Comparing the Effectiveness of Different Strategies for Primary Prevention of Cardiovascular Diseases through Anti-hypertensive Drugs

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Abstract (in English)

Abstract of thesis entitled: **Comparing the benefit of different strategies for primary prevention of cardiovascular diseases through anti-hypertensive drugs**

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Objective:

For primary prevention of cardiovascular diseases through anti-hypertensive drugs, the traditional blood pressure approach is to treat people with blood pressure above a certain threshold. The new overall risk approach is to treat people with an overall cardiovascular risk above a certain level in addition to the elevated BP. As the overall risk approach requires extra efforts and costs, it is important to know how much more effective the new approach is than the blood pressure approach. This study is to estimate and compare the number of major cardiovascular events that could be avoided by shifting the single blood pressure approach to the overall risk approach if the same percentage of people in a large, representative Chinese population is treated with anti-hypertensive drugs.

Methods:

The data used in this study come from the 2002 China National Nutrition and Health Survey. The sample of the survey was selected by a multi-steps cluster random sampling method from 132 counties of mainland China. The sample used in the analyses includes a subsample of 38,673 persons from the survey, who were 30-74

years old, without previous CVD, and had data on all of the following variables: age, sex, SBP, DBP, total cholesterol, HDL-C, smoking, and diabetes mellitus, which are required for projecting the future risk of cardiovascular disease. The blood pressure of those survey participants using anti-hypertensive drugs were adjusted for drug treatment effect before analyses.

The same number or percentage of people were identified from the 38,673 participants according to the criteria for drug treatment by the blood pressure and overall risk approaches respectively. Those selected for comparison are those with the highest blood pressure levels for the blood pressure approach and the highest overall cardiovascular risk for the overall risk approach. The risk prediction equation which is most suitable for Chinese populations was used to predict the risk for an individual by using the risk factors in the person. The absolute effectiveness for each prevention approach is estimated by multiplying the median cardiovascular risk of the selected patients with the relative risk reduction (RRR) of anti-hypertensive drug treatment derived from meta-analyses of RCTs. The difference in the absolute effectiveness between the two approaches is used to quantify how many more CVD events can be prevented in 1000 people treated by the ORA as compared to the BPA.

Results:

The average age of the participants is 48.1 years and women account for 53.3%. About 35% percent of the participants are urban residents. Overall, 27.4% of the

participants had hypertension; 22.7% had dislipidaemia; 4.0% had diabetes; 10.2% had obesity; and 28.9% were smokers.

When 2.5%, 5.5%, 10.1%, 15.5%, 20.7%, 25.7% or 33.0% of the 38,673 subjects were treated by anti-hypertensive drugs by using the two approaches respectively, 22 (95%CI: 17~28), 13 (11~16), 9 (8~10), 7 (6~8), 6 (5~7), 5 (4~6), or 4 (3~4) more CVD events could be avoided in every 1000 people treated if the blood pressure approach is shifted to the overall risk approach which is in general a 15% to 25% increase in CVD events prevented.

In the extremely high CVD risk group defined by the Chinese hypertension guidelines, 57.2% of them had a 10-year CVD risk lower than the expected 30%. In the high CVD risk group, 76.2% of them had a 10-year CVD risk lower than the expected 20%. If the same number of extremely high and high CVD risk patients are treated (6.5%), 24 (95%CI: 22~25) more CVD events could be avoided in every 1000 people treated if the approach recommended by the Chinese guideline is shifted to the overall risk approach which is a 51.3%(95%CI: 47.3%~54.6%) increase in the CVD event prevented.

There are 6.7% (2574) participants who were currently using anti-hypertensive drugs. More than half of the treated patients had a 10-year CVD risk lower than 15% below which even western guidelines would not recommend drug treatment. If the same number of patients were treated according to the overall risk approach, 35 (95%CI:

34~37) more CVD events could be avoided in every 1000 patients treated which is a 106.2%(95%CI: 101.5%~110.6%) increase in CVD events prevented.

Conclusions:

In the same number of people treated, the number of CVD events avoided for the overall risk approach is always larger than that of the blood pressure approach. The additional benefits of overall risk approach compared with the blood pressure approach decreases as the percentage of people from the total population is increased. The Chinese hypertension guideline substantively misclassified patients in recommending anti-hypertensive drug therapy. As a result, many low risk people were currently treated. If the current practice and guidelines are shifted to the overall risk approach, many more CVD events could be avoided with the same resources used.

Abstract (in Chinese)

論文摘要（中文）

降壓藥物進行心腦血管疾病初級預防的不同策略的效果的比較研究

目的：

在應用降壓藥物進行心腦血管疾病的初級預防時，傳統的高血壓策略是對血壓高于某一閾值的所有人進行降壓治療。新的綜合危險策略是對心腦血管疾病風險高于某一閾值的高血壓病人進行治療。由于綜合危險策略的實施需要更多檢測和更多費用，對新的綜合危險策略和傳統的高血壓策略的效果進行比較非常必要。本研究在一個大的有代表性的中國人口樣本中估計并比較了，如果對相同人數進行降壓藥物治療，并假設兩種策略都治療了該治療的病人，那么從高血壓策略轉為綜合危險策略可以多預防的心腦血管事件數。

方法：

本研究采用了 2002 年中國營養與健康調查的數據。該調查采用多階段分層整群隨機抽樣，調查對象是中國大陸 31 個省、自治區、直轄市（不包含香港和澳門）的常住人口。本研究分析了該調查中 30～74 歲，沒有 CVD 病史，心血管疾病風險預測變量數據完整（年齡、性別、收縮壓、舒張壓、總膽固醇、高密度脂蛋白膽固醇、吸煙狀態、是否患有糖尿病）的 38,673 位研究對象。正在進行降壓治療的研究對象的血壓在分析前先加上了估計的治療降壓值。

在 38,673 位研究對象中，分別應用高血壓策略和綜合危險策略選擇相同數量或比例的人進行假設的降壓藥物治療。應用高血壓策略時，選擇其中血壓最高者；應用綜合危險策略時，選擇其中心腦血管疾病整體風險最高者。我們利用心血管危險因素的數據，使用最適于中國人群的危險預測方程，估計了每個研究對象的心腦血管疾病基線風險。各預防策略的絕對效果則等于，被選的治療對象的心腦血管疾病基線風險的中位數乘以降壓治療的相對危險減少值（來自對 RCT 的 meta 分析結果）。然后，對各預防策略的絕對效果進行比較。

結果：

38，673 位研究對象的平均年齡是 48.1 歲，其中 53.3%是女性，35%是城市居民。27.4％的研究對象患有高血壓，22.7%有血脂異常，4.0%有糖尿病，10.2%肥胖，28.9%吸煙。

在 38，673 位研究對象中，假設資源允許對 2.5%，5.5%，10.1%，15.5%，20.7%或 25.7%的研究對象進行降壓藥物治療，那麼，如果從高血壓策略轉為綜合危險策略，每治療 1000 人，可以多預防 18 (95%CI: 14~23), 11(9~13), 7(6~8), 6(5~7), 5(4~5), 或 4 (4~5)例心腦血管事件，即总体上可多預防 15％～25％的心血管事件。

中國高血壓指南建議對高危和記高危者立即開始藥物治療。在將被中國指南分類為心腦血管疾病極高危的對象中， 57.2%的人 10 年內的心腦血管疾病預測風險低于指南標稱的 30%。在將被指南分類為高危的對象中，76.2%的人 10 年內的心腦血管疾病預測風險低于標稱的 20%。如果將中國指南推薦的應治療對象變為采用綜合危險策略選擇的應治療對象，那麼，在治療人數相同的條件下（全

部對象的 6.5%），每治療 1000 人，可以多預防 24（95%CI: 19~29）例心腦血管事件，即可多預防 51.3%(95%CI: 47.3%~54.6%)的心腦血管事件。

在全部 38，673 個研究對象中有 6.7%（2574 人）正在進行降壓藥物治療。正在進行降壓治療的人中，超過半數的人其 10 年心腦血管疾病風險低于 15%（即使西方國家的高血壓指南也不推薦在這些人中進行降壓治療）。如果應用綜合危險策略選擇相同數量的人進行治療，那么，每治療 1000 人，可以多預防 35（95%CI: 29~41）例心腦血管事件，即可多預防 106.2%(95%CI: 101.5%~110.6%)的心腦血管事件。

結論：

當治療人數相同時，應用綜合危險策略可預防的心腦血管事件數總是高于高血壓策略。隨著總人群中被治療者比例的增加，綜合危險策略相對于高血壓策略的額外收益越來越小。應用中國高血壓指南確定需要降壓藥物治療的對象時，有相當大比例的病人的危險被高估。因此，許多低危者被給予了藥物治療。在不增加治療人數的前提下，如果從當前的治療實踐或指南推薦的策略轉為綜合危險策略，可以大大增加可預防的心腦血管事件的數量。

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Abbreviations used in the thesis

APCSC: the Asia Pacific Cohort Studies Collaboration

ARR: Absolute Risk Reduction

BP: Blood Pressure

BPA: Blood Pressure Approach

CAD: Coronary Artery Disease

CHD: Coronary Heart Disease

CI: Confidence Interval

CNNHS: the China National Nutrition and Health Survey

CVD: Cardiovascular Disease

DBP: Diastolic Blood Pressure

FBG: Fasting Blood Glucose

HDL-C: High Density Lipoprotein Cholesterol

NNT: Number Needed to Treat

OGTT: Oral Glucose Tolerance Test

OR: Odds Ratio

ORA: Overall Risk Approach

RCT: Randomized Controlled Trial

RD: Risk Difference

RR: Relative Risk

RRR: Relative Risk Reduction

SBP: Systolic Blood Pressure

TC: Total Cholesterol

TG: Triglyceride

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Chapter 1 Introduction

1.1 Cardiovascular disease as a major disease burden

Cardiovascular disease (CVD) is a major cause of disability and premature death throughout the world. It is estimated that 17.5 million people died from cardiovascular diseases in 2005, accounting for 30% of all global deaths[1]. Forty-six percent of cardiovascular deaths and 79% of the disease burden due to CVD occurred in those aged 70 years or younger, the productive period of life[2]. Although the age-adjusted CVD mortality rate has been declining in most developed countries in recent decades[3], it still remains to be the number one cause of deaths and disease burden in these countries[4] because of population aging and unhealthy changes in life style. Meanwhile, a much underappreciated fact is that about 80% of cardiovascular deaths now occurred in low- and middle-income countries[1] where resources available for prevention and treatment of the disease are much limited due to other more competing priorities.

CVD contributes substantially to the escalating costs of health care and places a heavy burden on the economies of countries. CVD costs the health care of the European Union almost €110 billion in 2006. This represents a cost of €223 per annum per capita, around 10% of the total health care expenditure of the region[5]. The estimated total of direct and indirect costs of cardiovascular diseases in China in 2003 was 252.5 billion RMB, accounting for 21.0% of the costs for all diseases and

2.2% of gross domestic product (GDP)[6]. It also causes individuals and households a substantial financial burden. For example, surveys on health service use in 2003 in China found that inpatient treatment for common chronic diseases including coronary heart disease and stroke was as high as a half of the annual household income in urban areas and up to three times the annual household income in rural areas[7].

It has become and will continue to be a high priority for most countries to effectively prevent CVD and reduce its health effects. In the past decades, many epidemiological studies have been conducted to understand the causes, risk factors and natural history of the disease. These studies have identified important factors predisposing to the occurrence of severe cardiovascular complications. These factors are commonly known as CVD risk factors[8]. The CVD risk factors can be broadly divided into two categories: amenable factors and unamenable ones[9]. The former include age, sex, race, and family history of cardiovascular diseases, which in combination with the amenable factors determine the magnitude of a person's future risk of developing a major cardiovascular event. The amenable factors include high blood pressure, high blood cholesterol, obesity and diabetes, which mostly are consequences of unhealthy life style such as smoking, physical inactivity, and unhealthy diet.

Prevention of CVD can only be achieved by modifying the amenable risk factors. Lifestyle can be effectively changed through interventions such as health education

programmes, which are often delivered at a population level, namely the population approach. On top of the population approach, hypertension, hyperlipidemia and diabetes mellitus can be further effectively dealt with through medications at an individual level, namely the individual approach. Lowering blood pressure through anti-hypertensive drugs is one of the most effective methods for prevention of major cardiovascular events.

1.2 Preventing CVD: the blood pressure approach

Epidemiological studies have shown beyond reasonable doubt that the risk of CVD is positively related to blood pressure: the higher the blood pressure is, the greater the CVD risk will be. This implies that the CVD risk could be lowered if blood pressure is lowered. Antihypertensive drugs are thus given to those with a high blood pressure. If blood pressure is above a certain threshold level, anti-hypertensive drugs would be indicated (see Figure 1-1). We call this the blood pressure approach. This approach had been widely adopted in the early hypertension guidelines before the 1980s[10] and its modified version is still used in the recommendations of the United States Joint National Committee Seventh (JNC7) Report[11]. The JNC7 guidelines advise treatment of hypertension for all those with systolic/diastolic blood pressure above 140/90 mmHg or above 130/85 mmHg and having diabetes or chronic kidney disease at the same time. For similar arguments, the same approach is also applied to the definition, diagnosis and treatment of hyperlipidemia and impaired blood glucose.

