.26	0.06	1.15, 1.37
Hemorrhagic stroke				
	Scale	24.51	5.17	16.21, 37.05
	Shape	1.02	0.14	0.79, 1.32
Ischemic stroke				
	Scale	21.94	2.35	17.78, 27.07
	Shape	0.98	0.07	0.86, 1.12

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Table 4.6 Simulated results of comparisons between personalized strategy and control (24,000 simulated cohort)

Strategy	Risk Group	Subject	Person years	Number of incident stroke		
				Hemorrhagic	Ischemic	Overall
Personalized prevention						
	Male					
	0	56	993	3	7	10
	1	344	5931	19	54	74
	2	1216	20818	71	200	270
	3	1058	17944	65	183	249
	4	1591	26856	101	282	382
	5	1572	26394	103	285	388
	6	1507	25197	100	279	379
	7	1598	27134	99	268	367
	8	1623	27412	104	281	385
	9	761	12808	50	129	179
	9.5	674	11612	48	74	122
	Female					
	0	2429	43090	110	313	424
	1	2112	36411	118	333	451
	2	1074	18387	62	176	239
	3	1312	22252	81	227	308
	4	833	14061	53	147	200
	5	803	13482	52	146	198
	6	895	14964	59	166	225
	7	801	13601	50	134	184
	8	775	13090	50	134	184
	9	483	8129	32	82	114
	9.5	483	8105	35	53	88
	Total	24000	408671	1465	3953	5420
	Annual Incidence (per 1000)			3.59	9.67	13.26

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Strategy	Risk Group	Subject	Person years	Number of incident stroke		
				Hemorrhagic	Ischemic	Overall
Control						
	Male					
	0	56	991	3	8	11
	1	344	5917	22	62	84
	2	1216	20769	81	229	310
	3	1058	17891	75	210	285
	4	1591	26777	115	323	438
	5	1572	26315	118	326	444
	6	1507	25122	115	319	434
	7	1598	26511	124	344	469
	8	1623	26812	129	356	484
	9	761	12534	61	169	230
	9.5	674	11328	55	152	208
	Female					
	0	2429	42993	127	361	488
	1	2112	36326	136	383	518
	2	1074	18344	72	202	274
	3	1312	22186	93	261	353
	4	833	14019	60	169	229
	5	803	13442	60	167	227
	6	895	14920	68	189	258
	7	801	13289	62	173	235
	8	775	12803	61	170	231
	9	483	7955	39	107	146
	9.5	483	7907	40	109	149
	Total	24000	405151	1716	4789	6505
	Incidence			4.24	11.82	16.06
RR (Personalized prevention vs Control)				0.85 (0.82-0.89)	0.83 (0.81-0.84)	0.83 (0.82-0.85)

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Table 4.7 Cost-effectiveness analysis between personalized strategy and control

Strategy	Cost (NTD)	Incremental Cost	Utility	Incremental Utility	ICUR
Control	972,657	-	12.40	-	-
Personalized strategy	811,487	-161,170	12.57	0.17	Dominate

Table 4.8 Cost-effectiveness analysis between personalized strategy and control without adjustment of unspecific stroke

Strategy	Cost (NTD)	Incremental Cost	Utility	Incremental Utility	ICUR
Control	676,877	-	12.62	-	-
Personalized strategy	564,314	-112,563	12.76	0.14	Dominate

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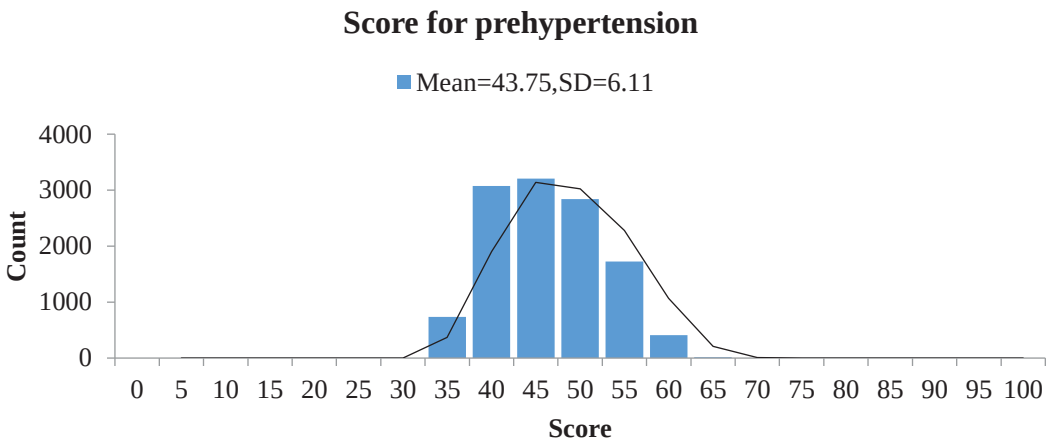
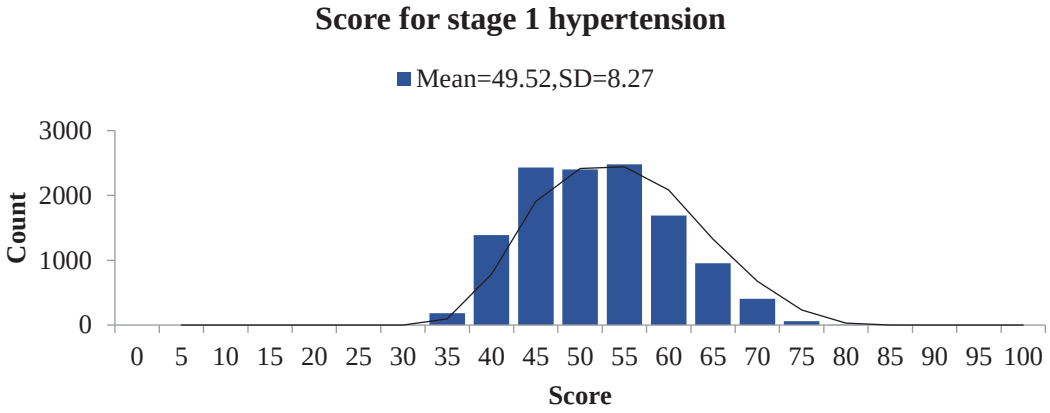
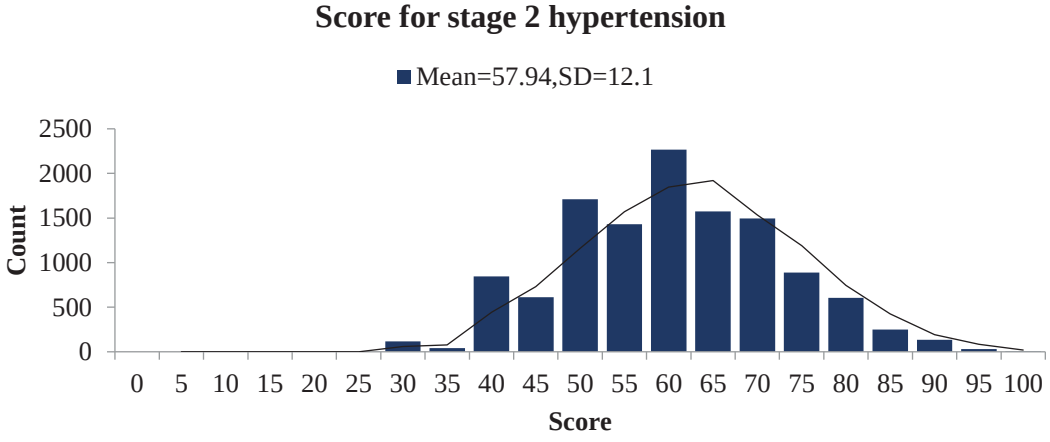
Figures of chapter 4

