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致 謝

人生是一連串的十字路口，面臨著接踵而至的抉擇。回想起十年前，還是醫七實習醫師時，因緣際會下我選擇了報考職業醫學與工業衛生研究所碩士班，在台大醫學系畢業之後隨即進入職衛所，在王榮德教授、鄭尊仁教授等師長的引領下，開啟了我在公共衛生、職業醫學與流行病學等領域的旅程。四年前，我的臨床訓練告一段落，在取得環境職業醫學專科和內科專科醫師執照後，我再次選擇進入職衛所博士班，期許自己能進一步精進公衛領域的知識和技能，並輔以臨床醫學訓練所習得之經驗和觀念，進而能夠在健康科學的研究上面貢獻個人的綿薄之力。

也許是偶然，也許是機緣，進入博士班之後，我開始接觸到了不同以往的研究領域：outcomes research 和藥物經濟學。期間每當被他人問起個人的研究專長或興趣時，有時候心中不免會有些許「掛羊頭賣狗肉」之尷尬，因為那樣的題目與本研究所的名稱，著實讓人很難直接連結在一塊兒。然而，越深入了解就越覺得這門學問可是精采且重要的呢！

健康照護者和相關領域研究者的首要顧念就是：「增進全體人民的健康」。我國自開辦全民健康保險以來，在增進國人的健康以及社會的公平正義上面確實貢獻良多。但是，如同許多先進國家，我國的健保也面臨相當程度的財務危機。經濟問題根源於有限的資源；在有限的資源的情形底下，如何去做最有效率的運用便是經濟學的核心。健康醫療問題，當然也不例外。近來美國的醫療改革，是一個當紅而且是正在進行當中的議題。哈佛大學策略大師 Michael Porter 便提出唯有以「病人的價值為核心(value-based)」的方向和策略，醫療改革才有可能獲致成功。何謂病人的價值？就是「花費每單位金錢所得到的健康療效(the health outcomes achieved per dollar spent)」。

在王老師的帶領和啟發下，我的研究大致上是朝著這樣的方向和目標在進行著。前兩年，在進行推動具有成本效果(cost-effectiveness)考量的臨床指引的同時，我們嚐試以全民健保資料庫來進行療效研究。當時我想到的題目是：分析高血壓患者在接受不同的降壓藥物治療下，預防中風發生的相對機率是否不同？然後開始去了解、整理並分析健保抽樣歸人檔。漸漸地，才發現其中困難重重，且健保資料庫本身有相當程度的限制和弱點。過程中也有許多不為人知的掙扎和辛酸。所幸，在王老師的鼓勵以及其他許多人的幫忙協助下，堅持走下去，總算達成了一點小小的成果—該論文在去年九月份被國際高血壓協會暨歐洲高血壓協會的官方期刊 *Journal of Hypertension* 接受，並在今年元月份刊出。後續，我們又接著完成標靶藥物 gefitinib 在後期非小型細胞肺癌患者用作第一線治療的成本效果分析，以及人類乳突病毒疫苗預防台灣婦女子宮頸癌的成本效果分析。

拿到博士學位，稱不上是什麼成就，但在個人的生涯中是一個重要的里程碑。但能走到這裡，當然得記住所有曾經給過我幫忙、協助和指教的人。我要特別感謝胡賦強老師在統計學方面的教導和協助、陳秀熙老師在醫療決策分析的指導和啟蒙、以及劉錦添老師在計量經濟學上面有系統且引人入勝的引導。我要謝謝所有研究助理們：黃昭菀、何子豪、張郁瑩、陳禛芳、陳玉蟬，他們在一系列研究中都曾參與協助解決過一些困難。還有後續幾篇論文的共同作者：林宗哲學長、李秉穎醫師、楊志新教授、周松男教授，他們對所參與的研究提供了很寶貴的意見和重要的建議。此外，我也要向我的學位口試委員們致謝：詹長權教授、郭育良主任、陳保中教授，他們所提出來的精闢的見解或批評指教，都是讓我成長再進步的動力。還有一位不能遺漏，那就是本所的客座教師，來自於美國的 Lynda M. Ewers，她幫我發表的第一篇 SCI 論文的英文部分做最後的校正與修飾，並且在我博士後研究的申請過程中給予寶貴的意見和協助。

當然，這一路走來，給予我最多的協助和指導的人，就是我的指導教授—王榮德老師。不論在工作上、課業上或生活上的問題，他在我低潮時給我鼓勵，在我困惑時為我開導提醒，個人的感激之情難以筆墨形容。王老師正直的人格、認真嚴謹的治學態度以及靈活又犀利的思路，為學生們樹立起一個卓著的標竿。且老師以身作則，時常勸勉我們要保持終生不斷學習的態度，更期許我們能「青出於藍更勝於藍」。這不是個容易達成的目標，但也唯有惕勵自己勇敢地、認真地、以自信且不失謙虛的態度往前邁進，方不致辜負老師的教導和期待。

最後，我要感謝我的家人。他們是我能克服困難，經過挫折而堅持下去的最重要的原動力。尤其是妻子瓊慧，如果沒有她持續而堅定的鼓勵、扶持和對家庭無微不至的照顧，我很難達成今天這樣的一點點成績。還有我的父母親和阿公，雖然他們在我進博士班之前都已不在人世，但他們對我的養育和教導，常在我心。

邦祥

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摘 要

背景　降血壓藥物治療能夠有效預防高血壓所造成的併發症。但目前醫學界對於何種降壓藥是最適當的第一線藥物並無完全一致的共識。針對臨床上降血壓藥物實際處方情形的了解，能夠幫助我們來改善對高血壓病患的治療成效。本論文的目的，首先希望探討台灣目前對單純高血壓患者的降壓藥物處方型態和趨勢，並且和國際上主要的高血壓臨床指引之建議做比較；然後我們進一步利用全民健康保險資料庫來進行效果研究 (outcome research)，探討不同種類的降壓藥物是否對預防高血壓患者併發中風的效果會有差異。

方法　首先我們利用全民健保資料庫 20 萬人抽樣歸人檔 (1997 至 2004 年)，從其中找出 6,536 位年齡在 30 歲以上，並且在 1998 年之後新診斷暨治療的單純高血壓病患，分析他們在 1998 至 2004 年間的所有降血壓藥物處方情形。

此外我們利用全民健保資料庫 100 萬人抽樣歸人檔來建立一個回溯型世代研究 (retrospective cohort study)，以進行降血壓藥物的效果研究。在 1999 年至 2004 年間，共有 29,759 位年齡在 30 歲以上之新診斷暨治療的單純高血壓病患。我們利用「時間相依之 Cox 比例危險模型 (time-dependent Cox's proportional hazards model)」來分析他們併發中風的風險性。

結果　我們發現國內新診斷單純高血壓病患的降壓藥物處方情形隨著其年齡、性別及就醫院所層級而有所不同。不論是單一降血壓藥物處方或是併用多重降壓藥物之處方，鈣離子阻斷劑 (calcium channel blocker) 是處方頻率最高之藥物；其次是乙型交感神經阻斷劑 (beta-blocker)。雖然利尿劑之費用最便宜，但它在單一降血壓藥物處方中之處方頻率僅 8.3%；在全體降壓藥物處方中之處方頻率也只有 19.9%。而血管升壓素受器阻斷劑 (angiotensin receptor blocker) 的處方率卻隨著時間遞增。利用多變數羅吉斯回歸分析控制相關變因後發現：醫學中心或區

域醫院之醫師開出較多之血管升壓素受器阻斷劑的處方。

在探討不同種類之降壓藥物對預防高血壓併發中風的效果研究當中，這29,759 位新診斷暨治療的高血壓病患在 6 年追蹤期間當中，總共有 1,078 個病人發生中風，其中包括 654 位缺血性中風患者。經校正過各危險因子後發現：藥物順從性低、年紀愈大、男性、合併糖尿病或心臟病之患者，有較高的中風風險。不同種類的降壓藥物並未被發現有中風風險的差異。但在進一步的分組分析當中，我們觀察到使用乙型交感神經阻斷劑的單純高血壓患者相對於沒有使用該類降壓藥者，具有較高之缺血性中風風險 (hazard ratio：1.3，95%信賴區間：1.0-1.6，P = 0.046)。

結論　我們的研究結果顯示台灣國內目前對高血壓之藥物治療的實際情況，距成本效果 (cost-effectiveness) 的目標仍有相當之差距；換句話說，在高血壓之藥物治療上仍有相當的改善空間。服藥順從性差是決定高血壓患者發生中風併發症的關鍵因素。本研究雖然沒有發現不同種類的降壓藥物會造成併發全體中風風險之差異性，但卻顯示使用乙型交感神經阻斷劑可能和較高的缺血性中風有關聯。這部分的因果關係仍需進一步的研究來加以否證。

關鍵辭：降血壓藥物、乙型交感神經阻斷劑、服藥順從性、成本效果、全民健康保險、藥物流行病學

ABSTRACT

BACKGROUND

Although antihypertensive pharmacotherapy is widely considered to reduce the premature mortalities and comorbidities associated with hypertension, no consensus has yet been reached as to the appropriate choice of first-line medication. Knowledge of existing prescription patterns in the treatment of newly-diagnosed hypertension can provide useful information for improving clinical practice in this field. The aims of this dissertation are to determine the prescription patterns and time trends for antihypertensive medication in newly-diagnosed cases of uncomplicated hypertension in Taiwan and to compare these with current clinical guidelines. Furthermore, we conducted an outcome research to assess the risk of stroke associated with various antihypertensive drugs among previously uncomplicated hypertensive patients.