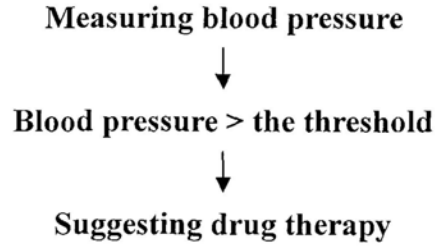

Figure 1-1 The blood pressure approach to primary prevention through anti-hypertensive drugs

The blood pressure approach has been used for decades. However, there is a fundamental question in this approach which has never been sufficiently emphasized and adequately addressed. That is how hypertension should be defined. Put it differently, what blood pressure value should be used as the cutoff to divide people into normotensive and hypertensive. Hypertension has generally been taken as a discrete disease entity. So patients diagnosed with it should require treatment. However, in the famous debate between Robert Platt and George Pickering[12], Pickering argued hypertension was not a disease in the conventional sense and there was no clear division between normal and pathological blood pressure. More recent studies showed firmly that the risk of cardiovascular events (including mainly stroke or myocardial infarction) is related to blood pressure at almost all levels, even when blood pressure is defined as "normal"[13 14]. It means that no matter what value is used to define hypertension it will be an arbitrary choice. Then the question would be how to define the need for pharmacological intervention? Some suggest that the threshold to initiate drug treatment be the blood pressure level above which intervention has

been empirically shown to be effective in reducing the CVD risk[15]. This is a reasonable argument but also means even lower blood pressure level will have to be used as the cutoff when antihypertensive drugs are shown to be effective in people with blood pressure below the current cutoff level. Thus no fixed threshold values for high blood pressure can ever be defined[14 16 17]. Indeed, no defined lower limit has thus far been found below which the benefits of blood pressure reduction would cease[18 19]. The terms hypertensive and normotensive defined by specific blood pressure levels survived only for the reason of convenience.

Indeed, the cutoff used for defining hypertension has constantly been declining in the past decades and lower and lower blood pressure levels are used. There is an important consequence for patients who are put on medication and those who finance the services. That is if a lower cut-off value in blood pressure is used, a larger number of people would be considered hypertensive and a smaller number of CVD events would be avoided in a given number of people treated. Conversely, if a higher cutoff value is used, fewer people will be indicated for medication and the average cost-effectiveness of drug treatment will then be better.

For example, in the United States, the age-adjusted prevalence of hypertension in those aged 18~74 years went up by about 50 percent after the hypertension threshold is lowered from 160/95 mmHg to 140/90 mmHg[20]. In China, in 2002 18.8% of those aged 18 years and older had hypertension, which is defined as systolic blood pressure 140mm Hg or above, and/or diastolic blood pressure 90mmHg or above, and/or

currently taking antihypertensive medication[21]. However, only 30.2% of them knew they had hypertension. Of those 30.2%, only 6.1% had their hypertension effectively controlled, 5.5% had not received any medication at all, and 18.6% were under treatment but failed to have their blood pressure effectively controlled. A low rate of effective control of blood pressure (i.e., blood pressure is reduced to 140/90 mmHg or lower) was also reported in the United States, Spain, Canada, France, and the United Kingdom, ranging from 13% in France to 25% in the United States[22].

In brief, the blood pressure approach uses arbitrary thresholds for defining what hypertension is. No fixed objective thresholds seem identifiable. A lower threshold would mean a larger number of people to be considered hypertensive and treated with drugs and a less favorable cost-effectiveness from the treatment. Furthermore, in practice blood pressure has not been effectively controlled in most of those who are reckoned to be hypertensive according to the current definition of hypertension.

More importantly, the blood pressure approach may not be the most cost-effective strategy for prevention as it is focused on the "disease" rather than the benefit from treatment. It is now evident that hypertension is only one of the many risk factors for cardiovascular disease[23 24], and the risk of cardiovascular morbidity or mortality in individuals with mild or moderate hypertension depends more on their constellation of risk factors than on their blood pressure alone[24-26]. These risk factors include older age, male sex, previous cardiovascular events, target organ damages such as left ventricular hypertrophy and renal disease, smoking, diabetes mellitus, dislipidaemia,

central obesity and sedentary life style. For example, a 40-year-old male with a blood pressure of 160/95 mmHg who is otherwise healthy and does not smoke would have a 10-year risk of cardiovascular events (stroke, myocardial infarction or coronary death) less than 10%. On the other hand, a man of the same age and with the same blood pressure (160/95) who smokes, is obese and has hyperlipidaemia would have a 10-year risk of approximately 30%[27].

Although drug therapy appears to be beneficial in most hypertensive patients, the risk and cost of antihypertensive drugs may outweigh the benefit of drug treatment in low risk patients[28]. In fact, a meta-analyses suggested that the benefit of treatment would exceed harm only when the baseline CVD mortality is greater than 0.6% per year[29]. The magnitude of benefit affects the benefit-harm balance and the cost-effectiveness of the intervention. So, apart from whether the intervention is qualitatively effective or not, the magnitude of the benefit is also important a message for decision making. If there is no benefit or there is more harm than good from the treatment, the patients would be better off if they are not treated at all. If the magnitude of the effectiveness is used to judge whether a person should be treated with anti-hypertensive drugs or not, would blood pressure remain to be the best indicator for drug treatment?

1.3 The absolute benefit and its implications for prevention policy

The main evidence underlying a decision to intervene is the possibility that the patient can benefit from the intervention. Theoretically, the best predictor of a patient's benefits from a treatment should be the best criteria to determine whether

the patient should receive the intervention. Although blood pressure had long been used to determine whether a patient should receive treatment or not, it is unlikely that blood pressure alone is the best predictor of a patient's benefit from treatment.

In order to facilitate the discussion, we need to define what a treatment benefit is.

1.3.1 Measures of therapeutic effect

In clinical trials, dichotomous outcomes such as death and disease are often used to quantify the effectiveness of a treatment or to find out whether treatment reduces or increases the risk of the outcome. The term "risk" here refers to the probability of the occurrence of an outcome event in a certain period of time. The effect of treatment is defined as the reduction or increases in the risk of the outcome event and can be expressed both in relative and absolute terms. The relative measures indicate the relative change in the risk caused by a treatment, while the absolute ones show the absolute change. The formulas of commonly used measures of therapeutic effect are summarized in Table 1-1[30].

Table 1-1 Formulas for commonly used measures of therapeutic effect

Measure of effect	Formula
Relative risk (RR)	EER#÷CER^
Relative risk reduction (RRR)	[(EER - CER)÷CER] or (1- RR)
Absolute risk reduction (ARR)	EER - CER
Number needed to treat (NNT)	1÷ARR

#EER: Event rate in the intervention group; ^CER: Event rate in the control group.

(Adapted from Barratt A and et al., Tips for learners of evidence-based medicine: 1. Relative risk reduction, absolute risk reduction and number needed to treat. CMAJ, 2004. 171(4): 353-8.)

1.3.1.1 Relative measures of effectiveness

The relative measures of effectiveness include the relative risk (RR) and the relative risk reduction (RRR). The relative risk (also known as risk ratio) is the ratio of the risk in the intervention group to that in the control group. The relative risk reduction is the percentage reduction of risk in the intervention group as compared to the control group. The relative indices are usually used to summarize the results in clinical trials. But they do not take into account the baseline risk of patients and therefore can severely distort the absolute impact of an intervention, in particularly when the outcome event in untreated patients is very rare or very common[31].

By baseline risk, in a randomized controlled trial, it refers to the risk in the control group, which is also known as the event rate in control group (CER). In practice, for an individual patient or a population, the baseline risk is often referred to the future probability of developing the concerned outcome event in the absence of treatment.

1.3.1.2 Absolute measures of effectiveness

The absolute risk reduction (ARR) is one of the most useful measures of absolute benefit. It is simply the arithmetic difference between the risk in the intervention group and that in the control group. So, it is also called risk difference (RD). According to the definition, the ARR is a product of the baseline risk (i.e., CER) and

the relative risk reduction. So, given the same relative benefit, the absolute benefit will vary in different populations or individuals if their baseline risk differs.

Another commonly used measure of absolute benefit is the number needed to treat (NNT)[32], which is clinically more meaningful. NNT is defined as the number of patients needed to be treated in order to obtain one desirable outcome event. NNT equals the reciprocal of the ARR.

1.3.2 Treatment decision should consider the absolute benefit

Meta-analyses of randomized controlled trials have shown that the relative risk reduction of blood pressure lowering drugs is largely consistent or homogeneous regardless of patient characteristics and therapeutic settings[33-40]. This implies that treatment of anti-hypertensive drugs would benefit similarly everyone who has hypertension regardless their current risk factors and co-morbidities and no discrimination should be made as regards who should be treated with the drugs.

However, a constant relative benefit would mean that the absolute benefit would differ if a person's age, sex or co-morbidities differ. Put it differently, the more likely a person is to develop a cardiovascular event in the future, the more likely he or she is to benefit from drug treatment. This future risk of cardiovascular diseases is determined by all the major cardiovascular risk factors a person has and is usually called the overall risk or baseline risk. Contrary to the constant relative benefit, the varying absolute benefit implies, importantly, that some will benefit more from drug

treatment than others and drugs should first be given to those who may benefit more if resources are limited.

For example, two patients with an identical blood pressure (150/96mmHg) but different profiles of other risk factors could have a 20-fold difference in the absolute cardiovascular risk and thus the chance of benefiting from treatment between the two patients with "mild hypertension" would differ significantly (see Box1[41]).

Box 1. The absolute benefit varies according to the baseline risk

Assume Relative Risk Reduction = 25%

Patient A:
35 years old female, blood pressure 150/96 mmHg, total cholesterol 5.0mmol/l, high density lipoprotein cholesterol 1.4mmol/l, nonsmoker, no diabetes.

10 year baseline risk of CVD	2.5%
ARR over 10 yrs	0.6%
CVD events avoided in 1000 persons treated over 10 yrs	6
NNT over 10 yrs	167

Patient B:
65 years old male, blood pressure 150/96 mmHg, total cholesterol 7.0mmol/l, high density lipoprotein cholesterol 1.0mmol/l , smoker, no diabetes.

10 year baseline risk of CVD	51.0%
ARR over 10 yrs	12.8%
CVD events avoided in 1000 persons treated over 10 yrs	128
NNT over 10 yrs	8

(Data from Wallis EJ, Ramsay LE, and Jackson PR. Cardiovascular and coronary risk estimation in hypertension management. Heart, 2002. 88(3): 306-12.)

For patient A, according to her risk factor profile, her estimated 10-year baseline risk of CVD is 2.5% and the absolute risk reduction will be 0.6%. This means 6 CVD

events can be avoided if 1000 such patients are treated. For patient B, according to his risk factor profile, his estimated 10-year baseline risk of CVD is 51%, about 20 fold that of patient A and his absolute risk reduction in 10 years of treatment will be 12.8%. This means 128 deaths could be avoided if 1000 such patients are treated. So, given the same relative benefit, the absolute benefit in patients with different baseline risks can differ significantly.

These arguments lead to an important conclusion for decision making: decisions about antihypertensive drugs must consider the absolute benefit. This implies that if the relative benefit is constant, the absolute benefit will be directly determined, and treatment decisions indirectly influenced, by an individual's baseline cardiovascular risk. This has laid down the foundation of the overall risk approach.

1.4 The new strategy: the overall risk approach

For primary prevention of cardiovascular diseases, the overall risk approach treats people who are at an overall cardiovascular risk above a certain level or threshold (Figure 1-2).

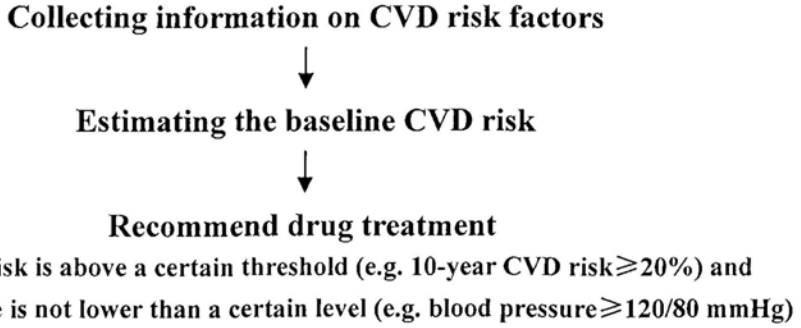

Figure 1-2 The Overall Risk Approach

For a long time, hypertension guidelines had been focused on blood pressure values, taking it as the only or main variable for determining the need and the type of treatment[42 43]. Although this approach was still maintained in the 2003 JNC 7 Guidelines[11], most international and national guidelines have adopted the principle of targeting antihypertensive drugs at people with an increased overall cardiovascular risk[44-49]. However, the methods used to estimate the CVD risk differ among guidelines. The European Society of Hypertension and the European Society of Cardiology (ESH-ESC) and the World Health Organization-International Society of Hypertension (WHO/ISH) guidelines suggested classifying the CVD risks of patients into several categories according to the severity of hypertension and the number of other risk factors[47 50]. This has the advantage of simplicity. On the other hand, the New Zealand Guideline[46] recommended a more accurate method of estimating the overall cardiovascular risk by using a risk prediction chart. Actually, the risk prediction chart is a simplified version of risk prediction equations, so far the most accurate methods to estimate a person's cardiovascular risk. The risk prediction equations are derived from large cohort studies and use major cardiovascular risk factors to project a person' CVD risk. The risk factors used in the equations generally include sex, age, blood pressure, cholesterol concentration, tobacco use, and diabetes mellitus[51-55]. Estimating the overall CVD risk in a person is the starting point in considering drug treatment in the overall risk strategy.