Figure 4.1 Distribution of risk scores for prehypertension, stage 1 hypertension, stage 2 hypertension in CHCIS

(A) Male







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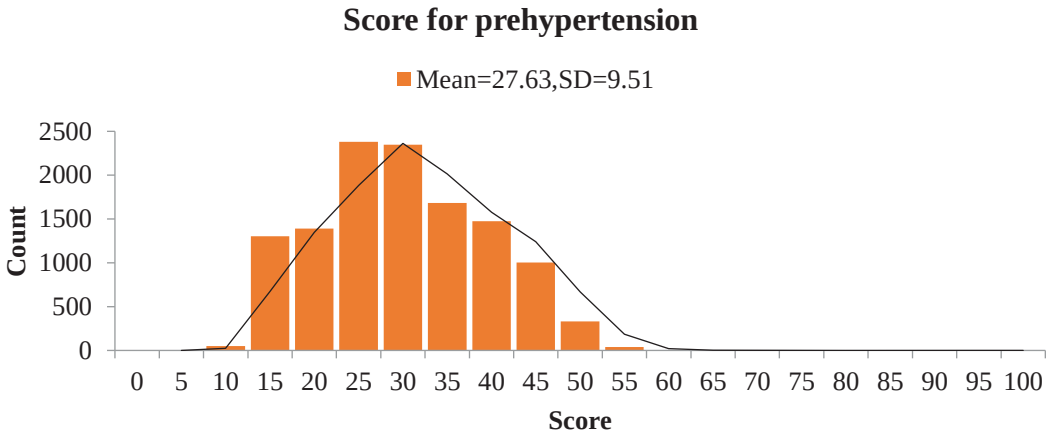
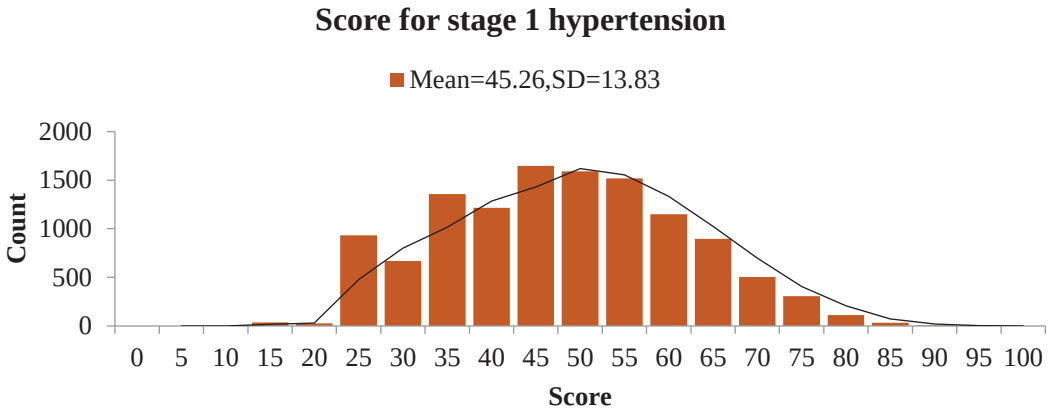
(B) Female