METHODS

First, a total of 6,536 newly-diagnosed patients with uncomplicated hypertension, aged over 30 years, were identified from the representative 200,000-person sample in the computerized reimbursement database of the National Health Insurance in Taiwan. These patients were followed from 1998 to 2004 with all diagnoses, prescription data and medication charges being retrieved for subsequent analysis.

For the outcome research of antihypertensive treatment, another retrospective

cohort study was undertaken, covering the period from 1997 to 2004, on a 1,000,000-person random sample obtained from Taiwan's National Health Insurance reimbursement database. Between January 1999 and December 2004, 29,759 patients aged 30 years or older were identified as newly-diagnosed uncomplicated hypertensive cases. They were followed up until the end of 2004. A time-dependent Cox's proportional hazards model was specified to analyze the risk of stroke development.

RESULTS

Prescription patterns varied by age, gender and clinical facilities, with mono-therapies being found to be dominant in the first year, albeit declining over time. Calcium channel blockers and beta-blockers were the most frequently prescribed antihypertensive drugs, either alone or in combinations. Although least expensive, the prescription rates of diuretics were low, at 8.3% for mono-therapies and 19.9% overall. The prescription rate for angiotensin receptor blockers was elevated considerably over time. After controlling for other related factors by multiple logistic regression analysis, angiotensin receptor blockers were found to be prescribed mainly by medical centers or regional hospitals.

Among the 29,759 uncomplicated hypertensive patients in the 1,000,000-person random sample of NHI reimbursement database, 1,078 new cases of stroke were identified and followed up for at least one month during the study period, including 654 ischemic stroke cases. After adjustment for various risk factors, the hazard ratio of

developing stroke was significantly higher for poor medication compliance (hazard ratio 1.5-1.9), old age, male, and comorbid diabetes mellitus and/or other heart diseases. Different categories of antihypertensive medications were not associated with differential effects on stroke development.

In the subsequent analysis, we found that patients receiving pharmacotherapy with beta-blockers were 1.3 (95% confidence interval 1.0-1.6) times more likely to develop ischemic stroke than those who had been treated with other types of antihypertensive medication.

CONCLUSIONS

The above findings indicate the existence of a gap between current clinical practice and the desired goal of cost-effectiveness in antihypertensive treatment in our country, which should be corrected. Poor medication compliance is a key determinant of developing stroke among hypertensive patients. Our research suggests that there has been no differential effect of antihypertensive medication on overall risk of stroke, whereas beta-blockers might be associated with more ischemic stroke. Further studies are needed to corroborate this hypothesis.

Keywords: antihypertensive therapy; beta-blocker; compliance; cost-effectiveness; National Health Insurance; pharmacoepidemiology

CONTENTS

FIGURES

TABLES

1. BACKGROUND

1-1 ANTIHYPERTENSIVE PHARMACOTHERAPY

Hypertension, a leading contributor to the global burden of diseases, continues its upward growth trend [1-4]. Poor control of this highly prevalent health concern can lead to the development of ischemic heart disease, stroke, heart failure or renal failure [3-7]. Numerous studies have shown that antihypertensive pharmacotherapy can effectively reduce the number of premature mortalities and comorbidities associated with hypertension and that good adherence to treatment promotes the effective prevention of various cardiovascular risks including stroke development [8-11].

As a result of various clinical trials and studies, a range of clinical guidelines on antihypertensive treatment have been published over the past decade [12-18]. Based on clinical evidence and cost-effectiveness [19-21], guidelines developed by the Joint National Committee (JNC) in the United States [13] and the National Institute for Health and Clinical Excellence (NICE) in the United Kingdom [15] recommended that diuretics (particularly thiazide-type diuretics) should be the drug of first choice for patients with no compelling indications. However, the results of various studies have shown that adherence to such clinical guidelines and recommendations are not at all uniform; indeed, they have been found to vary by time period and country, and by the characteristics of patients and

physicians [22-27].

1-2 HYPERTENSION IN TAIWAN

Along with its comorbidities, hypertension related conditions have accounted for almost a third of the total causes of death in Taiwan in recent years [28]; and indeed, in 2003 the total pharmaceutical expenditure on antihypertensive medication was US$0.32 billion, accounting for approximately 27% of the overall annual outpatient pharmaceutical expenditure on western-style medicines [29].

Taiwan's National Health Insurance (NHI) has not yet established a definite guideline for antihypertensive drug therapy. Given the enormous growth in healthcare expenditure within the NHI (from US$13.9 billion in 1997 to US$20.5 billion in 2005) [30] and the limited resources for healthcare, there is a clear need to explore physicians' practices, including prescription trends, in antihypertensive and other therapies [31,32].

1-3 STROKE AND HYPERTENSION

The incidence rate of stroke in Taiwan is higher than those reported in many western countries [33]. Cerebrovascular disease represents the second highest cause of death in Taiwan; at a mortality rate of 57.8 per 100,000 persons per year, this is even higher than the death rate for heart disease. Hypertension has been found to be the main modifiable risk factor for stroke [8,34], and although there have been studies examining the

incidence of stroke in Taiwan, the current data on risk assessment of stroke in hypertensive patients appear to be inadequate.

More importantly, several earlier studies have indicated higher incidences of stroke in hypertensive patients treated with beta-blockers than those treated with alternative drugs [35-40]. Consequently, it would seem important to assess whether such an association exists in regular daily practice, since the decisions for treatment in the real world are very complex.

1-4 National Health Insurance reimbursement database

The computerized reimbursement data from the National Health Insurance (NHI) in Taiwan provides us with a valuable opportunity to assess the real practice patterns of antihypertensive pharmaceutical therapies. The NHI program, which is a mandatory nationwide health insurance system, was implemented in Taiwan in March 1995. In contrast to the NHI systems of many Western nations, patients in Taiwan are free to choose care providers in a free and competitive healthcare market.

Given that the NHI coverage rate continues to rise, from 96.2% in 2000 to 98.3% in 2006, it is clear that almost the entire population of Taiwan is now covered by the system [41] and the total amount of out-of-pocket payments would be very low. Therefore, our study cohort, based on a nationwide representative random sample,

should be suitable for evaluating the relative safety of antihypertensive pharmaceutical therapies in the real world.

2 OBJECTIVE

The scope of this doctoral thesis involves exploring the pharmacoepidemiology of antihypertensive medication as well as the outcome evaluation for pharmaceutical therapies among the newly-diagnosed uncomplicated hypertensive patients based on the National Health Insurance reimbursement database.

The objectives of the first part are to determine antihypertensive medication prescription patterns and time trends among newly-diagnosed cases of uncomplicated hypertension in Taiwan, to attempt to identify the determinants of the choice of first-line drug therapy, and to investigate the pharmaceutical costs associated with different antihypertensive agents.

Following the above study, we conducted an outcome research to assess the risk of stroke development among the newly-diagnosed uncomplicated hypertensive patients treated with different antihypertensive drugs in the NHI reimbursement database.

3 PHARMACOEPIDEMIOLOGY OF ANTIHYPERTENSIVE DRUGS IN TAIWAN

3-1 METHODS

Study Population

This study uses a 200,000-person representative random sample from the computerized reimbursement database of the NHI, between January 1997 and December 2004. Details on the gender and date of birth of the patients, the date of prescription, commercial names of drugs, drug dosages/duration and costs for each prescription are recorded in the reimbursement files.

Patients initially identified were newly-diagnosed with essential hypertension on at least three occasions, were being treated for this condition, and had received their first antihypertensive medication between 1 January 1998 and 31 December 2004. In order to verify that a case was a new one, a period of at least one year was required (January to December of 1997) without any treatment and/or diagnosis relating to hypertension.

To prevent potential confounding by comorbidities in the prescription patterns of antihypertensive agents at different clinical facilities, patients diagnosed with suspected diabetes mellitus, ischemic heart disease, diseases of pulmonary circulation, other forms of heart diseases (including dysrhythmia and heart failure), stroke or renal diseases were

excluded from the sample. In order to ensure adherence to these criteria, any of the above diagnoses may not have appeared in any hospitalization file prior to the patient having been diagnosed as hypertensive, and the diagnoses may not have appeared more than three times in ambulatory outpatient files. We discarded those diagnoses appeared only once or twice in ambulatory outpatient files to exclude suspected or uncertain cases where claims were filed to allow for further diagnostic examination.

Prescription Patterns of New Cases of Hypertension

All antihypertensive drug prescription records from ambulatory care claims and prescriptions dispensed at contracted pharmacies were retrieved and analyzed for our sample of newly-diagnosed patients aged ≥30 years. Patients were stratified by gender and age, with age being split into two sub-groups: the younger group (30-54 years of age) and the older group (≥55 years). The clinical facilities were classified into four types, medical centers, regional hospitals, local hospitals and primary care clinics, based upon the level of medical care provided and the size of the institution as recognized by the NHI.

Antihypertensive drugs were categorized according to the 1999 World Health Organization–International Society Hypertension Guidelines for the Management of Hypertension (WHO/ISH, 1999) and the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation and Treatment of High Blood Pressure (JNC 7)

[12,13]. Six major categories of antihypertensive drugs generally are available, including angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARBs), beta-blockers, calcium channel blockers (CCBs), diuretics, and others (all other antihypertensive classes including alpha-blockers).

Prescriptions for a chronic disease in Taiwan, such as hypertension, most frequently involved the prescribing of drugs for 28- to 90-day periods, which would allow the patient visit a doctor every one to three months. Since each prescription may have contained different combinations of drugs and durations of medication, analysis of the data was undertaken using the prescription rate as calculated as the number of prescriptions containing a specific antihypertensive agent divided by the total number of prescriptions. A comparison of the prescription time trend was undertaken for each year, beginning with the first antihypertensive prescription. Daily drug costs, excluding all pharmacy service fees or other peripheral costs, were also calculated for each prescription. The drug costs are set by the Bureau of National Health Insurance and universally applied to clinical facilities regardless of their sizes.