1.5 Which predicts the absolute benefit better: baseline risk or blood pressure

The relation of baseline risk with the absolute benefit has been firmly demonstrated by empirical evidence from RCTs. A meta-regression of 22 blood pressure lowering RCTs for primary prevention of cardiovascular diseases[56] shows a linear relation between the baseline risk of cardiovascular diseases (i.e., the 5-year risk of major cardiovascular events in the absence of treatment) and the absolute benefit from treatment (i.e., the 5-year difference in the risk of major CVD events) (see Figure 1-3). The regression coefficient equals -0.3902 (P<0.0001). It represents the change in the absolute benefit (RD) for one unit change in the baseline CVD risk.

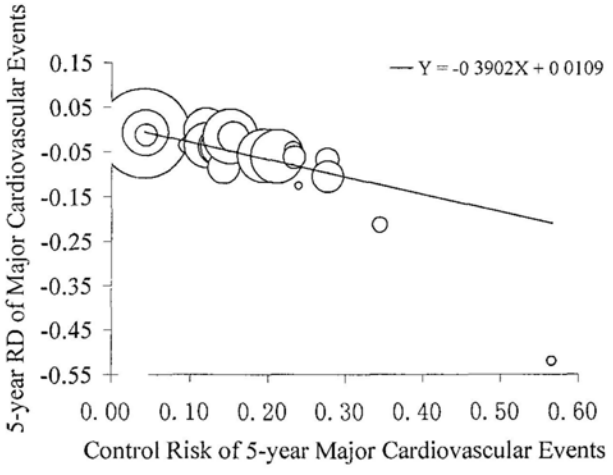

Figure 1-3 Baseline risk and absolute benefit: Results from a meta-regression of 22 blood pressure lowering RCTs.

(Source: Jiang Yu. "An investigation on the determinants of the effectiveness of anti-hypertensive drugs for primary prevention of cardiovascular disease: a systematic review of randomized controlled trials." Ph.D. Dissertation, The Chinese University of Hong Kong, Hong Kong, 2007.)

Notes: RD= risk difference.

Figure 1-4 shows that initial blood pressure is also strongly related to the absolute benefit. The regression coefficient is -0.0024 ($P<0.0001$). The regression coefficient indicates the strength of an association between two variables. However, when the independent variables are in different units of measurement (as in this case, the baseline risk is a probability and blood pressure is in millimeter mercury), a change of one unit in the baseline risk is not equivalent to one unit of blood pressure. Thus, the regression coefficient for blood pressure and that for baseline risk are not directly comparable and the difference between the two does not suggest one is a stronger determinant of the benefit than the other.

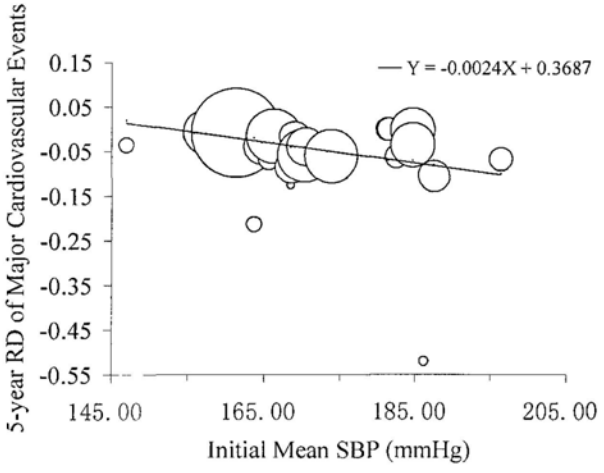

Figure 1-4 Initial mean systolic blood pressure and absolute benefit: results from a meta-regression of 22 BP lowering RCTs.

(Source: Jiang Yu. "An investigation on the determinants of the effectiveness of anti-hypertensive drugs for primary prevention of cardiovascular disease: a systematic review of randomized controlled trials." Ph.D. Dissertation, The Chinese University of Hong Kong, Hong Kong, 2007.)

In order to compare the two fairly, the change of one unit in baseline risk should be made ideally represent the same proportion of people in a population as the change of one unit in blood pressure does. A statistical way to resolve this problem is to convert the original values to the standard deviate, i.e., the difference between the mean and the observed value divided by the standard deviation (SD), before regression analyses, assuming the variables follow a normal distribution in the population. The standardized regression coefficient will represent the change in response to per standard unit (i.e., one SD) change in a predictor. If the distribution of blood pressure or baseline risk is approximately normal, then about 16% of people in the population will have a blood pressure or baseline risk above one standard deviation above the mean, and about 2.5% of people would have a blood pressure or baseline risk two standard deviations above the mean. So the change of one standard unit of baseline risk or blood pressure will represent the same percentage of the population.

Table 1-2 compares the standardized correlation coefficients between RD and the baseline risk with that between RD and blood pressure. The standardized coefficient of RD with baseline CVD risk is 75% greater than that with initial blood pressure, suggesting the relation between RD and baseline CVD risk is much stronger than that between RD and initial blood pressure. Thus the change of RD will be greater if the same percentage of population is selected for treatment according to baseline risk than that according to blood pressure.

Table 1-2 Comparing the standardized correlation coefficients for the relation of 5-year RD of cardiovascular deaths with BP and that with baseline cardiovascular risk

Independent variables	Standardized Coefficient (95% CI)
Initial Mean SBP	- 0.44 (-0.62, -0.27)
Control risk of 5-year cardiovascular deaths	- 0.77 (-0.90, -0.64)

(Source: Jiang Yu. "An investigation on the determinants of the effectiveness of anti-hypertensive drugs for primary prevention of cardiovascular disease: a systematic review of randomized controlled trials." Ph.D. Dissertation, The Chinese University of Hong Kong, Hong Kong, 2007.)

The above results show that the overall cardiovascular risk is a stronger predictor or determinant of absolute benefit from anti-hypertensive drug treatment than blood pressure, suggesting that the use of antihypertensive drugs should be determined by the overall cardiovascular risk rather than blood pressure alone.

1.6 Lack of direct comparison of the two approaches

However, as blood pressure and baseline risk are unlikely to follow exactly a normal distribution, the comparison of the standardized regression coefficients may be problematic and not reliable. More importantly, the comparison of standard coefficients does not tell how many additional cardiovascular events could be avoided by shifting from the blood pressure approach to the overall risk approach given the same percentage of the population are treated, which is important for making decisions.

It should be noted that the application of the overall risk approach often involves laboratory test of lipid and glucose level and a complex risk estimation process, while the BP approach is simple and easy to apply. The comparison of the coefficients, however, gives any direct idea neither about the comparison in the number of CVD events prevented in the two approaches nor about the additional number of cardiovascular events prevented to justify its additional costs.

1.7 Objectives of this study

We thus conducted this modeling study to estimate and directly compare the number of major cardiovascular events that could be avoided by shifting the blood pressure approach to the overall risk approach if the same percentage of people is treated with anti-hypertensive drugs for primary prevention of CVD. Various cutoff values in the baseline CVD risk and various percentages of a population put under drug treatment will be used to examine the changes in the additional benefit from the overall risk approach.

Further analyses were also conducted to estimate the additional number of major cardiovascular events that could be prevented by shifting the approach recommended in the current Chinese hypertension guidelines to the overall risk approach, assuming the same number of people be treated in the comparisons.

We also estimated and compared the number of CVD events prevented in those currently under antihypertensive drug treatment which reflects the actual current

practice with the number of CVD events that can be prevented if the same number of people are identified by the overall risk approach and treated with drugs.

Chapter 2 Methods

2.1 Selection of the study design

The objective of my study is to compare the absolute effectiveness of two approaches to identifying those who should be treated with blood pressure lowering drugs. The two approaches are the blood pressure approach and the overall risk approach. The best study design to compare the effectiveness of two interventions is the randomized controlled trial (RCT). In an RCT, subjects would be randomly assigned to different comparison groups so that all the prognostic (or confounding) factors would be balanced between groups and confounding effects can be minimized. A possible design of RCT to address my study question is shown in Figure 2-1. A representative sample of a general population is randomized into two groups to receive either the high CVD risk approach or the blood pressure approach. The same percentage of those with a high CVD risk and that of those with a high blood pressure can be identified and treated with drugs. The incidence of major CVD events can then be compared between the two groups and the relative effectiveness of the two approaches can be estimated.

Unfortunately, such an RCT is a pseudo experiment and does not differ from a non-randomized controlled study as those with high CVD risks and those with high blood pressure values are not determined at random and thus incomparable in potential confounding factors. Put it differently, the two approaches are not two interventions that can be randomly allocated but two different ways of selecting

(different types of) people for the same treatment. Thus, the RCT does not apply to my research question. Even if such a study could be conducted, it would require a large number of study subjects and years of follow up, which would be far beyond the feasibility for a PhD project. Furthermore, it is generally difficult in trials to recruit people representing the general population which would be the ideal population for my study question. Finally, one such study can only compare the two approaches at one single fixed cutoff value in blood pressure and CVD risk. Many such studies would be needed in order to compare the two strategies at various practical cutoff values. For the last three reasons, even a non-randomized controlled study is not feasible.

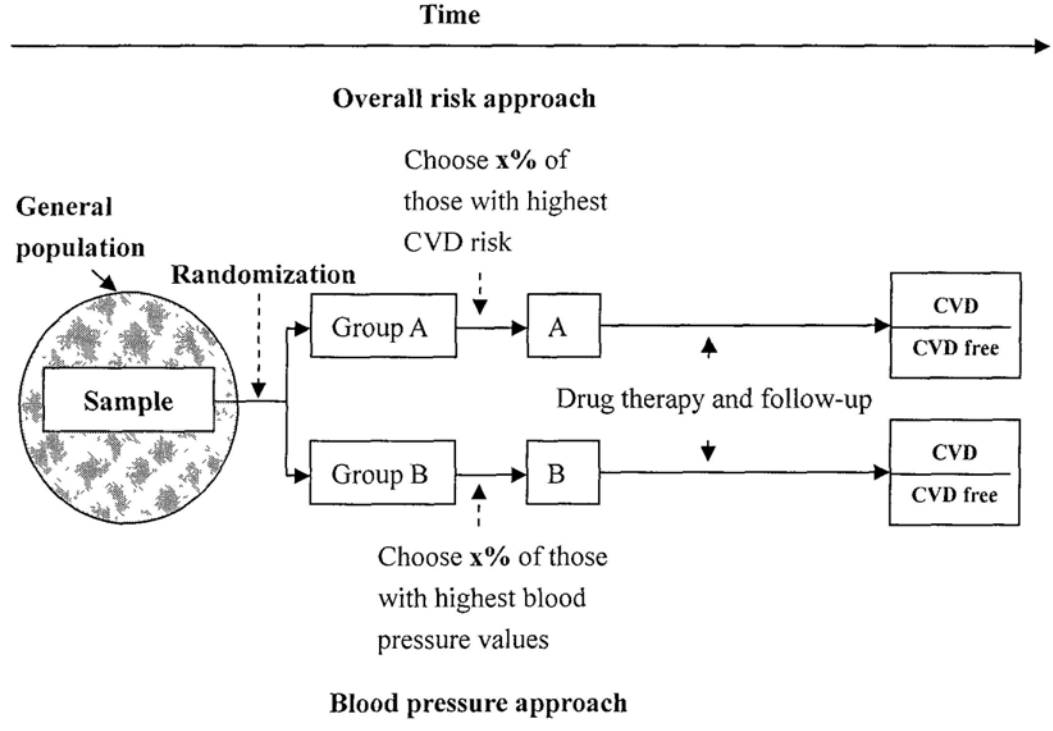

Figure 2-1 A possible design of a randomized controlled trial for my study

It seems that the only feasible method for addressing my study question is to compare the effectiveness of the two approaches estimated by the relative risk reduction established from meta-analyses of randomized controlled trials and the baseline CVD risk projected by using a risk prediction equation, such as the Framingham CVD risk equation, based on data on CVD risk factors collected from some large cross-sectional studies or surveys representative of a large general population. I will call such a study a modeling study.

There are two basic requirements for such a modeling study. First, data used should represent a large general population to which we hope our results are able to generalize. Second, in order to make fair comparisons, the number of patients selected from a population for treatment for the two approaches should be equal and the selection of patients should start from those with highest cardiovascular risks or blood pressure values in the population.

The detailed design of the modeling study is shown in Figure 2-2. First, based on data on CVD risk factors, we can project the 10-year CVD risk for everyone in the population by using a risk prediction equation. This risk will be taken as the future CVD risk in the absence of drug treatment and also used for identifying eligible people by their baseline CVD risk in the CVD risk approach.

Second, we select from the population a specific number or percentage of people with the highest blood pressure and take them as the study subjects for the blood pressure approach. We then place these subjects back to the total population pool and

select again the same number of people but with the highest CVD risks rather than highest blood pressure values and take them as the study subjects for the CVD risk approach. This means that a person identified by one approach can also be selected by the other and included in the analyses in both groups. The average projected 10-year CVD risk is then estimated separately for each of the two groups.

Third, the absolute effectiveness (that is the risk difference or the number of CVD events prevented in 100 people treated) is then estimated by multiplying the average CVD risk in a group by the relative risk reduction (RRR) estimated in published meta-analyses of randomized controlled trials of anti-hypertensive drugs compared with placebo.

Finally, the marginal absolute benefit that is the number of additional CVD events prevented in 100 people treated in the overall risk approach as compared with the blood pressure approach can be estimated as the difference in the RD between the two groups.