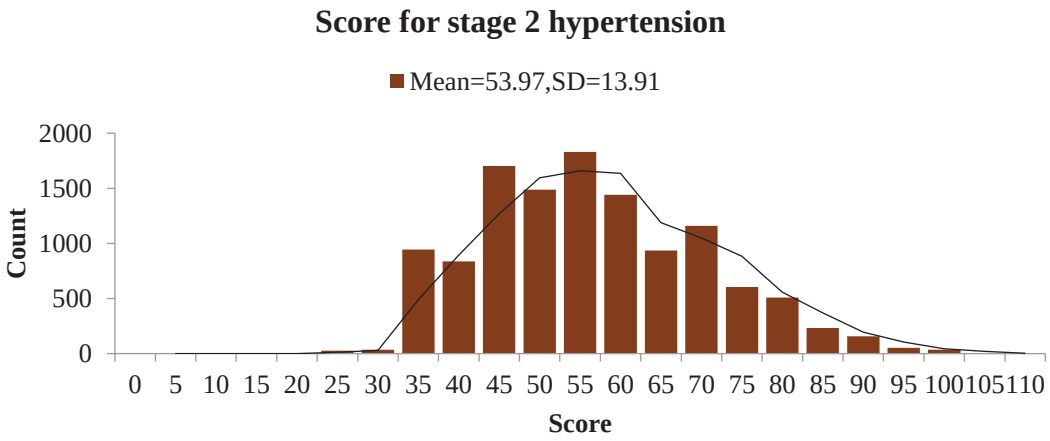


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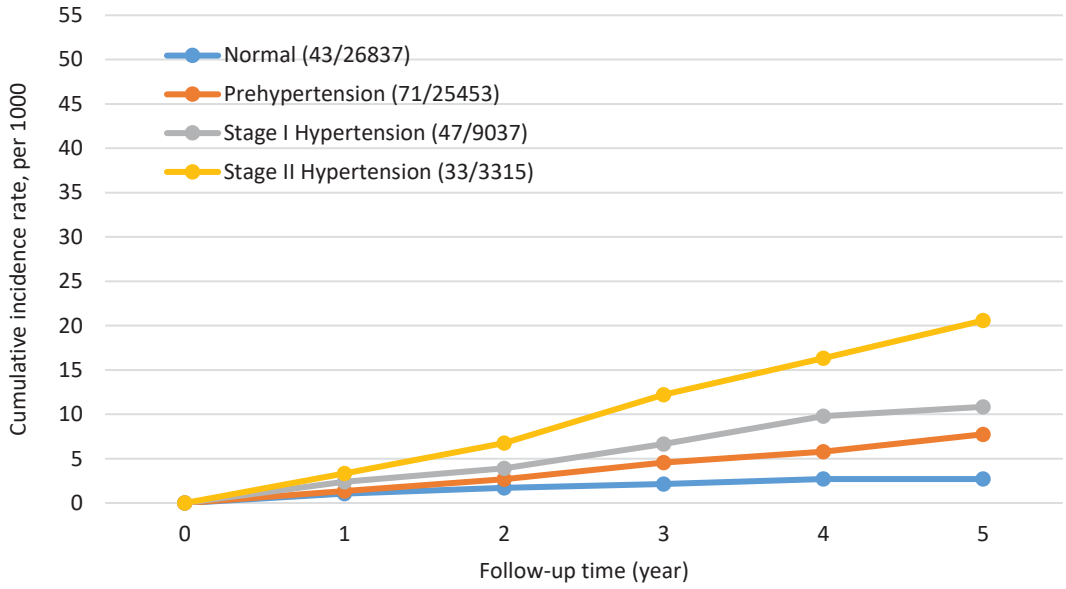
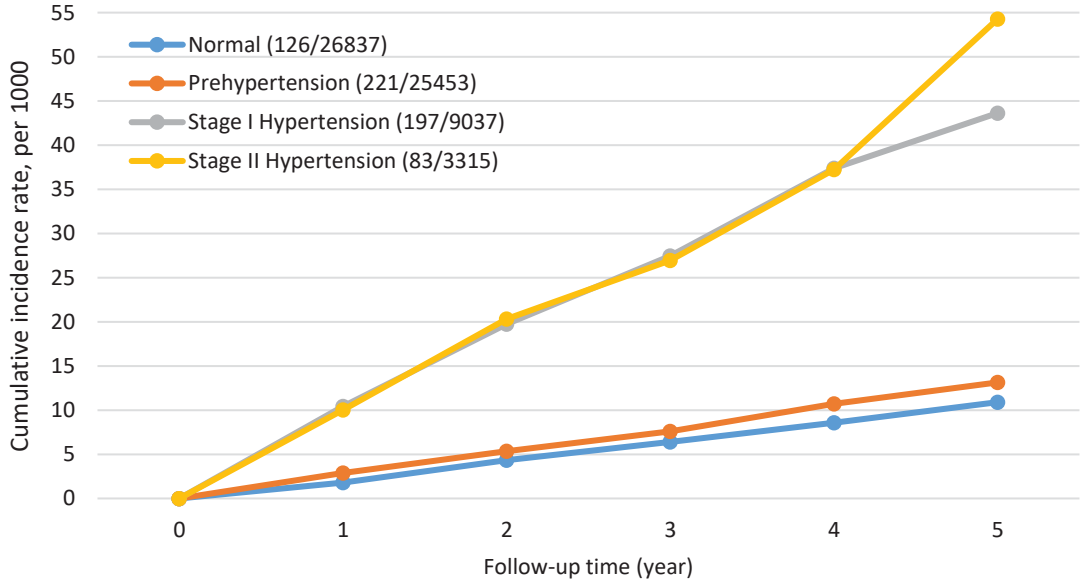
Figure 4.2 Cumulative incidence of stroke by blood pressure group