Statistical Analysis

After being weighted by duration of medication, daily drug costs are expressed as time-weighted means, while other results are expressed as means ± standard deviation

(SD). The Chi-square test was carried out to determine the statistical significance of the differences between the prescription rates, with the Cochran-Armitage test also performed to assess the linear time trends over the sample period from the time of the initial treatment. Means of daily drug costs were compared using the Student t-test. Finally, multiple logistic regression analysis was performed to identify possible influential factors as a result of the prescribing of a single class of antihypertensive medication as a mono-therapy. SAS version 9.1 for Windows was used for the analysis of all of the data in this study. All tests were two-sided, and a P value of <0.05 was considered statistically significant. Whenever multiple comparisons were performed, Bonferroni adjustments were made accordingly.

3-2 RESULTS

The dataset contained a total of 15,835 patients over the age of 30 years who had received their initial dose of antihypertensive drugs for essential hypertension between 1 January 1998 and 31 December 2004. Of this total, 9,299 were excluded on the basis that one or more earlier comorbidities had been recorded. We were therefore left with a total of 6,536 patients and 178,754 prescriptions for antihypertensive agents for subsequent analysis.

Of the total sample of 6,536 patients, 3,268 (50.0%) were women and 49.3% was

≥55 years old, with a mean of 55.9 and SD of 12.3 years. The mean follow-up duration after the first prescription of antihypertensive medication was 42.8 ± 27.2 months, while the average number of overall prescriptions was 27.3 ± 26.0. Each prescription included 1.64 ± 0.84 antihypertensive drugs prescribed for an average period of 22.3 ± 10.5 days. The mean number of actual medical visits over the entire period of study was 25.1 ± 24.5.

Antihypertensive Prescriptions among Newly-Diagnosed Patients

Over half of the prescriptions for newly-diagnosed cases of uncomplicated hypertension involved single antihypertensive drug therapy (n = 94,797; 53.0%), with women and older patients receiving more mono-therapies. Medical centers and regional hospitals prescribed more combination therapies, as compared with primary care clinics (Table 3.1). The percentage of mono-therapy treatments declined over time from the initial diagnosis, whereas there was a gradual increase in the percentage of combination therapies (Figure 3.1). The 10 most frequently prescribed antihypertensive regimens, ranked in order of prescribing frequency, were as follows: CCBs (17.7%), beta-blockers (14.5%), ACEIs (8.2%), CCBs + beta-blockers (7.7%), others (5.3%), diuretics (4.4%), CCBs + ACEIs (4.0%), ARBs (3.0%), CCBs + ARBs (2.6%), beta-blockers + diuretics (2.4%).

A summary of the total number of prescriptions for the different categories of antihypertensive drugs is provided in Table 3.2, where it is shown that the most frequently prescribed antihypertensive agents were CCBs (n = 92,574; 51.8%), with beta-blockers as the second most frequently prescribed, followed by ACE inhibitors, diuretics, others and ARBs.

The prescription rate for ARBs, which was the highest in medical centers (22.6%), was almost five times the rate for primary care clinics, and was also higher than the prescription rate for ACE inhibitors and diuretics. There was an increase with time in the number of prescriptions for ARBs, CCBs and diuretics, whereas the number of prescriptions for ACE inhibitors remained stable (Figure 3.2).

Mono-Therapies for New Cases of Uncomplicated Hypertension

Among all of the mono-therapy prescriptions, the most frequently prescribed antihypertensive agents were CCBs (n = 31,711; 33.5%) and beta-blockers (n = 25,835; 27.3%). Older patients (aged over 55 years) were treated with CCBs more often than younger patients, with beta-blockers being more frequently prescribed among the latter group.

The prescription rates for beta-blockers were higher among women and younger patients ($P<0.0001$), while the prescription rates for diuretics were higher among

women and older patients (P<0.0001). In contrast, ACE inhibitors and ARBs were more frequently prescribed for younger patients. Medical centers and regional hospitals were found to have prescribed ARBs much more often than primary care clinics (P<0.0001), where the prescribing of ACE inhibitors was found to be much more common (P<0.0001) (Table 3.3).

With the passage of time from the date of the initial therapy, there was a significant increase in the prescription rate for ARBs, from 3.8% in the first year to 10.3% in the seventh year (P<0.0001). There was also an increase over time in mono-therapies comprising diuretics; however, there was a reduction over time in the trends for mono-therapies involving beta-blockers or ACE inhibitors (P<0.0001). The time trends for mono-therapies are summarized in Figure 3.3.

Daily Drug Costs for Different Antihypertensive Mono-Therapies

The daily costs for mono-therapy medication, in order from low to high, are as follows. Diuretics were the cheapest with a mean of US$0.17, followed by beta-blockers (US$0.27) and others (US$0.28). The costs for CCBs and ACE inhibitors were almost the same (US$0.56), while the costs for ARBs, at a daily average of US$0.85, were about five times those of diuretics. With the exception of the class of 'other' drugs, the means of the daily drug costs did not vary significantly by gender, age or clinical

facility.

Factors Associated with Initial ARB Mono-Therapy Prescriptions

As Table 3.4 shows, following adjustment by multiple logistic regression analysis, those prescriptions involving ARBs as an antihypertensive mono-therapy were found to be associated with subsequent diagnoses of diabetes mellitus (odds ratio (OR) = 1.5; 95% confidence interval (CI) 1.4-1.7), regional hospitals (OR = 3.6, 95% CI 3.3-3.9), medical centers (OR = 5.8, 95% CI 5.3-6.2), and the period after the year 2001 (OR = 2.4 for 2001-2, and 4.5 for 2003-2004).

4 STROKE IN PHARMACOTHERAPY ON UNCOMPLICATED HYPERTENSIVE PATIENTS

4-1 METHODS

Study Population

We carried out a retrospective cohort study of a 1,000,000-person representative sample obtained from the NHI Research Database, covering the period from January 1997 to December 2004. The computerized reimbursement data file on the 21.4 million persons currently covered by the NHI includes three major elements, inpatient claims, ambulatory care claims and prescriptions dispensed at contracted pharmacies. These provide details of the patients' gender and date of birth, prescription date, drug dosage/duration, commercial names of drugs, and the cost for each prescription.

Patients were identified as hypertensive patients if they had diagnoses of hypertension on at least three occasions using the International Classification of Disease, 9th Revision, Clinical Modification (ICD-9-CM) coding system, and if they had received their initial antihypertensive medication between 1 January 1999 and 31 December 2004. In order to enroll only new cases, we stipulated that there must be a period of at least two years (January 1997 to December 1998) during which no antihypertensive treatment and/or diagnoses relating to hypertension were recorded.

Most physicians in Taiwan generally manage hypertensive patients in accordance to the recommendations of the US Joint National Committee [11,42] or the World Health Organization-International Society of Hypertension guideline [12], and the diagnoses as well as prescriptions reported by physicians in Taiwan are regularly audited by clinical experts in the Bureau of National Health Insurance to ensure that the claims adhere to current guidelines. Thus, the diagnosis of hypertension in the NHI reimbursement database is reliable.

In order to avoid the potential confounding, by comorbidity, of the choice of antihypertensive agents, we excluded all patients with suspected preexisting diagnosis of diabetes mellitus (DM), ischemic heart disease, diseases of pulmonary circulation, stroke, renal disease or other forms of heart disease (including dysrhythmia and heart failure). To ensure the correct application of these exclusion criteria, none of the above should have appeared in any hospitalization diagnoses prior to the patient being diagnosed as hypertensive, and they should not have appeared more than three times in the ambulatory outpatient files. The process of establishing the target population is summarized in Figure 4.1.

New Cases of Stroke

Follow-up of this study cohort was subsequently undertaken until the end of 2004 to determine whether any of sampled patients had developed a new stroke. Stroke was defined as a sudden neurological deficit of presumed vascular origin that lasted longer than 24 hours or leading to death [43]. Transient ischemic attacks were not included in this study. Diagnoses of stoke were categorized as subarachnoid hemorrhage, intra-cerebral hemorrhage, cerebral infarction, and acute but ill-defined cerebrovascular disease by ICD-9-CM codes. Clinical diagnoses of stroke have been shown to be reliable [44]. Nevertheless, to further secure the validity of diagnosis, only those patients with no previous history of stroke and being diagnosed as stroke after imaging examination by computerized tomography (CT), or magnetic resonance imaging (MRI) in one of the following conditions were considered to be new cases of stroke: (i) diagnosed during the period of hospitalization; (ii) diagnosed at an emergency room; or (iii) diagnosed as stroke at least three times at outpatient clinics.

Available Variables

Since all prescriptions for antihypertensive drugs are regularly reimbursed by the NHI in Taiwan, such records relating to all newly-treated hypertensive patients aged ≥30 years were retrieved from the reimbursement files on ambulatory care claims and prescriptions dispensed at contracted pharmacies. The different types of antihypertensive medication

were categorized according to the major drug classes of angiotensin-converting enzyme inhibitors or angiotensin-II receptor blockers, beta-blockers, calcium channel blockers, diuretics and 'others' (all other classes of antihypertensive drugs including alpha-blockers).

Patients were stratified by gender and age (at the time of the initial treatment for hypertension) under the four age groups of 30-44, 45-54, 55-64 and 65 or older. Those patients who developed comorbidity after their initial antihypertensive treatment were classified into the following categories: diabetes mellitus, coronary artery disease, renal disease, hyperlipidemia, and 'other' heart diseases.