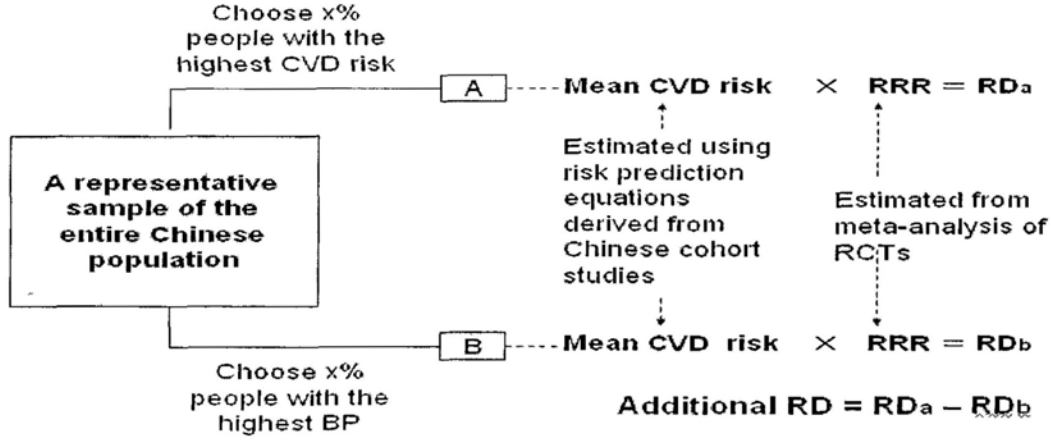

Figure 2-2 Modeling the absolute benefit of the two approaches by using cross-sectional data

Estimation of the absolute benefit in the two approaches is further described in Figure 2-3. The detailed process is as follows:

Step 1: Estimate the 10-year cardiovascular risk for all individuals in the entire population by using a risk prediction equation.

Step 2: Select an equal number of patients for drug treatment for the blood pressure approach and for the overall risk approach. The patients selected should have highest blood pressure values for the blood pressure approach and highest cardiovascular risks for the overall risk approach. Those already included in one approach are all potentially eligible for, and could be included in, the other approach.

Step 3: The average cardiovascular risk of selected patients is expressed in the median cardiovascular risk of the individuals' selected for treatment in one approach.

Step 4: The relative risk reduction (RRR) of anti-hypertensive drug treatment is derived from published meta-analyses of RCTs which compared anti-hypertensive drugs with a placebo.

Step 5: The estimated absolute benefit for each approach is expressed in a risk difference (RD) and estimated to be the average cardiovascular risk multiplied by the RRR. The difference in the RD between the two groups will be used to quantify how much better one approach is than the other. It is thus the number of additional CVD

events can be prevented in 100 treated in the overall risk approach as compared with the blood pressure approach.

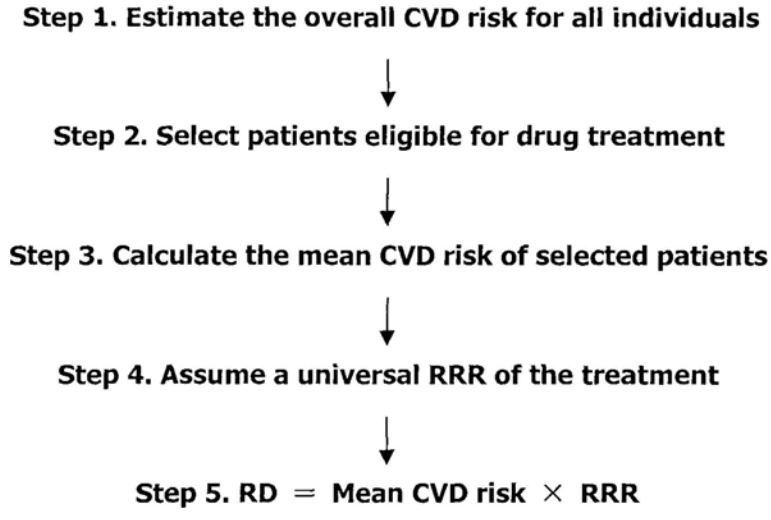

Figure 2-3 Estimation of the absolute benefit in the two approaches

The modeling study has a few advantages over trials or cohort studies:

As the relative risk reduction for anti-hypertensive drugs is derived from meta-analyses of randomized trials, it will be more precise than an estimate from any single trial or cohort study;

As a representative cross-sectional study for a population is much easier to conduct than trials or cohort studies, the representativeness of the results of a modeling study would be better than any possible trials or cohort studies;

Most importantly, various practical cutoff values in either the blood pressure approach or overall risk approach can be evaluated and compared between the two approaches in one single modeling study.

2.2 The 2002 China National Nutrition and Health Survey

My study used data from the 2002 China National Nutrition and Health Survey (CNNHS)[21], a cross-sectional survey of a nationally representative sample of the Chinese population which collected information on main cardiovascular risk factors in a subset of the whole surveyed population.

2.2.1 Study population

The study population of the 2002 CNNHS covered thirty-one provinces, autonomous regions and the municipalities directly under the central government, exclusive of Hong Kong, Macao and Taiwan. The survey aimed to interview all regular residents of selected households in its sample, including family members and non-family members such as relatives and baby-sitters who have been living in the household for no less than 6 months.

2.2.2 Sampling frame

As shown in Figure 2-4, a stratified, multistage, random cluster sampling process was used for subject selection. Administrative areas in China were divided into six categories according to whether they are urban or rural and the level of economic

development (from high to low): large cities, small or medium-sized cities, 1st class rural areas, 2nd class rural areas, 3rd class rural areas and 4th class rural areas. The large cities includes Beijing, Shanghai, Tianjin, Chongqing, Harbin, Shenyang, Dalian, Jinan, Qingdao, Ningbo, Nanjing, Guangzhou, Shenzhen, Zhengzhou, Chengdu, Xian, Wuhan, and Xiamen. All other cities fell into the category of small or medium-sized cities. The 1st class rural areas, which are the most developed rural areas in China, include those at the Yangtze River delta area, the Bohai sea rim area, and the southern coastal region. The 2nd class rural areas include those in the north China plain, the Sichuan basin, the southeast hilly area, and the Henan-Anhui-Hubei-Jiangxi middle Yangtze River region. The 4th class rural areas, which are the least developed areas, include those in the Hunan-Hubei-Sichuan-Guizhou region, the Qinling-Daba Mountains, the Guizhou-Guangxi-Sichuan-Yunnan plateaus, and the Loess Plateau. The rest of rural areas all fall into the 3rd class.

A 4-stage sampling method was used to draw the households for the survey. From each of the six area categories, twenty-two counties or cities were selected using a systematic sampling method and a total of 132 counties/cities were chosen at Stage 1 of the sampling. In Stage 2, three townships or districts were randomly chosen from each selected county/municipal district, and a total of 396 were chosen. In Stage 3, two villages or neighborhoods were randomly chosen from each of the selected townships/districts and a total of 792 were chosen. In Stage 4, ninety households

were randomly selected from each village/neighborhood, resulting in a total of 71,971 households and 243,479 persons eligible for the survey.

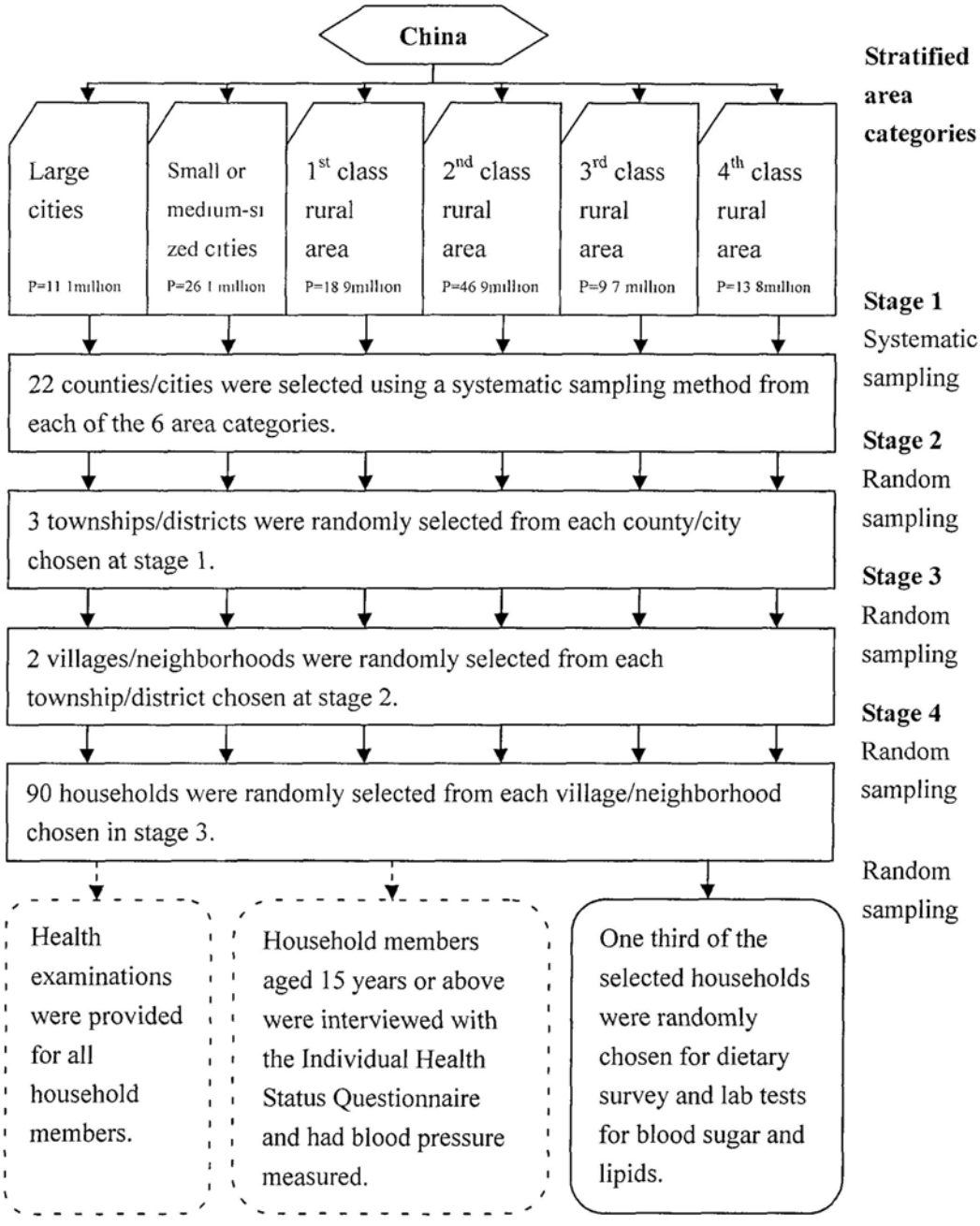

Figure 2-4 The sampling frame of the 2002 CNNHS

Notes: P= Population size

The demographic factors of the sampled subjects, including age distribution, sex ratio, dependency ratio, family size, and percentage of the minority ethnic groups, were compared with the 5th national population census data in 2000 and there is no statistically significant difference between them[57]. The results showed that the sampled population represents well the total Chinese population.

2.2.3 Subjects eligible for analyses in my study

The investigators reported that 10.1% of the 243,479 eligible subjects did not actually live at their registered addresses and 10.8% did not show up at the time of the survey. Thus, a total of 192,500 subjects attended the survey. Perhaps due to losses during data cleaning, records were available for 186,872 subjects in the final dataset. We only included in the analyses people aged 30~74 years free of stroke and having data on major cardiovascular risk factors including age, sex, systolic blood pressure, diastolic blood pressure, total cholesterol, high density lipoprotein cholesterol, smoking and diabetes diagnosis. We restricted age to 30~74 years because the CVD risk prediction equation used in the analyses is only suitable for adults aged 30~74 years. We excluded those with a history of stroke as we are only interested in primary prevention. We could have also excluded those with a history of CHD but the survey did not collect such data. Finally, a total of 38,673 persons are eligible and they were all included in my analyses. The great drop in the number of people eligible for my study is because only a small number of people were

randomly selected to have their blood cholesterol and glucose measured. Figure 2-5 shows the subjects flow of the 2002 CNNHS survey.

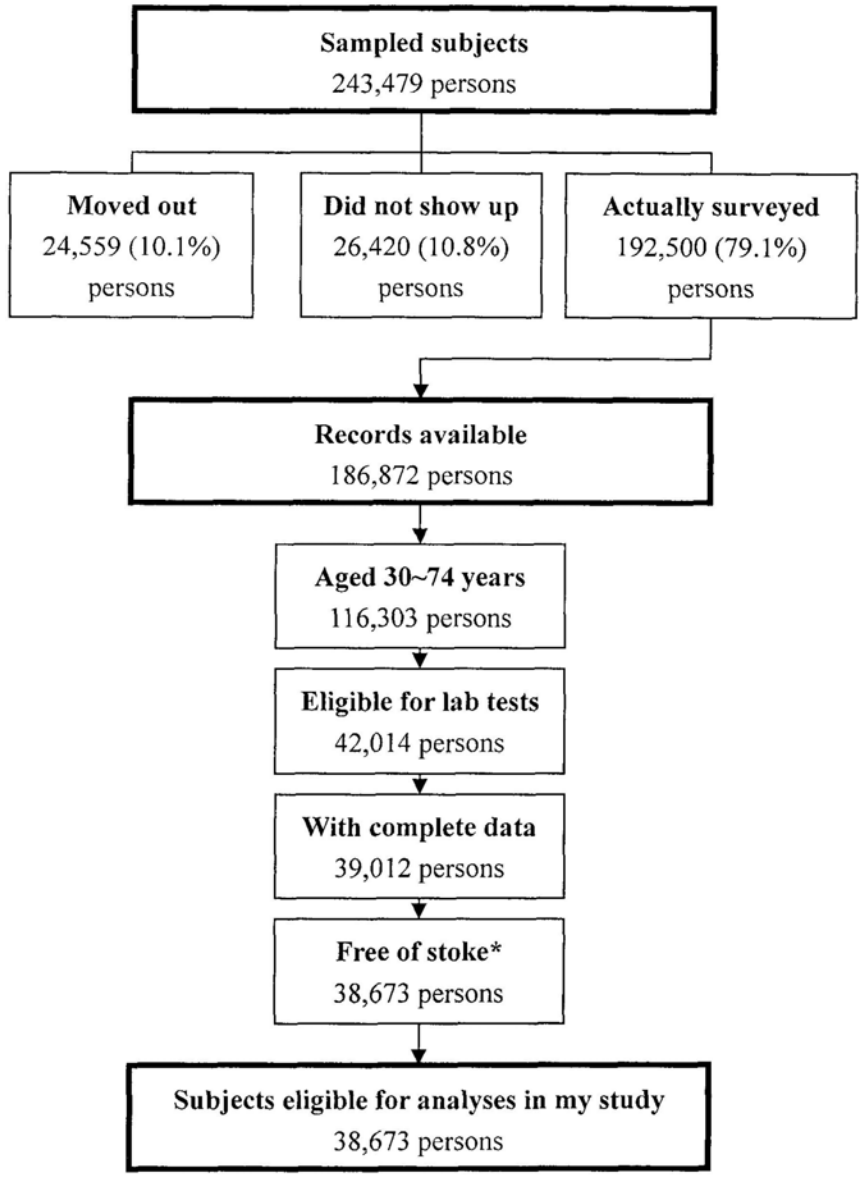

Figure 2-5 Subjects flow of the 2002 CNNHS Survey

Notes: *The history of myocardial infarction is not available in the 2002 CNNHS survey.