(A) Hemorrhagic stroke



(B) Ischemic stroke



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(C) Unspecific stroke

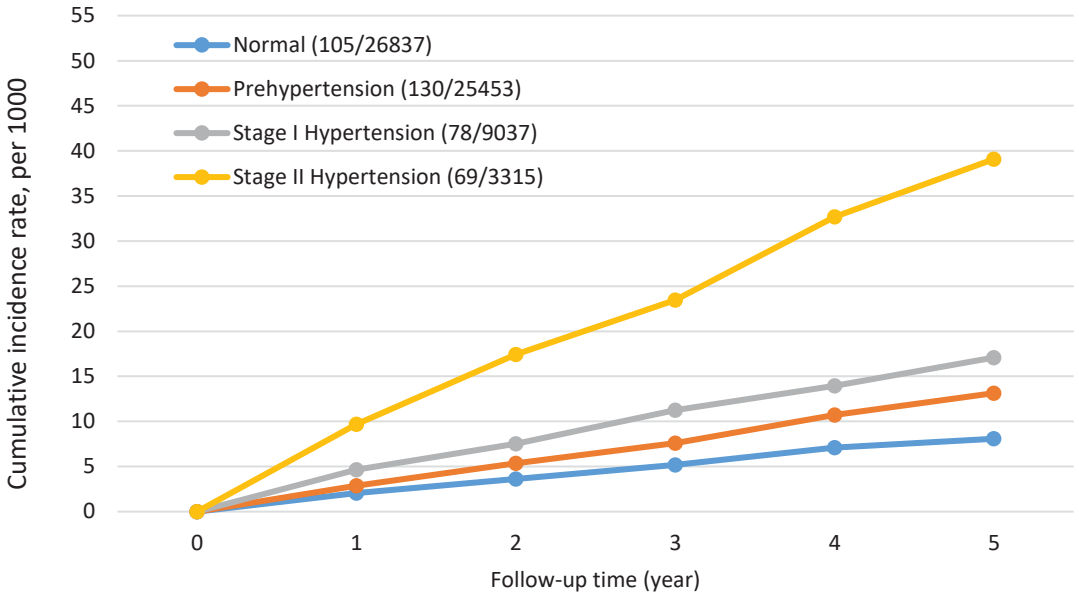

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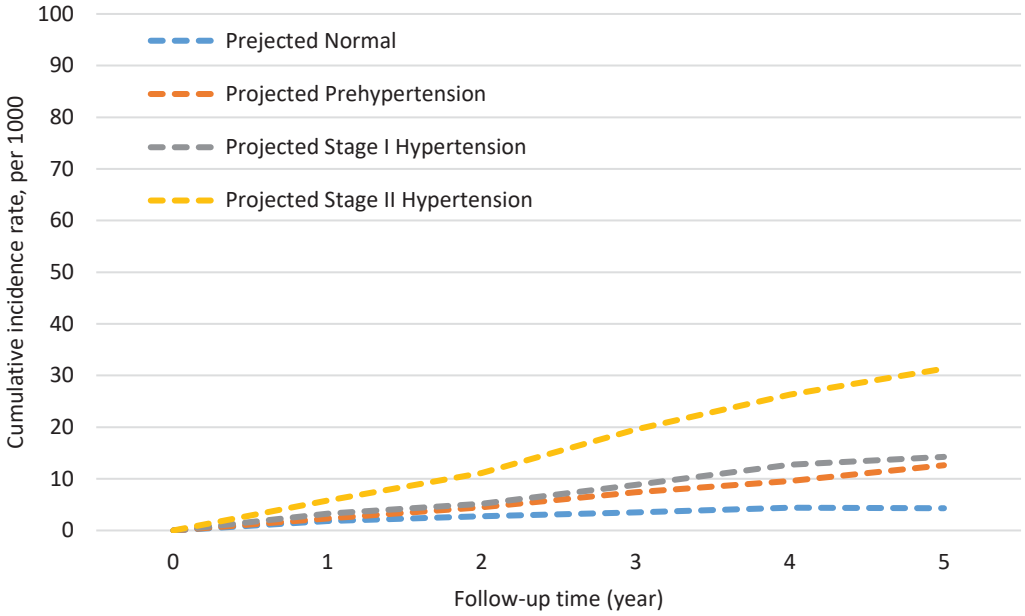
Figure 4.3 Projected cumulative incidence of stroke by blood pressure group after re-classifying unspecific stroke