Because each prescription for a chronic disease, such as hypertension, most frequently involved the prescribing of drugs for 28-day or 30-day periods, we analyzed the time-dependent variables on a month-by-month basis; i.e., periods covering 30 days. If patients had received a certain drug for more than seven days, they would be regarded as having used that drug during that particular month; but if they had received the drug for less than seven days during a month, then they were regarded as not having used the drug during that particular month.

The patient's compliance rate at time *t* was calculated as the cumulative number of months with prescribed antihypertensive drugs up to time *t* divided by the total number of months since the initial antihypertensive prescription up to time *t*.

Statistical Analysis

The SAS statistical software (Version 9.1; SAS Institute, Cary, North Carolina, USA) was used in data analysis. Many variables were assessed on a monthly basis, i.e., the state of every time-dependent variable was determined as the state of the patient at the beginning of each period which lasted for 30 days.

The evaluation of the effects of the various factors on stroke development among our cohort of uncomplicated hypertensive patients was undertaken using a time-dependent Cox's proportional hazards model with all the available variables from the reimbursement database, including gender, age, the specific class of antihypertensive medications prescribed, the drug compliance rate, the number of initial antihypertensive drug(s), the mean number of antihypertensive drug(s), and comorbidities, etc. The final regression model was obtained using the stepwise variable selection method with both the inclusion and exclusion P value criteria set at 0.15.

After the initial assessment for all types of stroke, we further performed subgroup analyses focusing on ischemic stroke and hemorrhagic stroke including intra-cerebral hemorrhage and subarachnoid hemorrhage, separately.

4-2 RESULTS

Basic Characteristics of the Study Cohort

During 1997 to 2004, a total of 123,988 patients aged ≥30 years were diagnosed as hypertension and had received antihypertensive pharmacotherapy among the 1,000,000-person representative sample obtained from the NHI reimbursement database of Taiwan. After excluding prevalent cases, 53,546 patients were identified as new cases of hypertension between 1 January 1999 and 31 December 2004. We further excluded 23,787 of these patients on the basis of one (or more) earlier recorded comorbidity, as well as those patients where either the follow-up period, or the interval between the initial antihypertensive pharmacotherapy and the incidence of stroke, was less than 30 days. Only the remaining 29,759 newly-diagnosed uncomplicated hypertensive patients were considered as the study cohort in the subsequent analysis (Figure 4.1).

Among the 29,759 patients, 14,352 (48.2%) were women and about half (46.4%) were ≥55 years old with a mean of 55.3 years and standard deviation (SD) of 12.5 years. The mean follow-up time was 38.8 months (SD 21.0 months), the average drug compliance rate was 42.1% (SD 31.3%), and the average number of antihypertensive drugs per prescription was 1.39 (SD 0.51). Yet, a total of 1,078 new cases of stroke were identified from the study cohort; among them, 654 (60.7%) cases were cerebral infarction type of stroke and 243 (22.5%) cases were hemorrhagic type while the other 181 cases (16.8%) were acute but ill-defined stroke.

Risks of Overall Stroke in Uncomplicated Hypertension

The results of the multivariate analysis of the effects of various factors associated with stroke development are summarized in Table 4.1. The stepwise method revealed that six variables remained in the fitted model. After adjustment for the effects of the relevant time-dependent and time-independent covariates, the hazard ratio was significantly higher for older patients, for male patients, and for those with higher average number of drugs. Patients with a poor compliance were 1.5 to 1.9 times more likely to develop stroke than those with good adherence to antihypertensive pharmacotherapy. Other significant risk factors for occurrence of stroke were comorbidities of diabetes mellitus and other heart diseases after initiating antihypertensive pharmacotherapy, with estimated hazard ratios of 1.6 and 1.5, respectively. No definite category of antihypertensive drugs was associated with a statistically significant hazard ratio.

Subgroup Analysis for Ischemic Stroke and Hemorrhagic Stroke

In the subgroup analysis focusing on ischemic stroke, seven variables stayed in the final time-dependent Cox's proportional hazards model with the stepwise variable selection method, which did not include the initial or mean number of antihypertensive medications. After adjustment for potential confounders, the estimated hazard ratio of developing ischemic stroke was 1.3 (95% CI 1.0-1.6; P = 0.046) for those patients receiving beta-blockers as compared to those without prescriptions of beta-blockers in the previous

month. The results for other covariates were similar with those in the analysis of overall stroke (Table 4.1).

Regarding the analysis for hemorrhagic stroke, old age (≥65 years), male gender, higher mean number of antihypertensive drugs (hazard ratio 1.7, 95% CI 1.3-2.2), and poor drug compliance (hazard ratios 1.7-3.1) were statistically significant covariates that stayed in the fitted model.

Ischemic Stroke in Hypertensive Patients Prescribed with Beta-Blockers

The crude incidence rates of ischemic stroke among patients receiving various categories of antihypertensive medication are shown in Table 4.2. After controlling for the effect of potential confounders using the time-dependent Cox's proportional hazards model, only the hazard ratio for beta-blockers was significantly greater than 1. Among the 98 ischemic stroke cases with antihypertensive pharmacotherapy containing a beta-blocker, 40 patients (40.8%) were receiving mono-therapy while the others were using combination therapy with other antihypertensive drugs. Such a proportion seemed similar to that of all patients receiving beta-blockers, or 35.4%.

The frequency distribution of acute ischemic stroke cases for various agents of beta-blockers is provided in Table 4.3. The hazard ratio of ischemic stroke was significantly greater for atenolol (1.4; 95% CI 1.1-1.9) according to the fitted

time-dependent Cox’s proportional hazards model.

5 DISCUSSION

5-1 PART I

This is one of the first studies of its kind to undertake an assessment of the national prescription patterns and time trends in Taiwan for antihypertensive medication for uncomplicated hypertension. We found that whether in mono-therapies or overall treatment, CCBs were the most commonly prescribed drugs, followed by beta-blockers. Amongst all of the mono-therapies, the lowest average daily medication costs were for diuretics, at less than one third of the costs for CCBs or ACE inhibitors, and about one fifth of the costs for ARBs. The prescription rate for diuretics was, however, surprisingly low, accounting for only 8.3% of all mono-therapies, and indeed the diuretic prescription rate was the second lowest of all, only after ARBs (5.7%).

Beginning in 2006-7, the National Health Research Institutes of Taiwan has begun to draft clinical guidelines for various health conditions, including the treatment of hypertension. However, most physicians seemed to accept the recommendation of the US JNC or the WHO/ISH guideline during the time of this study. The evidence-based clinical guidelines for antihypertensive treatment published by both the JNC in 2003 [13] and the NICE in 2004 [15] contained recommendations for low dosages of thiazide diuretics as the first-line drug for essential hypertension with no compelling indications. Such a

recommendation also appeared in the 2003 statement published by the WHO/ISH [45]; and indeed, diuretics have been found to be the mainly frequently prescribed class of antihypertensive drugs in the United Kingdom, Denmark, Canada and the United States [23,46-48].

Researchers have indicated a substantial potential for cost savings if thiazides are prescribed rather than other drugs being more expensive for treatment of hypertension [49,50]. Given that the prescription pattern in Taiwan appears to utilize more non-thiazide medications that are generally more expensive, this issue would be worthy of further study with the aim of comparing the cost-effectiveness of antihypertensive treatment in Taiwan with those of other countries.

Considerable variation in antihypertensive prescribing patterns exists internationally. Fretheim and colleagues compared the sale figures of antihypertensive drugs for six countries, reporting that thiazide diuretics accounted for 25% of consumption in the UK, while the corresponding figure for Norway was only 6% [48]. According to our assessment, thiazide diuretics accounted 7.2% of overall antihypertensive drugs prescribed for uncomplicated hypertension (prescription rate of 11.9%) in Taiwan. The relatively low prescription rate of thiazides for antihypertensive treatment seems similar to those of Norway and France, and is very different from the picture of the UK or Denmark.

In the absence of any guideline or effective regulations on prescribing behavior for

clinicians, the current prescription pattern in Taiwan is probably a reflection of the mixed effect of the preferences of physicians, the hypotensive efficacies of medications, and the tolerance levels of patients. Under a healthcare system of mixed conventional medicine and traditional Chinese medicine, Taiwanese patients appear to dislike diuretics for the treatment of hypertension possibly because of the label ‘diuresis’, a term generally regarded as treating ‘edema’ and affecting one’s kidney function in traditional Chinese medicine. We speculate that this may be an important reason for the relatively few prescriptions with diuretics for pharmaceutical treatment of uncomplicated hypertension in Taiwan. Another explanatory factor for the low use of diuretics is the intolerance for the side effects resulting in the lower continuity rate [51]. However, the finding of increasing trend of prescribing diuretics over treatment course elapsed seems not compatible with this hypothesis.

The mono-therapy prescription rate for diuretics, at less than 10%, albeit with a slightly increasing trend with the passage of time (as shown in Figures 3.2 and 3.3), also implies that diuretics are currently considered in Taiwan to be only a second- or third-line medication; thus, there would appear to be considerable room for improvement, in terms of greater adherence to the existent clinical guidelines based on evidence as well as cost-effectiveness [19,21].

The trend toward increasing numbers of prescriptions involving ARBs, as

summarized in Table 3.4, is also worthy of some attention. Indeed, the multiple logistic regression analysis indicated that the calendar year and the size of the clinical facility were actually the major determinants. We have also found that primary care clinics prescribed diuretics more frequently than the larger medical facilities. We suspect that differences in cost consciousness may be an important contributor to this particular phenomenon, because the current reimbursement policy within the NHI program seems less restrictive on medical centers and regional hospitals, as compared with primary local clinics.