2.2.4 Data collection in the CNNHS

Details of the questionnaires and diagnosis criteria used in the survey have been published elsewhere[21]. Information about the major CVD risk factors and disease history of the study participants were collected through the Individual Health Status Questionnaire, health examination and laboratory tests. I will only describe how data on major CVD risk factors were collected.

2.2.4.1 Smoking

Individuals aged 15 years or above were interviewed by using the Individual Health Status Questionnaire. Smoking habit was included in the questionnaire. Respondents aged 20 years or above were asked: "Have you ever smoked cigarettes consecutively or cumulatively for 6 months or longer in your entire life?" and "Did you smoke in the last thirty days for at least 1 cigarette per day, at least 1 cigarette per week, less than 1 cigarette per week, or not at all?" Individuals who smoked consecutively or cumulatively for 6 months or longer in their entire life were defined as ever smokers. Ever smokers who smoked in the last 30 days are defined as current smokers.

2.2.4.2 Blood pressure, height and weight

Health examination was conducted following standardized procedures by trained interviewers and repeated measurements in subgroups showed a high reproducibility in the measurements. All participants took a measurement for height and weight, but

blood pressure was measured only in those aged 15 years or above. Two consecutive blood pressure measurements were performed, and the mean value of the 2 readings was used as a person's usual blood pressure. The concordance rate between the blood pressure reading of the interviewer and that of the quality control inspector is 97% and 98% respectively for systolic and diastolic blood pressure. The height was measured to the nearest 0.1 cm. Fasting body weight was measured to the nearest 0.1kg.

2.2.4.3 Blood sugar and lipids

One third of all the eligible households were randomly selected for conducting the dietary survey and laboratory test for blood sugar and blood lipids. Fasting blood samples were collected. Plasma was separated immediately and all fasting glucose samples were measured within 4 hours. Oral glucose tolerance test (OGTT) was done for people whose fasting blood glucose (FBG) was 5.5mmol/l or higher to reduce the missed diagnosis of diabetes mellitus. Total cholesterol (TC), triglyceride (TG), and high density lipoprotein cholesterol (HDL-C) were tested in the laboratory of Chinese Center for Disease Control and Prevention. For external quality control, blind serum samples provided by the US Center for Disease Control were analyzed at regular intervals over the entire course of the laboratory analyses of the samples of the 2002 CNNHS.

2.2.4.4 History of major chronic diseases

Questions were asked on whether participants were diagnosed with hypertension, dislipidaemia, diabetes mellitus, and stroke, and whether they were under drug treatment for hypertension in the past two weeks.

2.3 Choosing the CVD risk prediction method

The realization that CVD results from a multifactorial process led to the creation of various risk assessment instruments, with the objective of synthesizing the impacts of a number of major risk factors into a single statement of the hazard of CVD. Equations that can be used to project a person's future CVD risk are derived from large cohort studies such as the Framingham Heart Study. They are normally multivariate regression functions and predict the chance of developing a CVD event in an individual in the future by combining all the major CVD risk factors a person has. Many CVD prediction equations have been developed in the past decades. They differ in a few major aspects: the source population, type of CVD events to predict, risk factors included, and definition of risk factors.

For simplicity and convenience of application, the future CVD risk can be approximated by counting the risk factors in a person. The more the risk factors a person has, the higher the future CVD risk will be. The 2005 Chinese hypertension guidelines[58], for example, still used this approach. The good approximation methods such as the New Zealand Risk Table are in fact derived from or based on the original

risk equations. As most CVD risk predictors such as age, blood pressure and cholesterol are continuous variables, taking them as categorical or binary variables will simplify the risk estimation process but compromise in the precision of the estimate.

The original risk equations for projecting the future CVD risk were used in my study so that I can more accurately estimate the risk. The following factors are considered in choosing the risk prediction model for my study:

- It must be suitable for Chinese populations. It would be best if it is derived directly from a Chinese population;
- It must be derived in those free of CVD at the beginning of the cohort study;
- Variables used in the equation must be available in my dataset;
- The equation must have been validated in a Chinese population or an Asian population;
- The equation must be able to predict the CVD risk for both men and women;
- It should be able to predict total or major cardiovascular events including both myocardial infarction and stroke as combination of major cardiovascular events are better than coronary heart disease or stroke alone for quantifying the total benefit of blood pressure lowering therapies;

If applicable, we will also consider the following additional factors:

- In general, the longer the observation of the original cohort study is, the better the prediction model would be. We are thus only interested in studies that have a follow-up period 5 years or more;

- In general, the larger the sample size of the original study is, the better the prediction model would be. We thus prefer prediction equations that are based on a large number of people;

- The better the goodness of fit between the observed and predicted risk is, the better the equation would be. we will use the one that has good goodness of fit;

- The bigger the area under the receiver-operating characteristic curve of the equation is, the better the model will be. We thus prefer the ones that can give higher area under the curve;

- The more widely used the equation is, the more preferable it would be to us.

Four possible equations are identified and compared in Table 2-1. Except for the Framingham equation[52], all of them are derived from a Chinese or Asian population.

The risk prediction equations[51 52] derived from the Framingham Heart Study (FHS) have been widely adopted in current guidelines about CVD management, including the 2005 Chinese hypertension guidelines. The Framingham prediction functions have been adapted to other populations by a process called "recalibration", which involves substitution of the Framingham baseline survival and mean values (or prevalence) of the major CVD risk factors from the applied population.

Unfortunately, the currently published recalibrated Framingham equation for Chinese populations[59] can only predict coronary heart disease. Furthermore, a validation study in another Chinese population found the recalibrated equation significantly overestimated the risk of coronary heart disease in both men (by about 97%) and women (by about 228%)[55].

The equation[59] derived from the Chinese Multi-provincial Cohort Study (CMCS) can only predict "hard" CHD (myocardial infarction, sudden death and other coronary deaths) and it has never been validated in other Chinese cohorts.

The equation[55] derived from the USA-People's Republic of China Collaborative Study of Cardiovascular and Cardiopulmonary Epidemiology cohort (the USA-PRC Study) has been validated in another Chinese cohort. But the equation can only predict coronary heart disease and ischemic stroke (IS).

The fourth equation[60] is derived from Asian cohorts and validated in Chinese cohorts. It predicts major cardiovascular events including myocardial infarction and stroke. The baseline age range of the Asian equation is from 30 to 74, wider than that in the two Chinese equations. The size of the cohort is also larger than the cohorts on which the two Chinese equations are based. The validation analyses showed that the overestimation of the outcome risk (about 10%) is similar to that of the two Chinese equations. Its discrimination ability is also similar to the other two Chinese equations. Precisely, the area under the receiver-operating characteristic curve is 0.76 (95%CI 0.73~0.79) in men and 0.80 (95%CI 0.75~0.84) in women.

We finally chose the APCSC equation for my study. The major disadvantage is the cohort studies on which the equation is based were conducted many years ago during which the CVD risk was lower than the current days.

Table 2-1 Comparison of CVD risk prediction equations that can potentially be used for my analyses

Equation	Source Population	Outcomes predicted	Cohort size	Length of follow-up (years of baseline measurement!)	Validation	Variables used
The USA-PRC equation[55]	35~59 year old Chinese without CVD in Beijing and Guangzhou	CHD, ischemic stroke, or ICVD#	9,903	15.1 years on average (1983~1984)	Validated in 17,329 Chinese subjects	Continuous variable: age, SBP, BMI, TC; categorical variable: sex, current smoker, diabetes
The CMCS equation[59]	35~64 year old Chinese without CVD in 11 provinces of China	"Hard" CHD*	30,121	10 years (1992~2002)	Have not been validated in other Chinese populations	Continuous variable: age, age^2; Categorical variable: sex, BP, smoking, diabetes, TC, HDL-C
The APCSC equation[60]	30-75 year old Asian persons without CVD	Non-fatal and fatal CVD	172,077	8 years on average (1961~1997)	Validated in 25,682 Chinese subjects of APCSC cohorts	Continuous variable: age, SBP, TC; Categorical variable: sex, smoking
The FHS[52] recalibrated equation for Chinese people[59]	30-74 year old people of European origin without CVD	CHD	5,573	12 years (1968~1975)	Validated in 17,329 Chinese subjects[55]	Continuous variable: age, age^2; Categorical variable: sex, TC, HDL-C, BP, smoking, diabetes

* "Hard" CHD: include myocardial infarction, sudden death and other coronary death. # ICVD events (ischemic cardiovascular disease events): include ischemic stroke and coronary events. !Years of baseline measurement: the years when baseline of the cohort was measured.

2.3.1 The APCSC equation for Chinese population

On the basis of the Asian cohorts in the APCSC[60], the generic equation for the calculation of the probability of experiencing a cardiovascular event within, for example, 8 years for an Asian man is

$$P_{(8)men} = 1 - \mathrm{S}_{(8)men}^{\exp\{0\ 065(age_i - \overline{age}) + 0.027(SBP_i - \overline{SBP}) + 0.095(TC_i - \overline{TC}) + 0.33(Smoke_i - \overline{Smoke})\}}$$

and for an Asian woman is

$$P_{(8)women} = 1 - S_{(8)women}^{\exp\{0.072(age_i - \overline{age}) + 0.023(SBP_i - \overline{SBP}) + 0.027(TC_i - \overline{TC}) + 0.31(Smoke_i - \overline{Smoke})\}}$$

Here $\mathrm{age_i}$, SBP_i, TC_i, and $Smoke_i$ are the values of the risk factors in the person for whom the CVD risk is predicted, $\mathrm{S_{(8)}}$ is the 8-year average survival free from cardiovascular events, $\overline{\mathrm{age}}$, $\overline{\mathrm{SBP}}$ and $\overline{\mathrm{TC}}$ are the average values of age, SBP and total cholesterol, and $\overline{\mathrm{Smoke}}$ is the prevalence of current smoking of the population to which the individual whose risk is estimated belongs. Using this equation, a person's probability of experiencing a cardiovascular event within 8 years is derived by substituting the values of the person's risk factors in the equation.

In clinical guidelines, the 10-year CVD risk is commonly used. Therefore, the 10-year CVD risk can be estimated by substituting in the equation the 8-year survival with the 10-year survival.

Ideally, the baseline CVD-free survival and the mean values of risk factors should be derived from the population to which the individual whose risk is estimated belongs.

Thus, we used the pooled data from the Chinese cohorts in the APCSC study (see Table 2-2). The baseline CVD-free survival is approximated by the complement of the 10-year cumulative incidence rate of CVD. The cumulative incidence rate of CVD at 10 years is calculated by $\left(1-e^{-10ID}\right)$, where ID refers to the incidence density of CVD at 10 years and is provided in the APCSC study.

Table 2-2 The baseline CVD-free survival and the average values of risk factors from pooled Chinese cohorts in APCSC

	Men	**Women**
Age (years)	47	46
SBP (mmHg)	121	120
TC (mmol/l)	4.5	4.4
Smoking (%)	68.4%	6.5%
Incidence density of CVD (per 1000 person-years)	3.29	1.82
Baseline 10-year CVD-free survival	0.9676	0.9819

In summary, the APCSC equation used in my analyses for the calculation of the probability of experiencing a cardiovascular event within 10 years

For a Chinese man

$$P_{(10)men} = 1 - 0.9676^{\exp\{0.065(age_i - 47) + 0.027(SBP_i - 121) + 0.095(TC_i - 4\,5) + 0.33(Smoke_i - 0.684)\}}$$

For a Chinese woman

$$P_{(10)women} = 1 - 0.9819^{\exp\{0.072(age_i - 46) + 0.023(SBP_i - 120) + 0\,027(TC_i - 4.4) + 0.31(Smoke_i - 0.065)\}}$$

2.3.2 Adjustment in variables used in the CVD risk prediction equation

2.3.2.1 Blood pressure

In the CNNHS survey, 6.7 percent subjects were taking antihypertensive drugs in the past two weeks. Without correction, this would lead to underestimation of a person's usual blood pressure (ie, blood pressure in the absence of any drug intervention) and consequently underestimate the reduction in cardiovascular risk by antihypertensive drug treatment.