(A) Hemorrhagic stroke



(B) Ischemic stroke

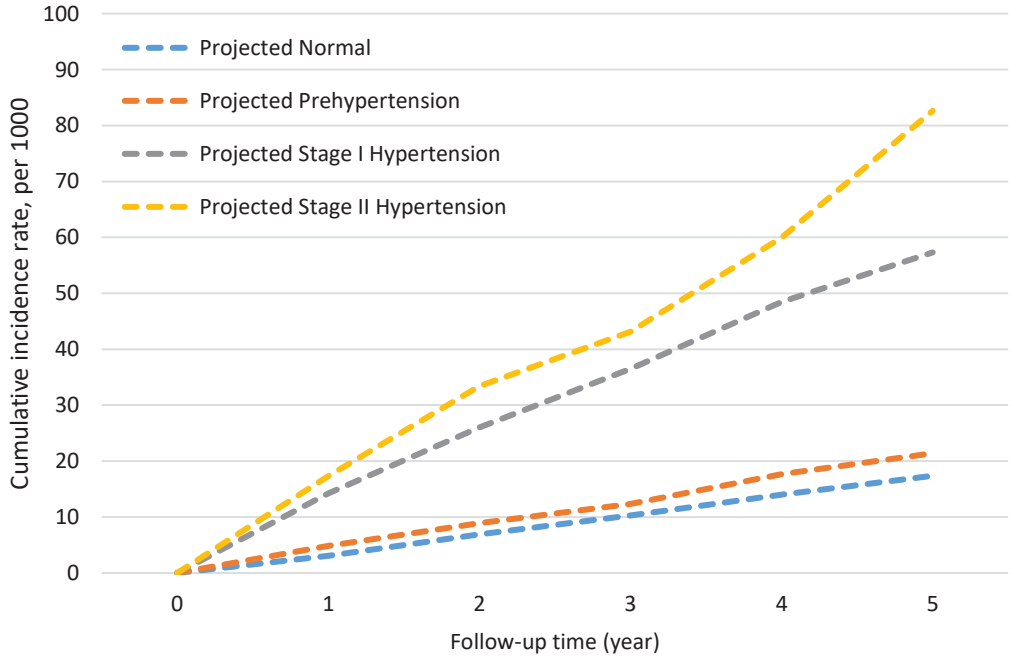


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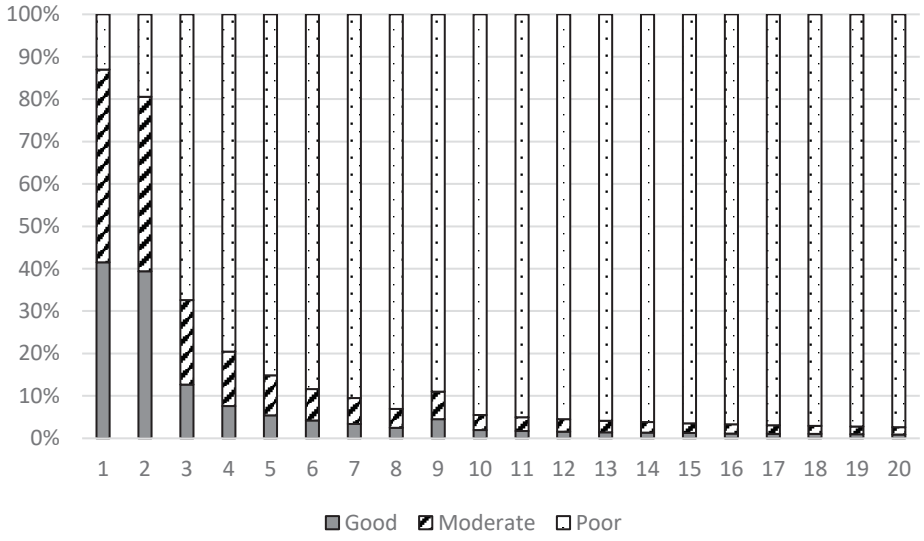
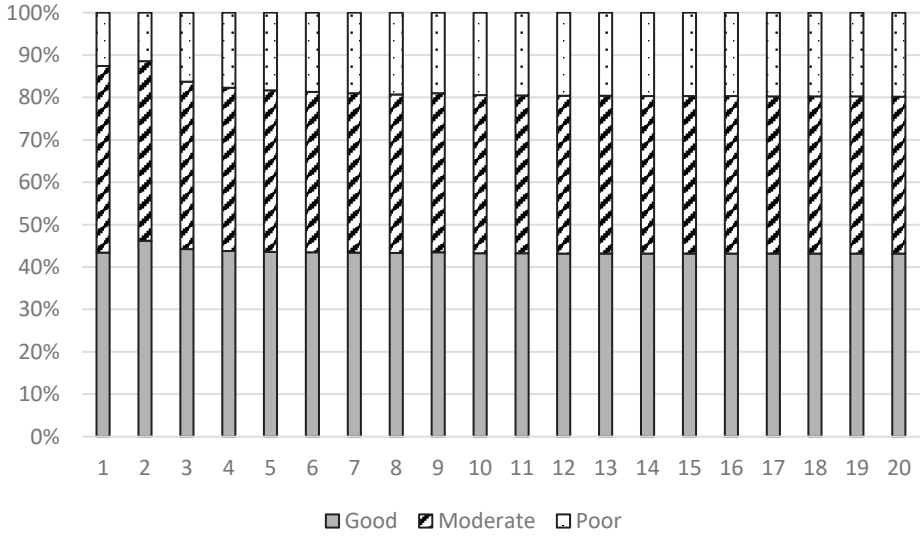
Figure 4.4 Annual transition probability of function states depending on time since stroke

(A) From poor function



(B) From moderate function



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(C) From good function

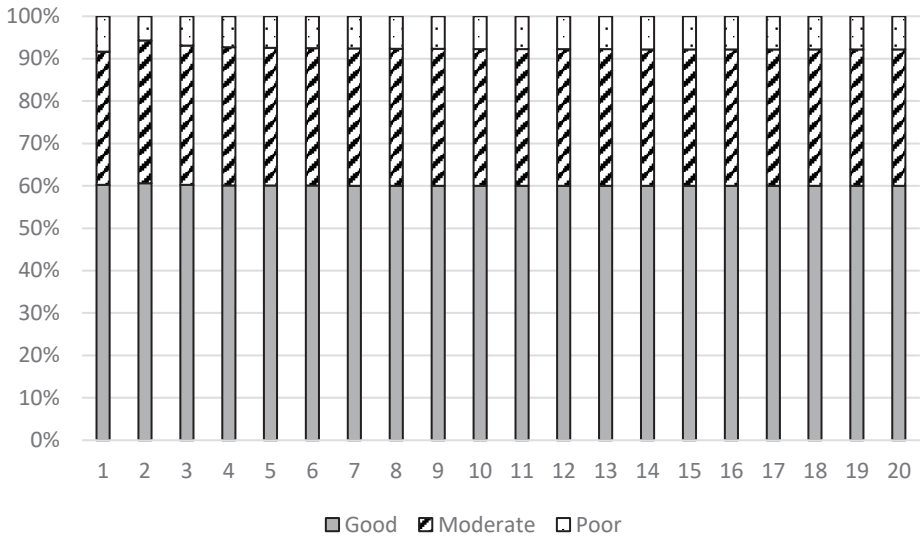

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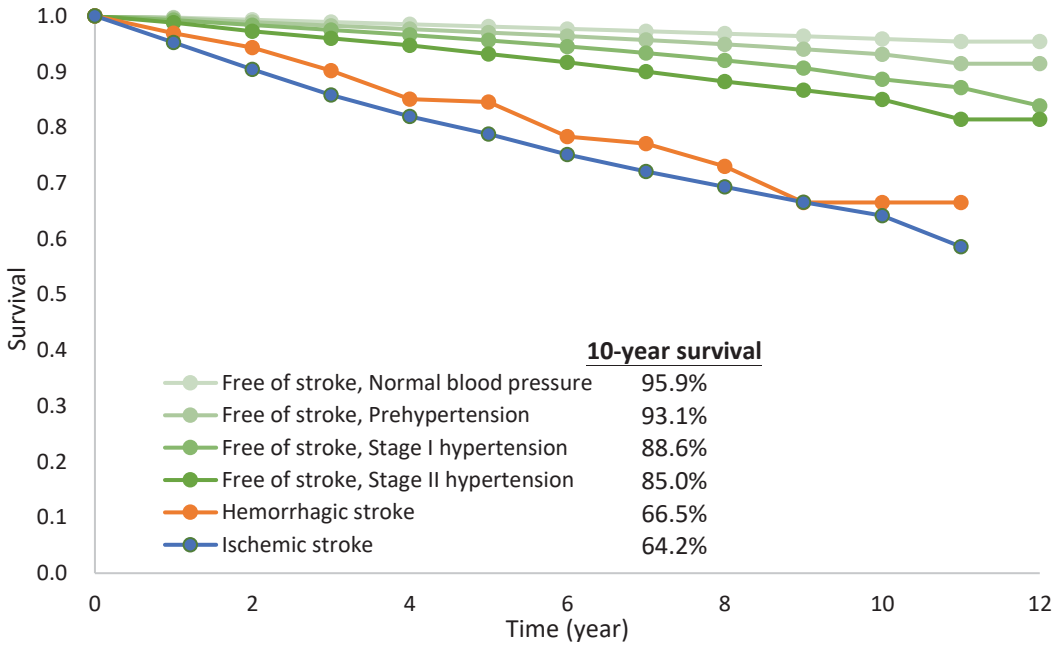
Figure 4.5 Cumulative survival by blood pressure and stroke with life-table and parametric methods