Another possibility is that physicians in large medical facility are more frequently exposed to new drugs and tending to readily accept the latest, or most up-to-date, medication as a means of keeping pace with current medical developments [52,53]. In fact, the number of ARBs on the market increased from 2 to 9 during the period of 1998-2004. Some studies suggest that promotional activities of pharmaceutical industry have a major impact on physicians' prescribing patterns [54,55]. As a result, we are somewhat concerned that many physicians in Taiwan, particularly those in the larger medical facilities, may be strongly influenced by the marketing effort from the major pharmaceutical companies. More evidence needs to be collected to corroborate these beliefs.

One of the limitations of this study is the potential confounding by severity of

disease for different levels of clinical facilities. Because the NHI reimbursement database has no link to details on patients' blood pressure levels or laboratory data, we were unable to directly compare the severity of hypertension among various groups of patients. Nonetheless, we have limited our study subjects to newly diagnosed cases of uncomplicated hypertension with mono-therapies, and for them there is no restriction on selection of doctors under the NHI in Taiwan. In such a way, hypertensive patients initially treated at different clinical facilities might not be so much different in severity. Moreover, Table 3.4 indicated that medical centers used more ARBs and less ACE inhibitors after adjustment for other determinants. As the efficacy of these two types of antihypertensive medication is similar [17], it seems that ARBs might be prescribed to substitute for some ACE inhibitors in medical centers or regional hospitals and this trend probably was unrelated to the different severity of hypertension.

The NHI database provides a 200,000-person sample representing almost 1% of the overall population of 22.9 million people in Taiwan; thus, we estimate that there may have been up to 0.75 million newly-diagnosed cases of uncomplicated hypertension in Taiwan during the seven-year period of this study. If the daily drug costs for uncomplicated hypertension could be reduced by an average of US$0.3-0.6, this would result in annual savings of up to US$82-163 million in overall pharmaceutical expenditure within Taiwan's NHI. If such action were extended to incorporate all

prevalent cases of hypertension throughout our country, the total amount of annual savings on costs for antihypertensive drugs could even run to US$0.2 billion. Under the current limited resources, this could clearly make the NHI much more sustainable [32].

PART II

We conducted a retrospective cohort study using the computerized reimbursement database to assess the risk of stroke in uncomplicated hypertensive patients treated with various antihypertensive medications. According to the fitted time-dependent Cox's proportional hazards model, the hazard ratios of developing stroke were significantly higher for older and male hypertensive patients and among those with comorbidities of diabetes and heart disease, which were compatible with many of the previous studies [33,56,57]. We also found that poor compliance with antihypertensive pharmacotherapy was an important risk factor in stroke development, for both ischemic and hemorrhagic types.

Although a higher risk of stroke for patients treated with beta-blockers has been documented in prior randomized controlled trials and meta-analyses of such studies [35-40], we found no evidence of a differential effect of antihypertensive pharmacotherapy on stroke risk when all stroke subtypes were included in the multivariate analysis. Our findings indicated that outcome research might provide additional evidence for improving clinical guidelines, as the processes in randomized clinical trials might not be able to take care of all conditions in the daily practices of clinicians.

For all types of stroke among these low risk, uncomplicated hypertensive patients

in our study, the control of their hypertension seemed to be a more important factor than the choice of antihypertensive agent because those patients who needed more combinations of antihypertensive drugs might have a higher risk of overall stroke. Such kind of trend was even more apparent for hemorrhagic stroke in the subgroup analysis despite the small number of cases.

The prior studies in this area have documented an association between poor medication compliance and the failure to control hypertension [11,58-60], and indeed, we did find that hypertensive patients with poor medication compliance remained at a higher risk of stroke than those with better medication compliance, which probably came as a result of their higher blood pressure (BP) level. This association was consistent for all types of stroke in our analysis. However, our results did not reveal a linear dose-response relationship, indicating the complexity of the behavior of such patients [59,61,62]. Nevertheless, the relatively low compliance rate in this real life data from Taiwan indicates a significant room for improvement in patients' adherence to antihypertensive pharmacotherapy.

In the subsequent analysis restricted to ischemic stroke, we observed an excess risk of ischemic stroke associated with beta-blocker therapy, when compared to treatment with other antihypertensive therapies. The possible mechanisms are not clear yet.

Some researchers attributed the modest effect on stroke prevention of beta-blockers

to their smaller ambulatory BP reduction, while Williams *et al.* [63] reported that beta-blockers could have inferior cardiovascular outcome resulted from different effects on central aortic pressures and hemodynamics despite similar effects on brachial BP. We had no BP control data from the NHI reimbursement database. However, since only newly-treated uncomplicated hypertensive patients were enrolled for this study, the likelihood of initiating beta-blockers after patients' hypertension became severer might be low [64]. Moreover, the number of antihypertensive medication, which was taken as a proxy for the severity of hypertension, was not a significant factor for developing ischemic stroke in our analysis.

It seemed that the greater risk of ischemic stroke for beta-blockers could not be directly attributed to severer hypertension or higher BP. Thus, we suspected that the progression of atherosclerosis, aggravated by the slowing down of the circulatory system, as a direct result of the use of beta-blockers, might be responsible for the increased risk of ischemic stroke development.

This study has some limitations. First of all, because of protection of privacy, we are not allowed to link the NHI reimbursement database with private medical records to obtain the BP measurements or results of laboratory tests. The BP data are important in predicting the risk of stroke, nonetheless, we have associated the exposure of antihypertensive drugs directly with the clinical outcome rather than the surrogate - BP.

Another concern is the potential residual confounding of the differential distributions of higher body mass indices (BMI), serum triglyceride levels, creatinine concentration levels, and fasting blood glucose levels in patients treated with different antihypertensive medications [65], despite covariates with later development of DM, hyperlipidemia, and renal disease have been controlled in the regression model. We hoped to consider BMI, as well. However, since the current recommended practice does not differentiate between the prescriptions of antihypertensive medications based upon the BMI, we suspected that BMI would not likely confound the effect of antihypertensive drugs upon developing stroke, as was supported by several studies showing that the association between a high BMI and stroke was substantially attenuated after adjustment for hypertension and other major risk factors [66-68].

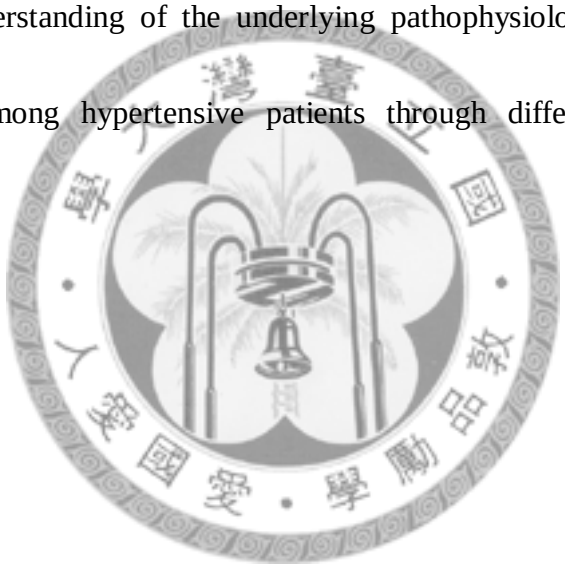
6 CONCLUSION

The initial prescription patterns for antihypertensive therapies for uncomplicated hypertension in Taiwan seem to be inconsistent with the current international clinical guidelines. Although diuretics are the least expensive class of antihypertensive drugs, they are nevertheless being used as a second- or third-line choice of medication, with a notably low prescription rate. There has been a growing trend in the prescribing of ARBs as the initial choice of therapy for uncomplicated hypertension, particularly in medical centers and regional hospitals. These results indicate a need for greater awareness of the evidence-based guidelines for antihypertensive drug therapy amongst physicians and the general public.

Given the existence of the national health insurance system in Taiwan, there is still significant room for improvement in the cost-effectiveness of antihypertensive treatment [19,31]. We recommend reaching a consensus on this matter and developing a domestic clinical guideline taking cost-effectiveness into consideration as soon as possible.

Moreover, the importance of good compliance with antihypertensive therapy can never be overstated with regard to effective prevention from stroke or cardiovascular

complications. The control of hypertension played a major role in determining the risk of stroke among the previously uncomplicated hypertensive patients. After controlling other major potential confounding factors, we found no differential risks of stroke related to any type of antihypertensive medication, whereas some unintended association between the pharmacotherapy with beta-blockers and a higher risk of ischemic stroke was observed in the subgroup analysis. Further studies will be required to gain a better understanding of the underlying pathophysiological mechanisms of preventing stroke among hypertensive patients through different antihypertensive medications.



DISCLOSURE

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Table 3.1 Prescription patterns of antihypertensive therapies for newly-diagnosed uncomplicated hypertension patients, 1998-2004[a]

Variables	Treatment regimen								Total No. of prescriptions[c]
	Mono-therapy[b]		Two-drug combinations[b]		Three-drug combinations[b]		Four(+)-drug combinations[b]		
	No.	%	No.	%	No.	%	No.	%	
Patient gender									
Male	44 738	51.36#	31 494	36.16#	6 815	7.82#	4 058	4.66#	87 105
Female	50 059	54.62	31 927	34.84	6 024	6.57	3 639	3.97	91 649
Patient age (years)									
<55	40 357	50.67#	29 784	37.39#	6 130	7.70#	3 380	4.24	79 651
≥55	54 440	54.93	33 637	33.94	6 709	6.77	4 317	4.36	99 103
Type of clinical facility[d]									
Medical center	16 721	48.76#	12 693	37.02	3 897	11.37#	978	2.85#	34 289
Regional hospital	14 809	49.75#	10 453	35.11#	3 687	12.39#	819	2.75#	29 768
Local hospital	18 258	59.03#	9 745	31.51#	2 395	7.74#	531	1.72#	30 929
Primary care clinic	44 997	53.73	30 520	36.44	2 860	3.42	5 369	6.41	83 746
Total Nos.	94 797	53.03	63 421	35.48	12 839	7.18	7 697	4.31	178 754

[a] Total sample number = 6 536 patients.