The reduction of blood pressure due to drug treatment is positively related to original blood pressure. It is reasonable to assume there is a linear relationship between the initial blood pressure and blood pressure after treatment. Based on a meta-analyses of blood pressure lowering trials [56], the weighted coefficient between SBP in the treatment group and that in the placebo control group is 1.06. In my analyses, blood pressure of those under anti-hypertensive drug treatment will be replaced by their blood pressure multiplied by 1.06. As there were no data on drug treatment of hyperlipidemia, no similar adjustment could be made for the cholesterol concentration.

2.3.2.2 Other variables

Whenever a cardiovascular risk factor in the survey is defined differently from that used in the cardiovascular risk prediction equations, the more stringent definition will be used in my analyses. For example, current smoking is defined in my analyses as ever smokers who smoked at least one cigarette a day in the last 30 days instead of those who ever have smoked.

2.4 Deriving the relative effectiveness of anti-hypertensive drugs

The relative effectiveness of anti-hypertensive drug treatment in people without previous cardiovascular disease has been estimated by a meta-analyses of randomized controlled trials comparing blood pressure lowering drugs with a placebo[56]. The relative risk reduction on major cardiovascular events is 0.27 (95% CI 0.22~0.31). The major cardiovascular events include stroke, myocardial infarction, heart failure, and death from any cardiovascular causes. This RRR is used to estimate the absolute effectiveness or risk difference in my study. Other meta-analyses of the matter showed very similar results.

2.5 Further comparisons of the two approaches

Our main objective is to investigate whether the overall risk approach could prevent more CVD events, and importantly by how many more, than the blood pressure approach given the same number of people treated at various practical cutoff values

in the CVD risk. By using the same comparison rationale and methods, I also made the following two comparisons.

First, how many more CVD events could be prevented in the same number of people treated if the current Chinese hypertension guidelines are shifted from a "half-hearted" overall risk approach to a complete overall risk approach? Currently the Chinese hypertension guidelines recommend drug treatment according to a person's blood pressure and an overall CVD risk that is approximated by counting the risk factors a person has. The risk approximation method is derived from the Framingham risk prediction model and tends to substantively over-estimate the risk in Chinese people.

Second, how many more CVD events could be prevented if the actual current practice is shifted to the overall risk approach? We used those who were currently receiving blood pressure lowering drug treatment to represent the current practice. The effectiveness of the current practice is estimated by using the RRR of anti-hypertensive drugs and the average risk of those who are currently under anti-hypertensive drug treatment. The benefit is compared with that estimated if the same number of people are identified from the total population and treated under the overall risk approach.

2.6 Statistical analyses

2.6.1 CVD risk prediction

The APCSC equation as described in page 40 is used in my study to estimate the 10-year CVD risk for all study participants and in all analyses.

2.6.2 Descriptive statistics

Frequency tables and histograms were used to display the distribution of the major cardiovascular risk factors and 10-year CVD risk. Prevalence rate of major cardiovascular risk factors were described by age, sex and region. For variables that fit approximately the normal distribution or distributed symmetrically, means are used to describe the average level. For variables that do not fit the normal distribution or distributed skewly, medians are used to describe the average level. For example, as the distribution of CVD risk is not normal, medians are used.

2.6.3 Univariate statistical analyses

The 95% confidence interval of the differences in the median of the CVD risk were calculated by the bias-corrected and accelerated (BCa) bootstrap method by using a software named 'Resampling Stats'[61]. Bootstrapping[62], also known as resampling or Monte Carlo estimation is a nonparametric method of statistical inference. It uses repeated samples from the same original data to compute the test statistic. The distribution of this statistic as computed for a very large number of runs of the resampling process is used to estimate the variance of the statistic (such as the

median) in the underlying population, thereby allowing the sampling error of the statistic to be estimated. The BCa bootstrap[63] adjusts for both bias and skewness in the bootstrap distribution. 1000 runs of resampling are used in estimating each of the 95% CI for the median in this thesis.

2.6.4 Sensitivity analyses

Sensitivity analyses were used to assess how robust the results were to uncertainties and assumptions about the data and the methods that were used.

1) Data were re-analyzed by using DBP to choose the subjects for drug treatment in the blood pressure approach or using the highest rank of DBP and SBP to choose the subjects for drug treatment in the blood pressure approach. Results show that SBP is the best index for the blood pressure approach.

2) Data were re-analyzed after varying the increment of change in SBP in those already receiving treatment from 0% to 10% and varying the relative benefit of treatment from 25% to 33%. None of these changes made a substantive effect on the relative increase in CVD events avoided by shifting from the ORA to BPA.

3) Data were re-analyzed using the Framingham risk prediction equation. There is a family of Framingham equations for predicting different outcomes. These are all highly correlated. Understandably, sensitivity analyses using different endpoints showed the same pattern for the relative difference but varying patterns for the additional CVD events avoided between the ORA and BPA.

Chapter 3 Description of the participants

3.1 Demographic characteristics

Included in the analyses are 38,673 participants out of 112,477 participants who were aged 30~74 years and without self-reported stroke in the 2002 China National Nutrition and Health Survey. These 33.5% residents of the surveyed participants were randomly selected for blood lipids and sugar measurements.

The demographic characteristics of the 38,673 participants included in my analyses are summarized in Table 3-1. The average age of participants is 48.1 years; 53.3% are women; 34.7% are urban residents.

There are slightly more old adults (60~74 year old) and more women in the study participants than in the whole Chinese population (according to the Chinese National Census in 2000). But the difference is not statistically significant ($P>0.05$) (see Table 3-2 and Table 3-3).

As is planned, approximately an equal number of study participants are sampled in each region stratum. As a result, the region distribution of the study participants is thus significantly different from the whole Chinese population ($P<0.05$) (see Table 3-4).

Table 3-1 Demographic characteristics of all 38,673 study participants

Characteristics	N	%
Age (years)		
30 ~ 34	5292	13.7
35 ~ 39	6118	15.8
40 ~ 44	4557	11.8
45 ~ 49	6048	15.6
50 ~ 54	5347	13.8
55 ~ 59	3863	10.0
60 ~ 64	3193	8.3
65 ~ 69	2627	6.8
70 ~ 74	1628	4.2
Gender		
Male	18062	46.7
Female	20611	53.3
Region*		
Large cities (most developed)	6902	17.8
Small or medium-sized cities	6514	16.8
1st class rural area	6518	16.9
2nd class rural area	6179	16.0
3rd class rural area	6662	17.2
4th class rural area (least developed)	5898	15.3

*Classified according to the economic development level.

Table 3-2 Comparison of the age distribution of all 38,673 study participants with that of the total population of China

Age groups	Population of China* (P_i) (%)	Study Participants (S_i) (%)	$(S_i - P_i)^2 / P_i$
30 - 34	20.7	13.7	2.38
35 - 39	17.7	15.8	0.21
40 - 44	13.2	11.8	0.15
45 - 49	13.9	15.6	0.22
50 - 54	10.3	13.8	1.21
55 - 59	7.5	10.0	0.79
60 - 64	6.8	8.3	0.32
65 - 69	5.7	6.8	0.23
70 - 74	4.2	4.2	0.00
Total	100.0	100.0	5.52

Chi square = 5.52, Degree of freedom = 8 , P>0.5

Notes: * Data from the Chinese National Census in 2000.

Table 3-3 Comparison of the gender distribution of all 38,673 study participants with that of the total population of China

Gender	Population of China* (P_i) (%)	Study Participants (S_i) (%)	$(S_i - P_i)^2 / P_i$
Male	51.5	46.7	0.45
Female	48.5	53.3	0.48
Total	100.0	100.0	0.93
Chi square = 0.93, Degree of freedom = 1 , P>0.25			

Notes: * Data from the Chinese National Census in 2000.

Table 3-4 Comparison of the region distribution of all 38,673 study participants with that of the population of China

Region	Population of China* (P_i) (%)	Study Participants (S_i) (%)	$(S_i - P_i)^2 / P_i$
Large city	8.8	17.8	9.33
Small or medium-sized cities	20.6	16.8	0.69
1st class rural area	15.0	16.9	0.24
2nd class rural area	37.1	16.0	12.00
3rd class rural area	7.7	17.2	11.87
4th class rural area	10.9	15.3	1.76
Total	100.0	100.0	35.89
Chi square = 35.89, Degree of freedom = 5 , P<0.005			

Notes: * Data from the Chinese National Census in 2000.

3.2 Overall distribution of cardiovascular risk factors

Table 3-5 shows the prevalence rate of main cardiovascular risk factors in all participants included in the analyses. Overall, 27.4% participants had hypertension; 22.7% had dislipidaemia; 4.0% had diabetes mellitus; 10.2% had obesity; and 28.9% were smokers. Except for smoking, the prevalence rate of hypertension, dislipidaemia and diabetes is highest in large cities and lowest in the least developed rural area. The prevalence rate of all the cardiovascular risk factors, except for smoking, is higher in elderly persons than in the young. The smoking rate in men (57.9%) was markedly higher than that in women (3.5%).

Table 3-5 Prevalence rate of cardiovascular risk factors* by region, gender, and age, in all 38,673 participants (to be continued)

Categories	No.	Hypertension (%)	Dislipidaemia (%)	Diabetes (%)	Obesity (%)	Smoking (%)
All	38673	27.4	22.7	4.0	10.2	28.9
Region						
Large cities (most developed)	6902	35.2	26.0	9.6	16.6	26.3
Small or medium-sized cities	6514	27.5	26.1	5.3	12.0	26.4
1st class rural area	6518	28.6	22.2	2.7	9.9	31.3
2nd class rural area	6179	25.4	17.9	2.2	7.6	28.5
3rd class rural area	6662	28.0	24.9	2.6	9.3	30.8
4th class rural area (least developed)	5898	18.1	18.4	1.0	4.8	30.3

Table 3-5 Prevalence rate of cardiovascular risk factors* by region, gender, and age, in all 38,673 participants (continued)

Categories	No.	Hypertension (%)	Dislipidaemia (%)	Diabetes (%)	Obesity (%)	Smoking (%)
Gender						
Male	18062	28.9	25.7	3.8	8.5	57.9
Female	20611	26.0	20.2	4.2	11.7	3.5
Age (years)						
30 - 34	5292	7.2	17.2	0.6	6.6	26.3
35 - 39	6118	12.4	20.1	1.4	8.1	28.8
40 - 44	4557	18.6	21.3	2.3	9.7	29.7
45 - 49	6048	25.0	22.8	3.2	10.1	30.7
50 - 54	5347	33.4	25.8	4.5	12.8	30.4
55 - 59	3863	39.1	25.4	6.7	11.4	29.9
60 - 64	3193	46.0	26.7	7.7	12.5	29.6
65 - 69	2627	52.8	26.2	9.6	13.0	26.8
70 - 74	1628	57.0	25.1	8.4	11.0	23.9

*Hypertension is defined as SBP≥140mmHg or DBP≥90mmHg or taking antihypertensive drugs in the past two weeks; Dislipidaemia is defined as TC≥5.7mmol/l or TG≥1.7mmol/l or HDLC≤0.9mmol/l; Diabetes is defined as FBG≥7.0mmol/l or OGTT≥11.1mmol/l or diagnosed by all county or above-county level hospital; Obesity is defined as BMI≥28; Smoking is defined as ever smokers who smoked at least 1 cigarette per day in the last 30 days.

3.3 Distribution of blood pressure

Table 3-6 and Table 3-7 present the percentage and cumulative percentage distribution of the participants by their diastolic and systolic blood pressure values. 7.8% of people had a SBP greater than 160 mmHg and 18.9% had a DBP greater than 90 mmHg. If the cut off values are moved down to 140 mmHg for SBP and 80 for DBP as suggested in recent guidelines, 20.7% and 48.5% respectively will be considered to have a blood pressure that is not optimal.

Figure 3-1 and Figure 3-2 show graphically the distribution of DBP and SBP of the participants. Both of them follow approximately a normal distribution.