(A) Lifetable method



(B) Parametric estimate

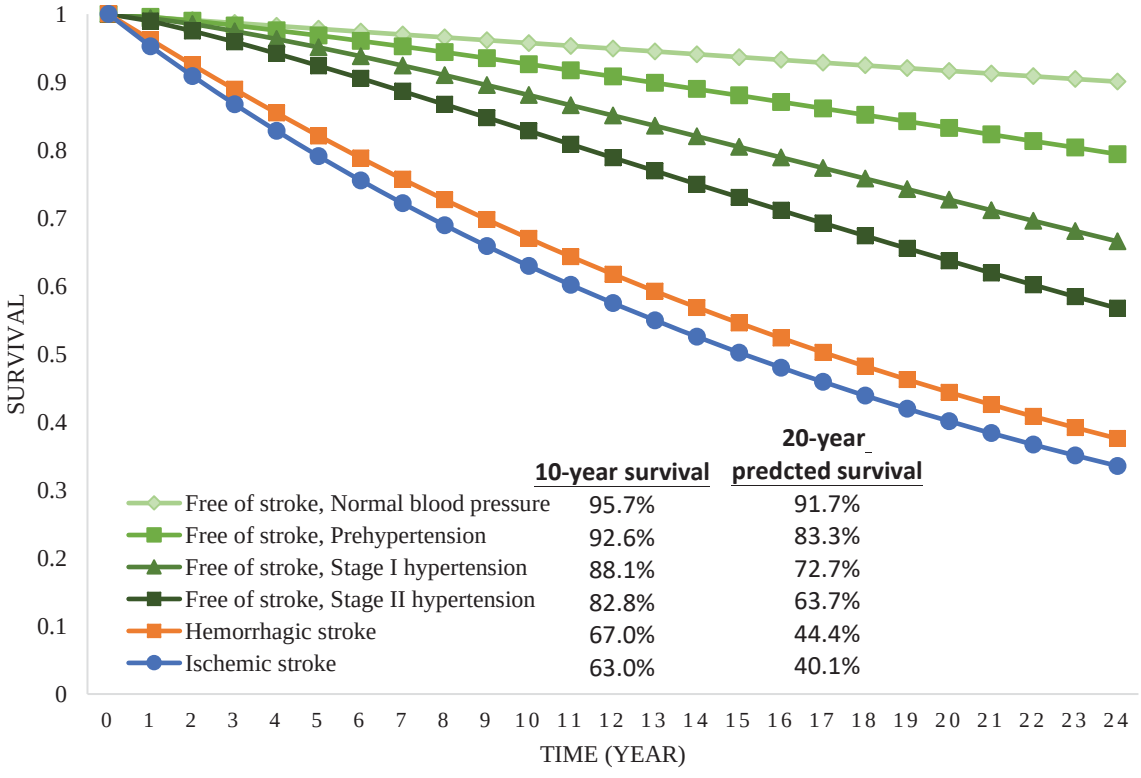


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Figure 4.6 The scatter incremental cost utility plot for personalized hypertension prevention strategy compared to control