[b] No. refers to the number of prescriptions under each treatment regimen; % refers to the percentage of the total drugs prescribed under the four treatment regimens.

[c] As a result of missing data, the sum of the total number of prescriptions over the four types of clinical facilities is smaller than the overall number of prescriptions.

[d] Pairwise group comparisons are performed taking primary care clinics as the reference.

[#] Significant P value with the Bonferroni-adjusted α-level, P<0.0025

Table 3.2 Distribution of antihypertensive drugs for newly-diagnosed uncomplicated hypertension patients, by gender, age and clinical facility, 1998-2004 [a]

Variables	Class of drug [b]												Total No. of prescriptions [b]
	Diuretics		Beta-blockers		CCBs [c]		ACE inhibitors [c]		ARBs [c]		Others		
	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	
Patient gender													
Male	15 525	17.82#	34 703	39.84#	46 468	53.35#	22 825	26.20#	10 635	12.21#	15,212	17.46#	87 105
Female	19 981	21.80	40 941	44.67	46 106	50.31	21 306	23.25	10 339	11.28	8,826	9.63	91 649
Patient age (years)													
<55	13 556	17.02#	39 445	49.52#	40 270	50.56#	21 282	26.72#	10 421	13.08#	7,578	9.5#	79 651
≥55	21 950	22.15	36 199	36.53	52 304	52.78	22 849	23.06	10 553	10.65	16,460	16.61	99 103
Type of clinical facility [d]													
Medical center	7 729	22.54#	14 463	42.18#	18 675	54.46#	6 169	17.99#	7 764	22.64#	3,122	9.10#	34 289
Regional hospital	6 025	20.24	12 320	41.39#	17 058	57.30#	6 170	20.73#	5 637	18.94#	2,958	9.94#	29 768
Local hospital	5 005	16.18#	11 303	36.54#	17 849	57.71#	5 464	17.67#	3 594	11.62#	3,905	12.63#	30 929
Primary care clinic	16 745	19.99	37 540	44.83	38 988	46.56	26 322	31.43	3 966	4.74	14,053	16.78	83 746
Total Nos.	35 506	19.86	75 644	42.32	92 574	51.79	44 131	24.69	20 974	11.73	24,038	13.45	178 754

[a] Total sample number = 6 536 patients.

[b] No. refers to the number of prescriptions for each class of drug; % refers to the percentage of the total prescriptions for the six classes of drugs. As a result of missing data, the sum of the total number of prescriptions over the four types of clinical facilities is smaller than the overall number of prescriptions. The sum of the prescription rates for all six classes of drugs exceeds 100% because the average prescription contained more than one drug.

[c] CCBs = calcium channel blockers; ACE = angiotensin-converting enzyme; ARBs = angiotensin receptor blockers.

[d] Pairwise group comparisons are performed taking primary care clinics as the reference.

Significant P value with the Bonferroni-adjusted α-level, P<0.0017

Table 3.3 Distribution of mono-therapy antihypertensive drug prescriptions for newly-diagnosed uncomplicated hypertension patients [a]

Variables	Class of drug [b]												Total No. of prescriptions [b]
	Diuretics		Beta-blockers		CCBs [c]		ACE inhibitors [c]		ARBs [c]		Others		
	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	
Patient gender													
Male	2 974	6.65#	11 602	25.93#	14 881	33.26	7 004	15.66	2 561	5.72	5 716	12.78#	44 738
Female	4 849	9.69	14 233	28.43	16 830	33.62	7 619	15.22	2 822	5.64	3 706	7.40	50 059
Patient age (years)													
<55	2 366	5.86#	13 627	33.77#	12 083	29.94#	7 134	17.68#	2 677	6.63#	2 470	6.12#	40 357
≥55	5 457	10.02	12 208	22.42	19 628	36.05	7 489	13.76	2 706	4.97	6 952	12.77	54 440
Type of clinical facility [d]													
Medical center	1 067	6.38#	4 474	26.76#	5 841	34.93#	2 255	13.49#	2 099	12.55#	985	5.89#	16 721
Regional hospital	1 026	6.93#	4 144	27.98	5 690	38.42#	1 710	11.55#	1 272	8.59#	967	6.53#	14 809
Local hospital	1 363	7.47#	4 171	22.84#	8 186	44.84#	1 728	9.46#	920	5.04#	1 890	10.35#	18 258
Primary care clinic	4 367	9.71	13 043	28.99	11 991	26.65	8 927	19.84	1 089	2.42	5 580	12.40	44 997
Total Nos.	7 823	8.25	25 835	27.25	31 711	33.45	14 623	15.43	5 383	5.68	9 422	9.94	94 797

[a] Total sample number of prescriptions = 94 797.

[b] No. refers to the number of prescriptions for each class of drug; % refers to the percentage of the total prescriptions for the six classes of drugs. As a result of missing data, the sum of the total number of prescriptions over the four types of clinical facilities is smaller than the overall number of prescriptions. The sum of the prescription rates for the four types of clinical facilities exceeds 100% because the average prescription contained more than one drug.

[c] CCBs = calcium channel blockers; ACE = angiotensin-converting enzyme; ARBs = angiotensin receptor blockers.

[d] Pairwise group comparisons are performed taking primary care clinics as the reference.

[#] Significant P value with the Bonferroni-adjusted α-level, P<0.0017

Table 3.4 Multiple logistic regression estimates of ARB and ACE inhibitor mono-therapy prescription characteristics for newly-diagnosed uncomplicated hypertension patients, 1998-2004 *

Variables	ARBs		ACE inhibitors	
	OR	95% CI	OR	95% CI
Patient gender				
Female (reference)	1.00	–	1.00	–
Male	0.99	0.94-1.05	1.07	1.03-1.11
Patient age (years)				
30-54 (reference)	1.00	–	1.00	–
≥55	0.74	0.70-0.78	0.75	0.72-0.78
Geographical region				
Northwest (reference)	1.00	–	1.00	–
Midwest	0.74	0.68-0.80	0.98	0.93-1.02
Southwest	0.67	0.62-0.72	0.86	0.82-0.90
Eastern	1.34	1.19-1.52	1.39	1.29-1.49
Offshore islands	2.78	2.21-3.49	0.45	0.35-0.57
Type of clinical facility				
Primary care clinics (reference)	1.00	–	1.00	–
Local hospitals	2.17	1.98-2.38	0.43	0.41-0.45
Regional hospitals	3.55	3.26-3.87	0.52	0.49-0.55
Medical centers	5.77	5.32-6.25	0.63	0.60-0.66
Time elapsed since initial therapy				
1 year or less (reference)	1.00	–	1.00	–
2-3 years	1.00	0.92-1.09	0.93	0.89-0.97
4-7 years	1.12	1.03-1.21	0.95	0.90-1.00
Comorbidity after hypertension †				
Diabetes mellitus	1.55	1.42-1.68	1.36	1.28-1.44
Ischemic heart disease	1.10	1.02-1.19	0.78	0.73-0.82
Stroke	1.02	0.93-1.11	0.98	0.91-1.05
Chronic renal disease	1.07	0.94-1.22	0.92	0.83-1.02
Calendar years				
1998-2000 (reference)	1.00	–	1.00	–
2001-2002	2.35	2.12-2.62	0.87	0.83-0.91
2003-2004	4.45	4.01-4.94	0.79	0.75-0.83

* The odds ratio (OR) for each variable was adjusted for all other variables listed in the table.

† The reference group is subjects with no corresponding comorbidity for each category after hypertension.

Table 4.1 Fitted multiple time-dependent Cox's proportional hazards models to identify the risk factors of stroke among the newly-diagnosed uncomplicated hypertensive patients

	All types of stroke			Ischemic stroke		
Variable	Case No.	HR*	(95% CI)	Case No.	HR†	(95% CI)
Age (years)						
30-44	101	1.00	–	43	1.00	–
45-54	196	1.49	(1.17-1.90)	118	2.12	(1.50-3.01)
55-64	270	2.60	(2.07-3.27)	165	3.77	(2.70-5.28)
≥ 65	511	4.75	(3.83-5.88)	328	7.26	(5.28-9.99)
Gender						
Women	388	1.00	–	232	1.00	–
Men	690	1.82	(1.61-2.07)	422	1.90	(1.61-2.23)
Mean number of antihypertensive drugs‡¶						
<1.5 drugs	690	1.00	–	432	1.00	–
≥1.5 drugs	388	1.25	(1.10-1.42)	222	1.09	(0.92-1.29)
Drug compliance rate‡						
≥ 70%	185	1.00	–	126	1.00	–
40-69%	215	1.51	(1.22-1.86)	132	1.37	(1.05-1.78)
20-39%	248	1.79	(1.46-2.20)	156	1.66	(1.28-2.16)
< 20%	430	1.92	(1.58-2.34)	240	1.62	(1.25-2.09)
Comorbidity‡						
Diabetes mellitus	98	1.64	(1.33-2.03)	62	1.65	(1.26-2.16)
Other heart diseases	122	1.51	(1.24-1.84)	76	1.48	(1.15-1.89)
Renal diseases	33	1.11	(0.78-1.57)	27	1.47	(0.99-2.17)
Antihypertensive drugs‡						

ACE inhibitors or ARBs	133	0.95	(0.78-1.16)	90	1.05	(0.83-1.33)
Beta-blockers	138	1.04	(0.86-1.27)	98	1.27	(1.00-1.60)
CCBs	188	1.01	(0.85-1.21)	128	1.13	(0.91-1.40)
Diuretics	64	0.96	(0.74-1.25)	39	0.96	(0.68-1.34)
Others	41	0.84	(0.61-1.15)	35	1.11	(0.78-1.58)

ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blocker; CCB = calcium channel blocker; HR = hazard ratio.