Table 3-6 Frequency distribution of systolic blood pressure in all 38,673 participants

SBP (mmHg)	Antihypertensive drug treatment in the past 2weeks						Total		
	No (n=36099)			Yes (n=2574)			(n=38673)		
	No.	%	Cumulative %	No.	%	Cumulative %	No.	%	Cumulative %
≥180	477	1.3	1.3	507	19.7	19.7	984	2.5	2.5
170 ~ 179	439	1.2	2.5	263	10.2	29.9	702	1.8	4.4
160 ~ 169	890	2.5	5.0	423	16.4	46.3	1313	3.4	7.8
150 ~ 159	1362	3.8	8.8	418	16.2	62.6	1780	4.6	12.4
140 ~ 149	2771	7.7	16.5	436	16.9	79.5	3207	8.3	20.7
130 ~ 139	4474	12.4	28.8	296	11.5	91.0	4770	12.3	33.0
120 ~ 129	7972	22.1	50.9	155	6.0	97.0	8127	21.0	54.0
110 ~ 119	8809	24.4	75.3	58	2.3	99.3	8867	22.9	76.9
100 ~ 109	6232	17.3	92.6	16	0.6	99.9	6248	16.2	93.1
90 ~ 99	2310	6.4	99.0	2	0.1	100.0	2312	6.0	99.1
80 ~ 89	363	1.0	100.0	0	0.0	100.0	363	0.9	100.0

Table 3-7 Frequency distribution of diastolic blood pressure in all 38,673 study participants

DBP (mmHg)	Antihypertensive drug treatment in the past 2weeks						Total		
	No (n=36099)			Yes (n=2574)			(n=38673)		
	No.	%	Cumulative %	No.	%	Cumulative %	No.	%	Cumulative %
≥110	401	1.1	1.1	325	12.6	12.6	726	1.9	1.9
105 ~ 109	285	0.8	1.9	283	11.0	23.6	568	1.5	3.3
100 ~ 104	873	2.4	4.3	333	12.9	36.6	1206	3.1	6.5
95 ~ 99	1174	3.3	7.6	506	19.7	56.2	1680	4.3	10.8
90 ~ 94	2793	7.7	15.3	342	13.3	69.5	3135	8.1	18.9
85 ~ 89	3302	9.1	24.5	259	10.1	79.6	3561	9.2	28.1
80 ~ 84	7576	21.0	45.4	291	11.3	90.9	7867	20.3	48.5
75 ~ 79	6089	16.9	62.3	119	4.6	95.5	6208	16.1	64.5
70 ~ 74	6710	18.6	80.9	76	3.0	98.4	6786	17.5	82.1
65 ~ 69	3467	9.6	90.5	19	0.7	99.2	3486	9.0	91.1
60 ~ 64	2660	7.4	97.9	18	0.7	99.9	2678	6.9	98.0
<60	769	2.1	100.0	3	0.1	100.0	772	2.0	100.0

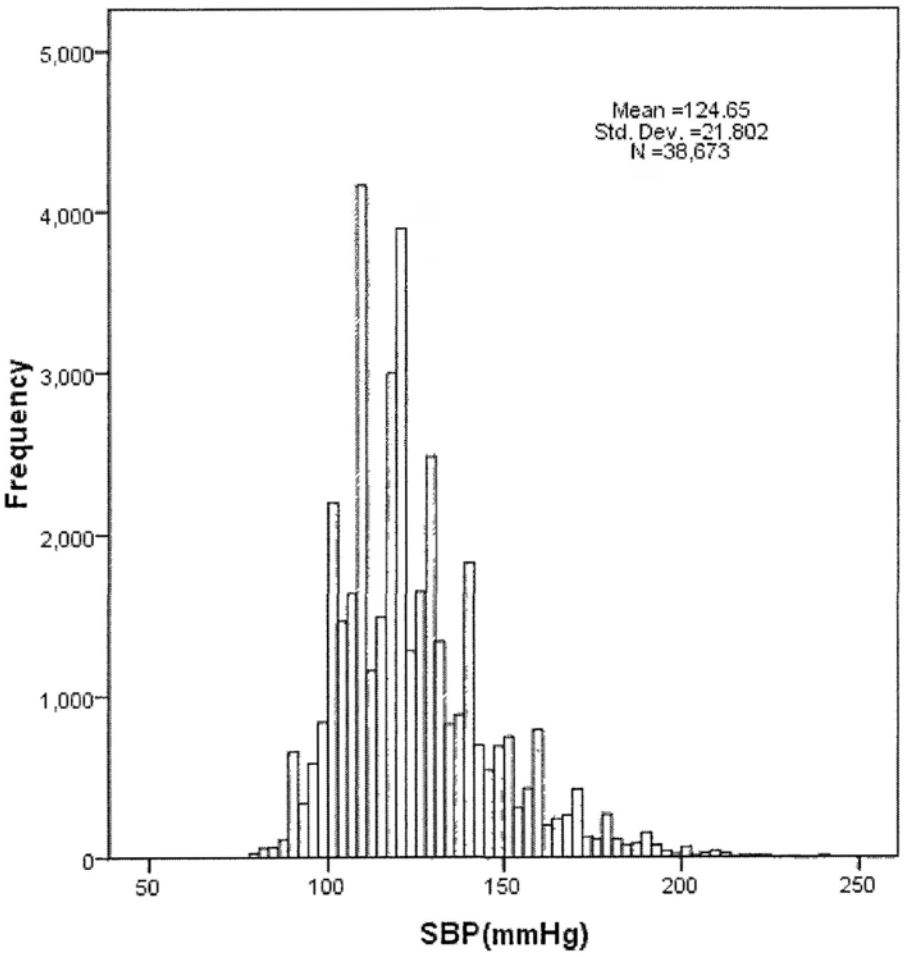

Figure 3-1 The frequency distribution of systolic blood pressure in all 38,673 study participants

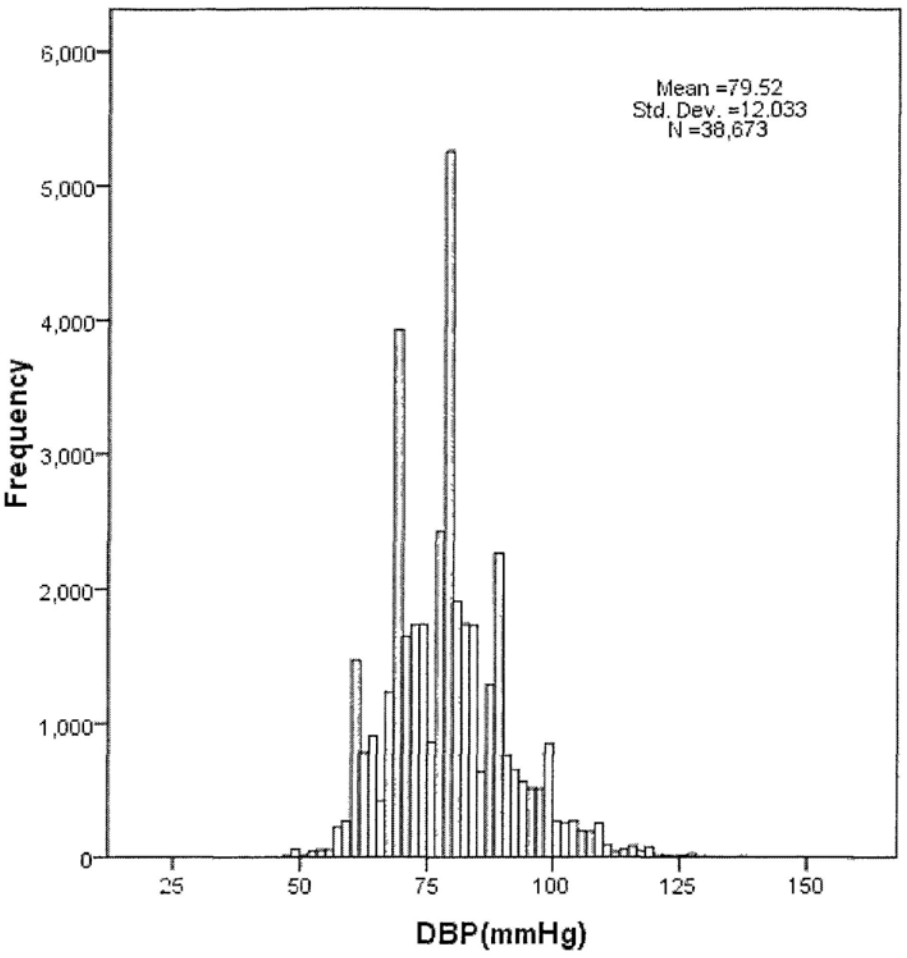

Figure 3-2 The frequency distribution of diastolic blood pressure in all 38,673 study participants

Table 3-8 provides the percentages of participants with hypertension who were aware that they had hypertension, of those who were being treated with antihypertensive drugs, and of those who had their BP controlled. Overall, 30.5% of those with hypertension were aware of the diagnosis, 24.3% were on drug treatment to lower their blood pressure, and 5.2% had blood pressure controlled.

Among those with hypertension, more women (34.1%) were aware of their hypertension than men (26.8%). The treatment and control rate was also higher in women than in men. The rate of awareness, treatment and control of hypertension is about twice as high in urban residents as that in rural residents. The rate of awareness, treatment and control of hypertension is also increased with age. Those with higher CVD risks had a higher rate of awareness and treatment of hypertension.

Most importantly, the awareness and treatment rate is higher in those with a higher CVD risk. However, the actual control rate decreases as the CVD risk increases, which is in a trend opposite to what the overall risk approach would aim to achieve. This pattern may be partly explained by the fact that those with a very high CVD risk have on average a high blood pressure which is more difficult to be reduced to a normal level.

Table 3-8 Percentage of persons with hypertension* who were aware of it, treated, and controlled, by region, gender and age

		No.	Aware (%)	Treated (%)	Controlled (%)#
Total		10580	30.5	24.3	5.2
Region					
	Urban	4219	41.6	34.8	8.7
	Rural	6361	23.1	17.4	2.9
Gender					
	Male	5215	26.8	20.5	4.5
	Female	5365	34.1	28.0	5.9
Age (years)					
	30 - 44	1988	16.1	10.9	3.2
	45 - 59	4807	30.7	24.1	5.0
	60 - 74	3785	37.8	31.6	6.6
10-year CVD events risk					
	≥30%	870	51.7	45.2	0.0
	20~29%	1128	40.9	33.0	1.9
	15~19%	1070	38.5	31.3	4.4
	<15%	7512	25.3	19.6	6.4

*Hypertension is defined as SBP≥140mmHg or DBP≥90mmHg or taking antihypertensive drugs in the past two weeks.

This is the proportion of hypertensives under drug treatment and with SBP <140 mm Hg and DBP <90 mm Hg.

3.4 Distribution of blood lipids

Table 3-9~Table 3-12 present the frequency distribution of TC, HDL-C, TC:HDL-C ratio and TG. Due to lack of data on the usage of cholesterol lowering drugs, results in these tables are not corrected for the effect of cholesterol lowering drug treatment.

Figure 3-3 ~ Figure 3-6 show graphically the distribution of TC, HDL-C, TC:HDL-C ratio and TG. All of them follow approximately a normal distribution.

Table 3-9 Frequency distribution of total cholesterol in all 38,673 study participants

TC		No.	%	Cumulative %
mg/dl	mmol/l #			
≥280	≥7.28	143	0.4	0.4
270 - 279	7.02 - 7.27	66	0.2	0.5
260 - 269	6.76 - 7.01	87	0.2	0.8
250 - 259	6.50 - 6.75	175	0.5	1.2
240 - 249	6.24 - 6.49	246	0.6	1.9
230 - 239	5.98 - 6.23	393	1.0	2.9
220 - 229	5.72 - 5.97	639	1.7	4.5
210 - 219	5.46 - 5.71	850	2.2	6.7
200 - 209	5.20 - 5.45	1288	3.3	10.1
190 - 199	4.94 - 5.19	1815	4.7	14.7
180 - 189	4.68 - 4.93	2589	6.7	21.4
170 - 179	4.42 - 4.67	3194	8.3	29.7
160 - 169	4.16 - 4.41	4035	10.4	40.1
150 - 159	3.90 - 4.15	4598	11.9	52.0
140 - 149	3.64 - 3.89	4589	11.9	63.9
130 - 139	3.38 - 3.63	4384	11.3	75.2
120 - 129	3.12 - 3.37	3768	9.7	85.0
110 - 119	2.86 - 3.11	2677	6.9	91.9
100 - 109	2.60 - 2.85	1637	4.2	96.1
90 - 99	2.34 - 2.59	888	2.3	98.4
<90	<2.34	612	1.6	100.0

1 mmol/l = 1 mg/dl × 0.026

Table 3-10 Frequency distribution of high density lipoprotein cholesterol in all 38,673 study participants

HDL-C		No.	%	Cumulative %
mg/dl	mmol/l #			
≥80.0	≥2.08	697	1.8	1.8
75.0 - 79.9	1.95 - 2.07	590	1.5	3.3
70.0 - 74.9	1.82 - 1.94	1046	2.7	6.0
65.0 - 69.9	1.69 - 1.81	1804	4.7	10.7
60.0 - 64.9	1.56 - 1.68	3164	8.2	18.9
55.0 - 59.9	1.43 - 1.55	4614	11.9	30.8
50.0 - 54.9	1.30 - 1.42	6134	15.9	46.7
45.0 - 49.9	1.17 - 1.29	7125	18.4	65.1
42.5 - 44.9	1.11 - 1.16	3600	9.3	74.4
40.0 - 42.4	1.04 - 1.10	2721	7.0	81.4
37.5 - 39.9	0.98 - 1.03	2630	6.8	88.2
35.0 - 37.4	0.91 - 0.97	1719	4.4	92.7
32.5 - 34.9	0.85 - 0.90	1202	3.1	95.8
30.0 - 32.4	0.78 - 0.84	895	2.3	98.1
25.0 - 29.9	0.65 - 0.77	591	1.5	99.6
<25.0	<0.65	141	0.4	100.0

1 mmol/l = 1 mg/dl × 0.026

Table 3-11 Frequency distribution of TC:HDL-C ratio in all 38,673 study participants

TC:HDL-C ratio	No.	%	Cumulative %
≥ 8.0	38	0.1	0.1
7.0～7.9	48	0.1	0.2
6.0～6.9	206	0.5	0.8
5.0～5.9	951	2.5	3.2
4.0～4.9	4438	11.5	14.7
3.0～3.9	14471	37.4	52.1
2.0～2.9	17261	44.6	96.7
< 2.0	1260	3.3	100.0

Table 3-12 Frequency distribution of total glyceride in all 38,673 study participants

TG		No.	%	Cumulative %
mg/dl	mmol/l #			
≥200	≥2.26	2665	6.9	6.9
190 - 199	2.15 - 2.25	399	1.0	7.9
180 - 189	2.03 - 2.14	489	1.3	9.2
170 - 179	1.92 - 2.03	610	1.6	10.8
160 - 169	1.81 - 1.91	759	2.0	12.7
150 - 159	1.70 - 1.80	885	2.3	15.0
140 - 149	1.58 - 1.69	1181	3.1	18.1
130 - 139	1.47 - 1.57	1580	4.1	22.2
120 - 129	1.36 - 1.46	1798	4.6	26.8
90 - 119	1.02 - 1.35	8264	21.4	48.2
60 - 89	0.68 - 1.01	13156	34.0	82.2
30 - 59	0.34 - 0.67	6817	17.6	99.8
<30	<0.34	70	0.2	100.0