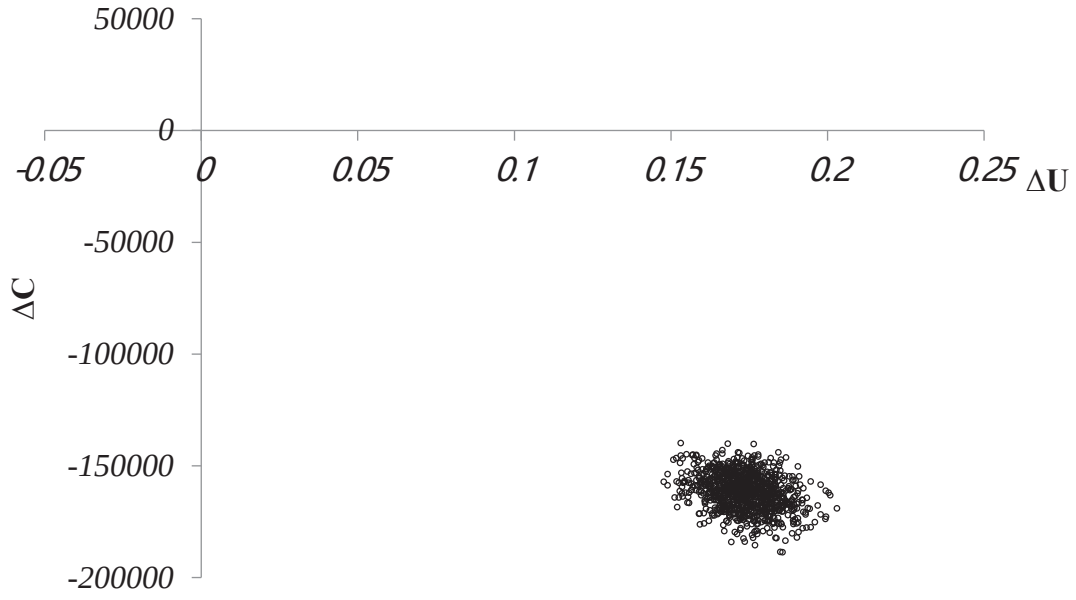

Figure 4.7 The acceptability curve for personalized prevention for hypertension

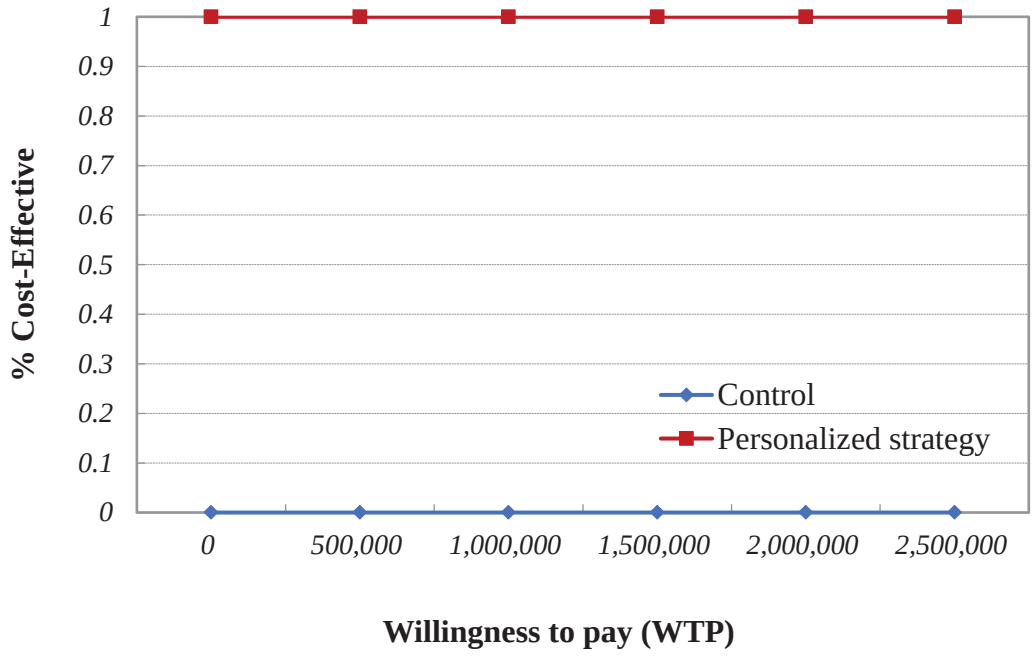

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Figure 4.8 The scatter incremental cost utility plot for personalized hypertension prevention strategy compared to control without adjustment of unspecific stroke

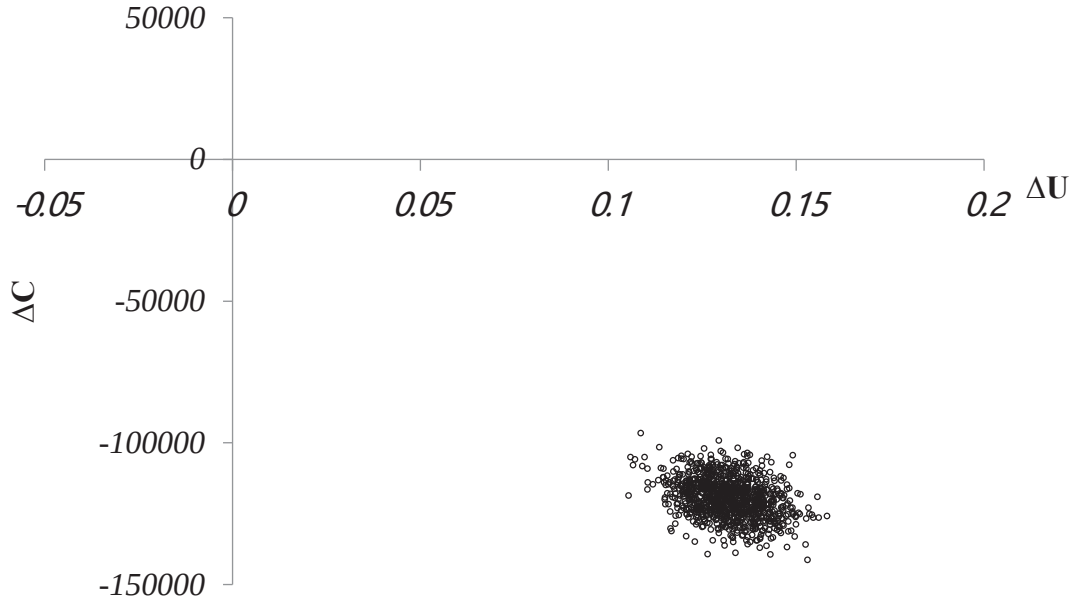
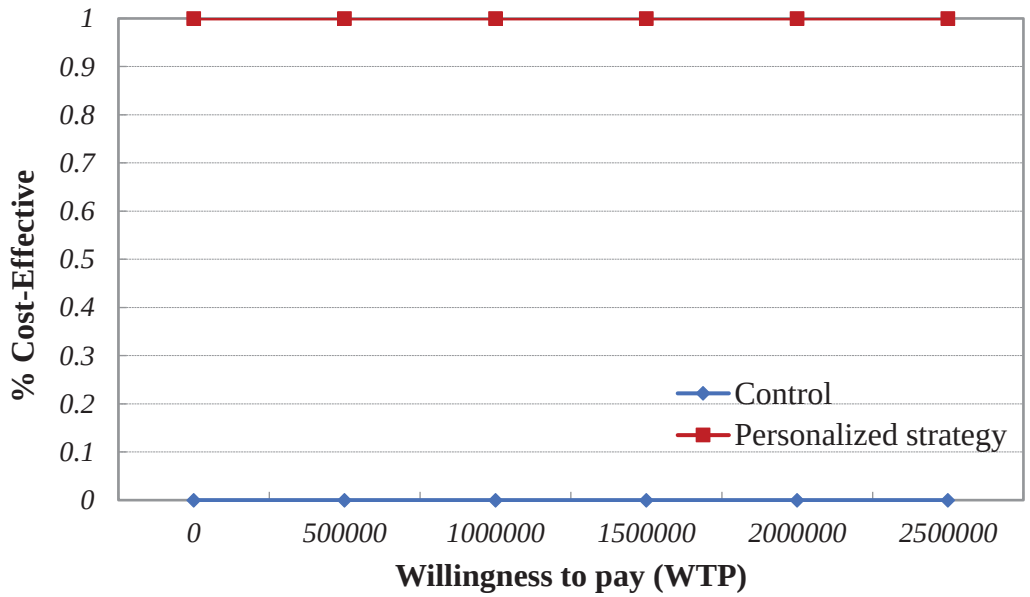


Figure 4.9 The acceptability curve for personalized prevention for hypertension without adjustment of unspecific stroke



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Chapter 5. Discussion

In this thesis, we demonstrate that personalized prevention for hypertension, comprising of population-based primary prevention, prophylactic anti-hypertension drugs for subjects with high risk profiled pre-hypertension, and one-time carotid ultrasound screen for subjects with high risk profiled stage 1 and stage 2 hypertension followed by intra-arterial stenting for patients with >70% carotid stenosis, is dominant against control in terms of quality-adjusted life year gained from the prevention of stroke. Our results show that the personalized prevention program not only prevents stroke by 17%, results in 0.17 QALY gained per person in a 20-year time horizon, but also leads to an average NTD 161,170 less expenditure per person.