* The hazard ratio for each variable was controlled for age, gender, mean number of antihypertensive drugs, medical compliance, and comorbid diabetes mellitus and/or other heart diseases after antihypertensive treatment.

† The hazard ratio for each variable was controlled for age, gender, medical compliance, and comorbidities after antihypertensive treatment including diabetes mellitus, other heart diseases and renal diseases.

‡ Time-dependent variables mean states of variables in the previous month. The patient number of each subgroup for the time-dependent variable varies by time.

¶ Mean number of antihypertensive drugs was derived from the time-weighted mean of the number of antihypertensive drugs for each monthly prescription since the initial treatment.

Table 4.2 Incidences of ischemic stroke among the newly-diagnosed uncomplicated hypertensive patients receiving various antihypertensive drugs

Antihypertensive drug	Ischemic stroke (case No.)	Prescription (person-months)	Crude event rate (1000 years^{-1})	Adjusted HR*
ACE inhibitors or ARBs	90	157 424	6.9	1.05
Beta-blockers	98	175 109	6.7	1.27†
CCBs	128	210 892	7.3	1.13
Diuretics	39	66 990	7.0	0.96
Others	35	41 072	10.2	1.11

ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blocker; CCB = calcium channel blocker; HR = hazard ratio.

* The adjusted hazard ratio for each category of antihypertensive drug has been controlled for age, gender, medical compliance, and comorbidities after antihypertensive treatment including diabetes mellitus, other heart diseases and renal diseases.

† $P<0.05$

Table 4.3 Frequencies of ischemic stroke cases with different beta-blockers

Drug	Ischemic stroke (No. of cases)	Prescription (person-months)	Crude event rate (1000 years^{-1})
Atenolol	56	90,427	7.4
Bisoprolol	9	25,586	4.2
Propranolol	15	23,191	7.8
Carvedilol	9	11,053	9.8
Betaxolol	4	7,188	6.7
Acebutolol	0	7,163	0
Metoprolol	0	4,225	0
Labetalol	2	3,518	6.8
Carteolol	2	1,103	21.8
Other	1	1,655	7.3
Total	98	175,109	6.7

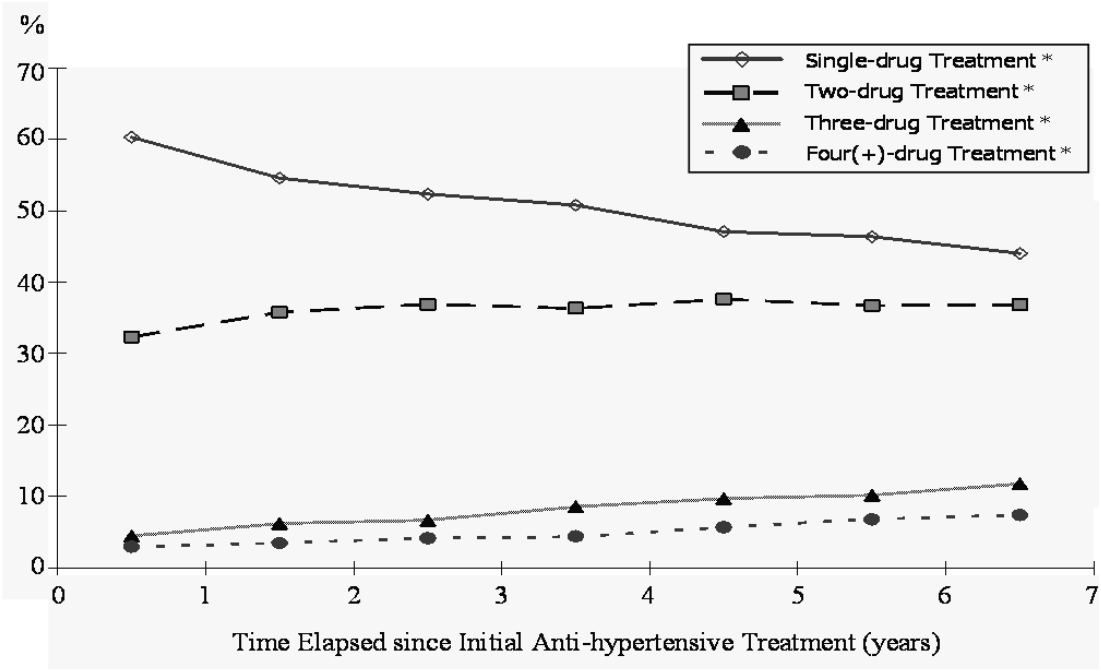


Figure 3.1. Prescription pattern time trends for combinations of mono-, two-, three- and four(+)-drug treatment therapies

* indicates P <0.0125 under the Cochran-Armitage trend test, being significant with Bonferroni adjustment for multiple comparisons (P < 0.05/4 = 0.0125).

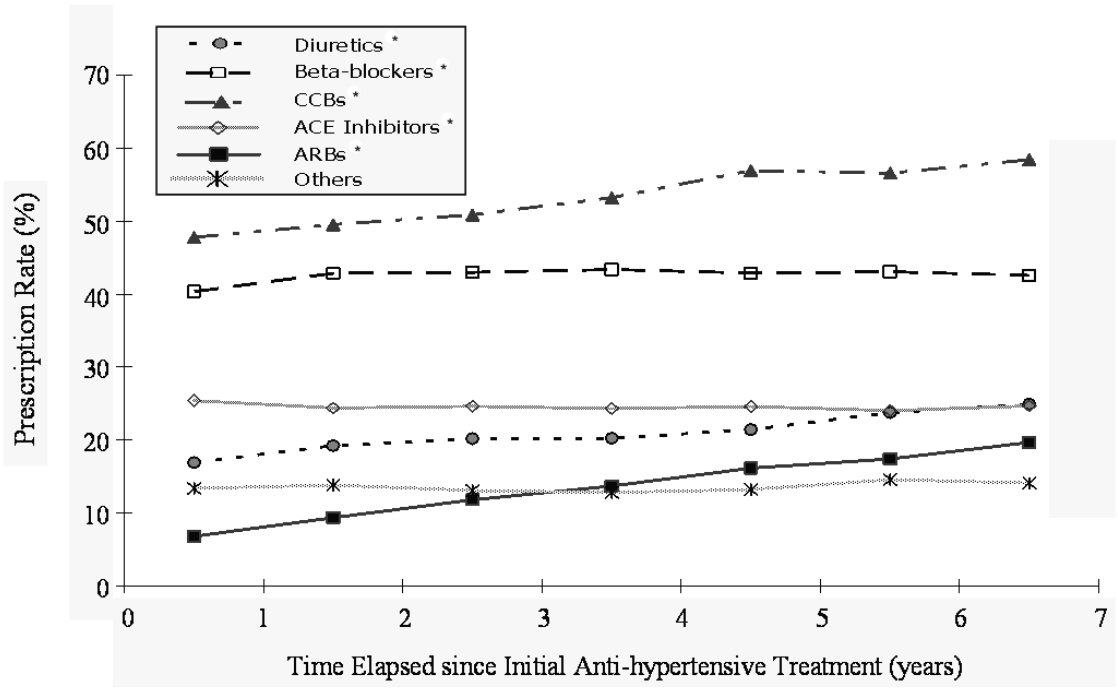


Figure 3.2. Prescription distribution time trends for antihypertensive agents

* indicates P<0.0083 under the Cochran-Armitage trend test, being significant with Bonferroni adjustment for multiple comparisons (P < 0.05/6 = 0.0083)

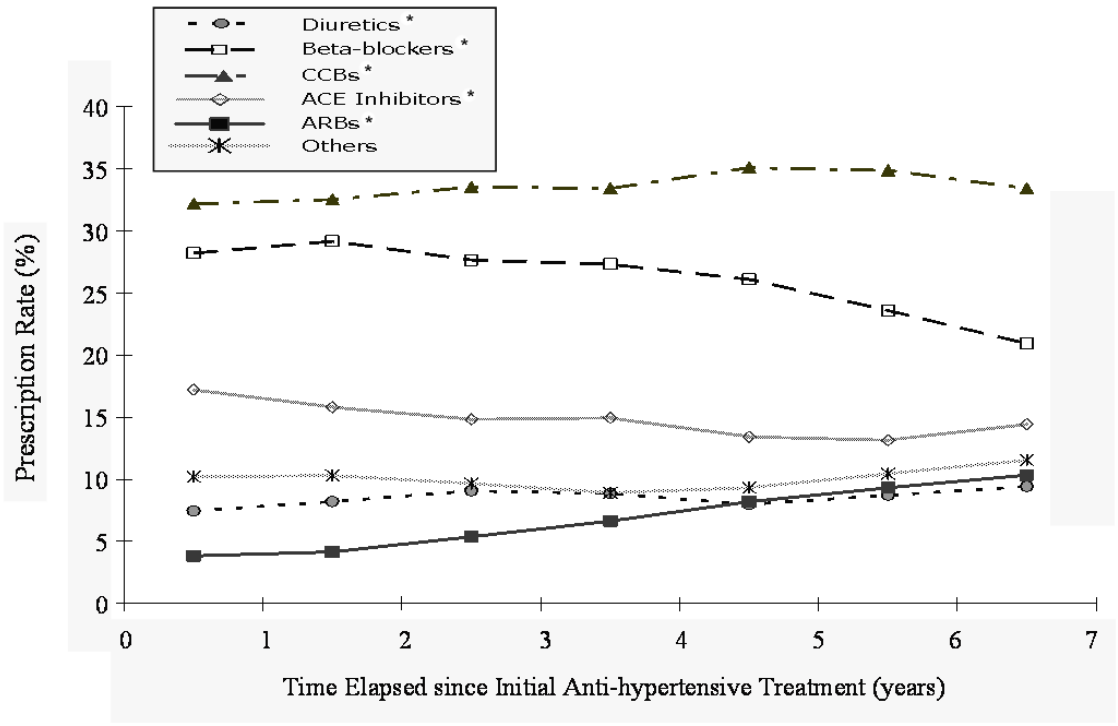


Figure 3.3. Time trends for single-drug antihypertensive treatment

* indicates P <0.0083 under the Cochran-Armitage trend test, being significant with Bonferroni adjustment for multiple comparisons (P < 0.05/6 = 0.0083)

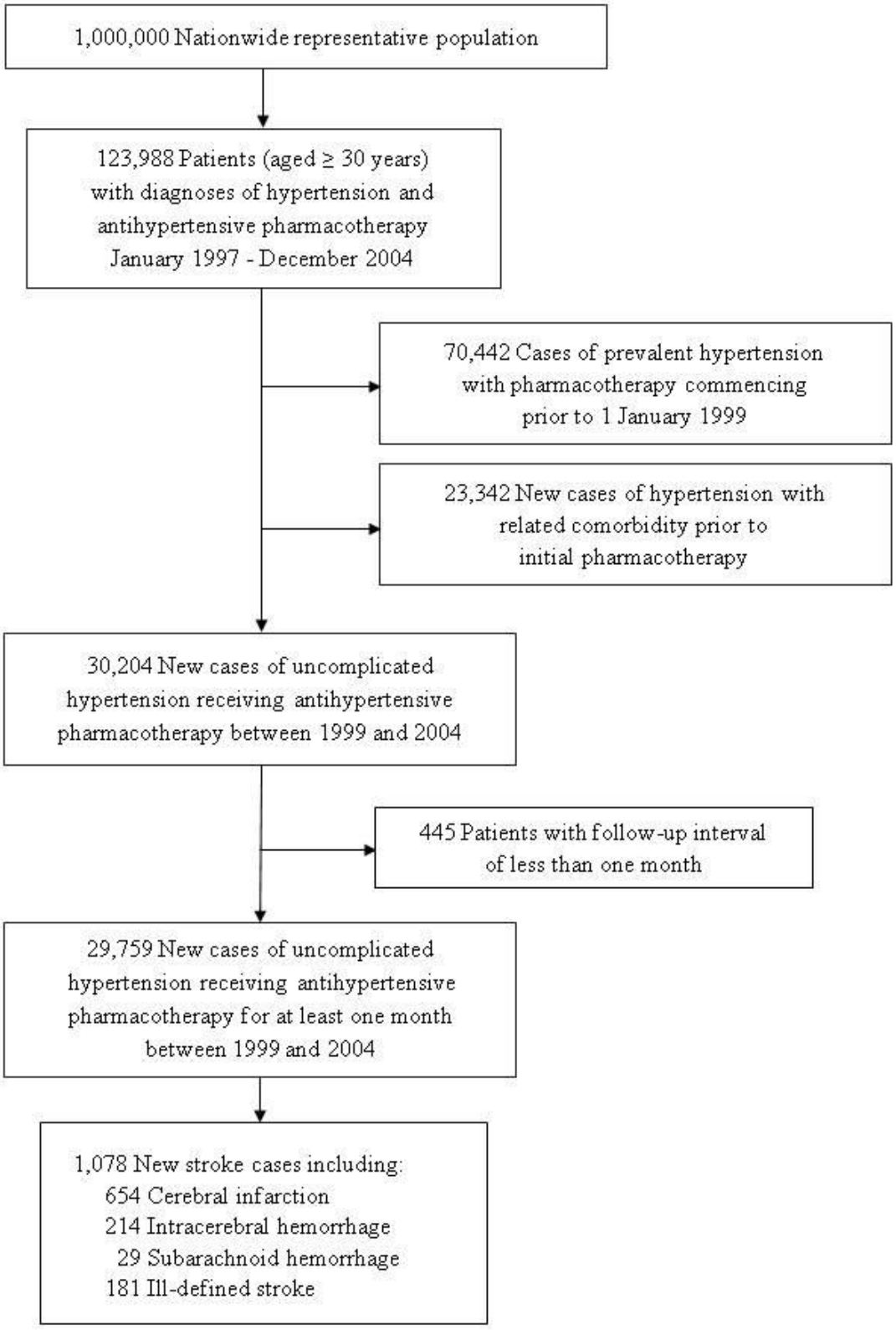


Figure 4.1 Selection process of the study cohort.

APPENDICES

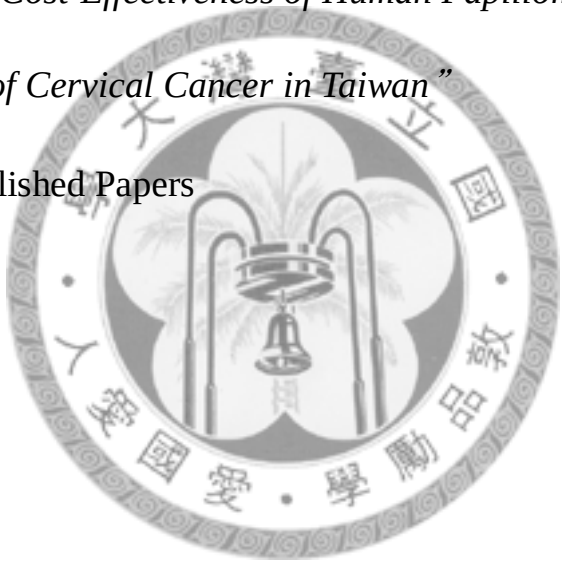
A. Outline of the National Health Insurance Research Database

B. Bibliography of My Work

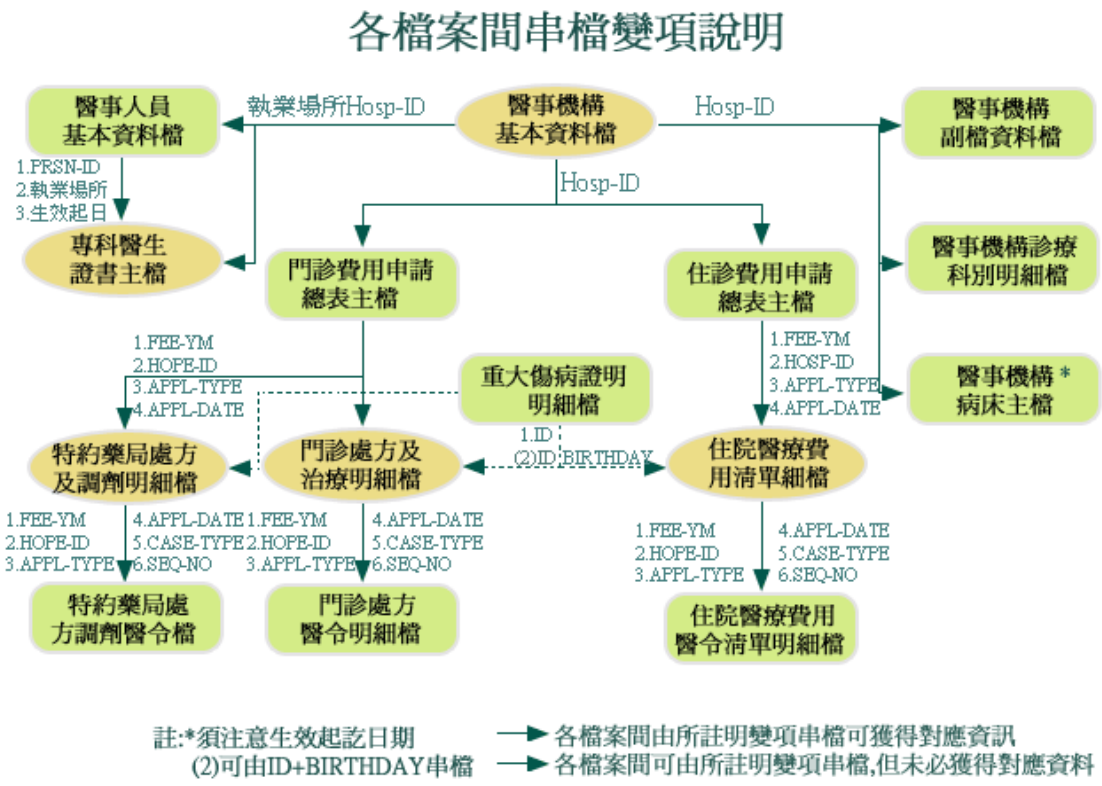
C. Manuscript of "*Cost-Effectiveness Analysis of Gefitinib as a First-Line Treatment for Advanced Non-Small Cell Lung Cancer in Taiwan*"

D. Manuscript of "*Cost-Effectiveness of Human Papillomavirus Vaccine for Prevention of Cervical Cancer in Taiwan*"

E. Reprints of Published Papers



APPENDIX A



[Source: National Health Research Institutes. National Health Insurance Research Database: coding book. http://www.nhri.org.tw/nhird/file_date/connect2.gif]

APPENDIX B

Bibliography of My Work :

1. Wang JD, **Liu PH**, Ho TH. Promotion of cost-effectiveness clinical guidelines for sustainable management of National Health Insurance. ***Taiwan Medical Journal*** 2007; 50(5):234-239. (*in Chinese*)
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