This framework of personalized prevention for hypertension is a better strategy considering risk stratification approach given more individual information to predict the occurrence of stroke, to avoid the disability and death of stroke, and to devise interventions of randomized control trials or simulating models. Although the best design for the evaluation of stroke prevention is randomized controlled trial (RCT) in alignment with the principle of evidence-based medicine, the advantage of our proposed simulation model is an alternative method to convey useful evidence-based information before conducting RCT or while a large population-based RCT is not

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feasible to launch in community. Particularly, the Markov decision model based on two Markov processes including hypertension and stroke was designed to simulate the natural course of stroke development in a hypothetic population which has never been proposed by other study. It is one of the contributions for this study.

The personal risk profile is the starting point to the personalized prevention strategy. In this thesis, we apply the built predictive model for hypertension derived from a community-based cohort in northern Taiwan (KCIS) and the estimates of hypertension stage-specific incidence of stroke to another community in mid-west Taiwan (CHCIS) to stratify the cohort into different risk groups for hypertension. The CHCIS cohort used in this thesis (from 40 years old) is elder than the KCIS cohort (from 30 years old)[11]. This majorly accounts for the reason why CHCIS cohort had higher prevalence of stage 1 and stage 2 (35.7% in Male and 26.2% in female) than that in KCIS (28.7% in Male and 16.9% in female). Therefore, the distribution of the risk scores in CHCIS is also higher compared to the distribution in KCIS cohort in the same hypertension stage. If we focus on patients with stage 1 and stage 2 hypertension, which are less affected by young age group at 30s and 40s, patients in stage 2 hypertension in CHCIS are younger than KCIS in both men (1 year difference) and female (2 year difference). Men with hypertension in CHCIS are also less educated, have infrequent regular exercise, more elevated fasting glucose, and more betel quid

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chewing and alcohol drinking. The trend is similar in female, except for education level. In other words, it is likely the disease burden of hypertension could be higher in CHCIS than in KCIS and so is the disease burden of stroke. It is worthwhile to make an effort on preventive program to the population of Changhua. The clinical weights used in the current analysis derived from KCIS is age, gender, and hypertension state specific analysis, which we believe is also applicable to the CHCIS cohort. Though the further validation study is needed.

Our idea of giving anti-hypertensive medicine to pre-hypertension with high risk population had been proposed in previous studies. Systolic blood pressure of 130-139 mmHg, which was considered high-normal pre-hypertension, is now defined stage 1 hypertension by American Heart Association 2017 guidelines of hypertension management [38]. They recommended population in this range should be evaluated their cardiovascular risk and pharmacologic treatment should be given if the risk is high. This principle is matched with our program design, aimed for giving early medicine control to high risk individuals in pre-hypertension state. We had proved this strategy is cost-effective focusing on stroke reduction. However, more comprehensive analysis including other hypertension complication, such as heart failure, myocardial infarction, chronic renal disease, should be studied in further.

Stroke prevention using population-based carotid ultrasound screening is not

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recommended. The United States Preventive Service Task Force had it guideline against generalized screening for asymptomatic carotid stenosis with ultrasound [39]. Although the ultrasound is sensitive, harmless and not expensive, the low prevalence of severe carotid stenosis (<2%) in general population would make lots of false positive. The problem is we don't have biomarkers to identify who need to be screened. To specify the population with higher stroke probability, developing risk score model for stroke might be helpful. We tried to applied the risk score model for hypertension as a surrogate of stroke risk because they shared many common risk factors. More precise stroke-specified model and ultrasound screening on these high risk subjects can be a potential topic in the future.

There are some limitation in the current study. Firstly, our parameters of function-specific QALY are borrowed from literatures. Taiwanese-based study is needed for better fit to this study cohort. Secondly, we used NHI database to identify stroke cases. However, we have just outpatient record but lack of inpatient claim data. This will cause the missing of some severe stroke patient that dead during hospitalization, who never had a chance to visit outpatient clinic. Therefore, we would underestimate the stroke incidence and stroke mortality. In addition, our decision tree has not included other hypertension-related outcome, such as acute myocardial infarction and chronic kidney disease. Therefore, the benefit of prevention of

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hypertension from other severe outcomes would be underestimated. Thirdly, the ICD9 436~438 coding for unspecific cerebrovascular disease making it difficult to clarify the stroke type. For example, Moyamoya disease, coding as 437.5, may cause either hemorrhagic or ischemic stroke; transient global amnesia, coding as 437.7, is not even a stroke. Although we tried to allocate these unspecific stroke into hemorrhagic or ischemic stroke by expectation-maximization algorithm, the fundamental solution is to get more detailed NHI data of both outpatient and inpatient. Another solution is including only 430~434 to identify cases with stroke. This method can achieve sensitivity of 94.5% to 97.3%[40]. We had attempted to analyze the cost-utility with and without adjusting for unspecific stroke and they are both cost-effective despite the cost saving and increased utility are reduced slightly after adjusting.

In conclusion, this study demonstrates that personalized prevention for hypertension, comprising of the population-based primary prevention, prophylactic anti-hypertension drugs for subjects with high profiled pre-hypertension, and ultrasound screen for subjects with high profiled stage 1 and stage 2 hypertension , is dominant against control in terms of quality-adjusted life year gained from the prevention of stroke.

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