1 mmol/l ＝1 mg/dl × 0.0113

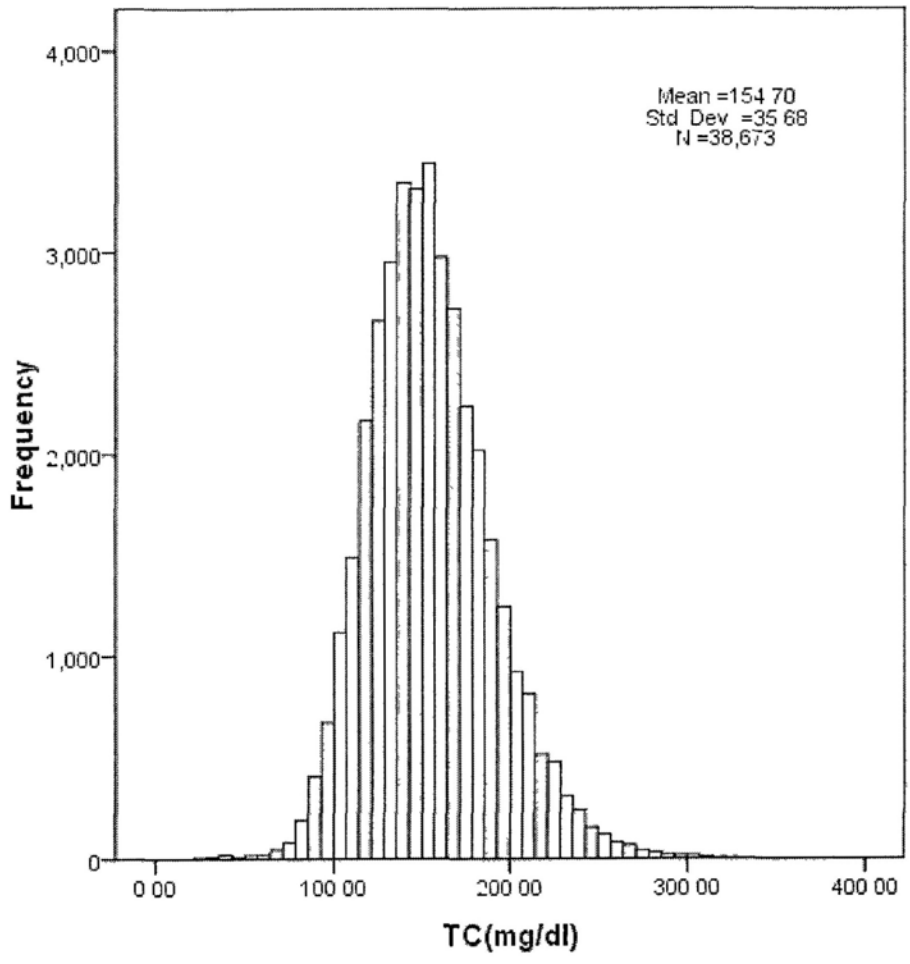

Figure 3-3 The frequency distribution of total cholesterol in all 38,673 study participants

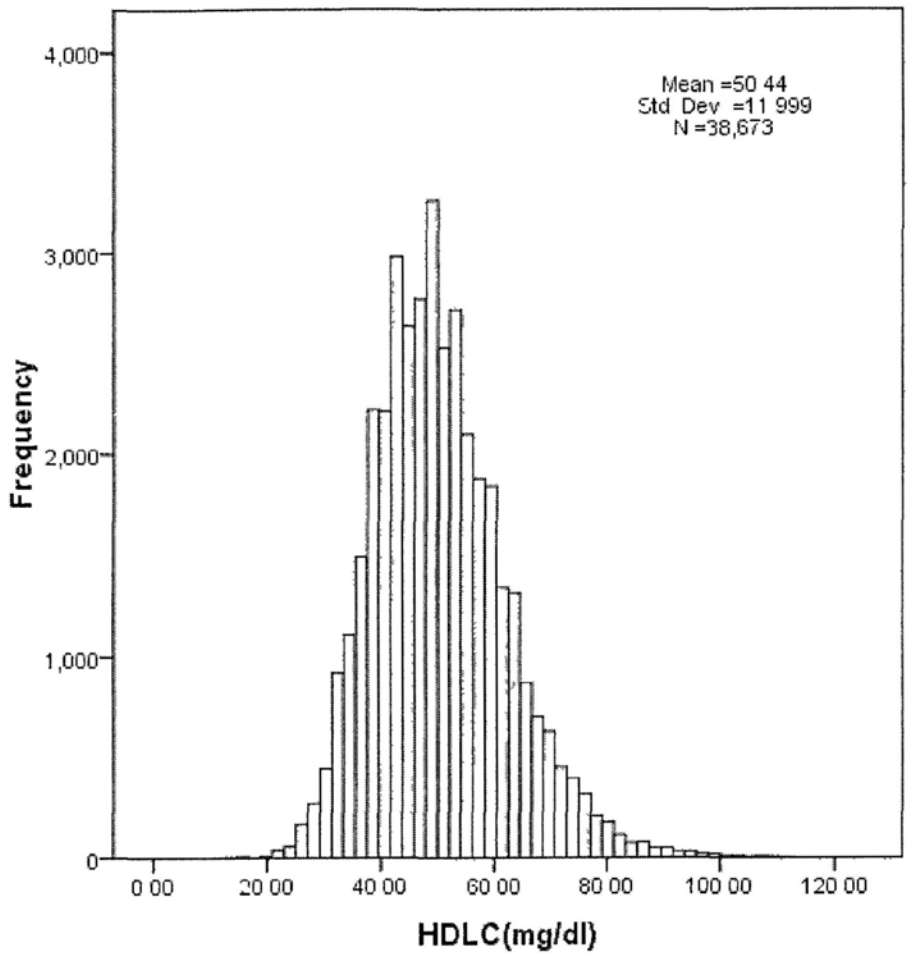

Figure 3-4 The frequency distribution of high density lipoprotein cholesterol in all 38,673 study participants

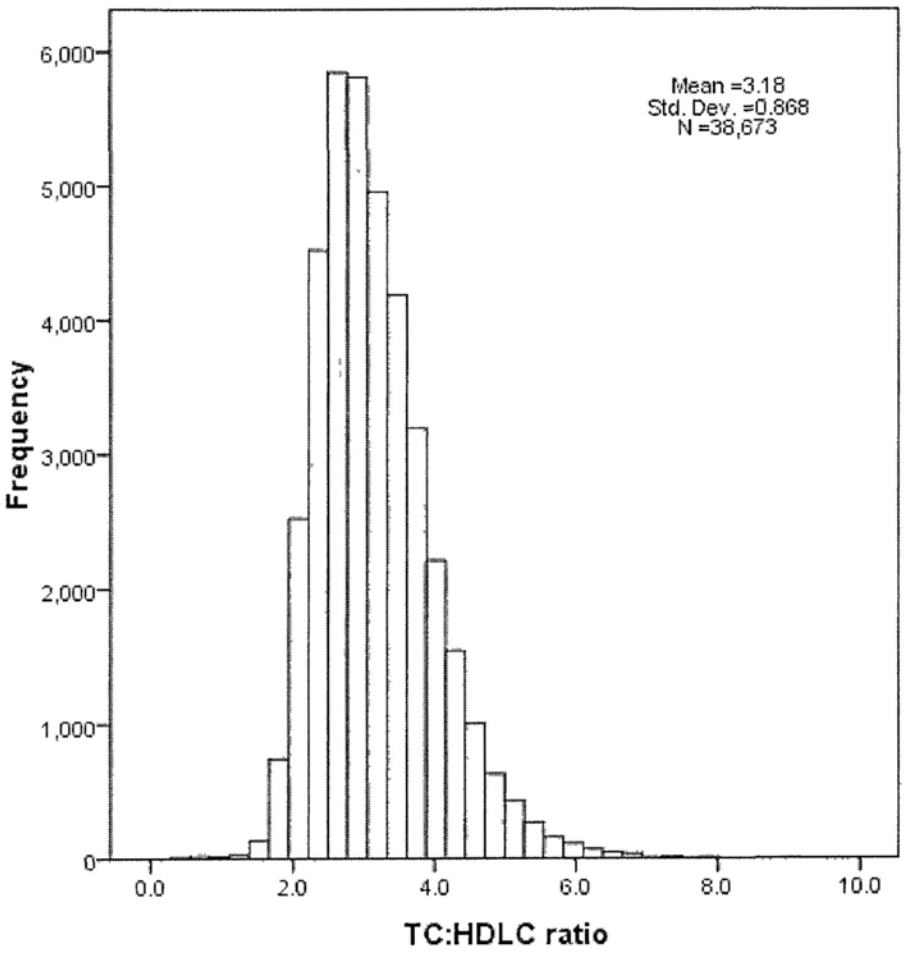

Figure 3-5 The frequency distribution of TC:HDL-C ratio in all 38,673 study participants

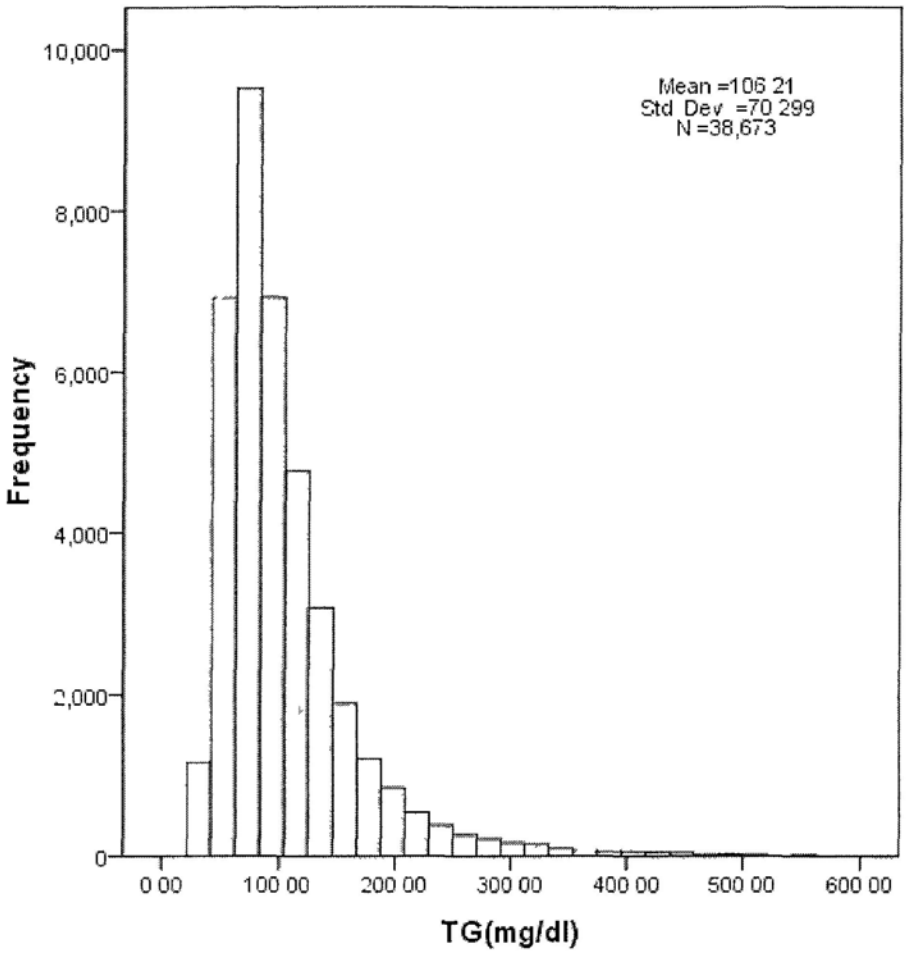

Figure 3-6 The frequency distribution of total glyceride in all 38,673 study participants

Table 3-13 summarizes the proportion of participants with increased TC, HDL-C and TG according to the criteria set by the prevention and treatment guidelines of dislipidaemia in China[64]. 4.3% of participants had increased total cholesterol; 15.0% had increased total glyceride; 7.9% had low high-density-lipoprotein. Totally, there are 22.7%(8792) participants had dislipidaemia.

Table 3-13 Prevalence rate of dislipidaemia* in all 38,673 study participants

	Blood Lipids	No.	%
TC			
Normal	<200mg/dl (5.20mmol/l)	34918	90.3
Marginally increased	201~219mg/dl (5.21~5.71mmol/l)	2082	5.4
Increased	⩾220mg/dl (5.72mmol/l)	1673	4.3
HDL-C			
Normal	⩾35mg/dl (0.91mmol/l)	35616	92.1
Low	<35mg/dl (0.91mmol/l)	3057	7.9
TG			
Normal	<150 (1.70mmol/l)	32866	85.0
Increased	⩾150mg/dl (1.70mmol/l)	5807	15.0
Total dislipidaemia	TC≥5.72mmol/l or TG≥1.70mmol/l or HDLC<0.91mmol/l	8792	22.7
TC:HDL-C ratio			
	⩾ 6.0	292	0.8
	5.0～5.9	951	2.5
	4.0～4.9	4438	11.5
	<4.0	32992	85.3

* Based on the most recent diagnosis criteria used in China.

3.5 Distribution of blood glucose

Table 3-14 presents the frequency distribution of fasting blood glucose and the cumulative percentage distribution. Due to lack of data on the usage of diabetes drugs, results in Table 3-14 are not corrected for the effect of blood glucose lowering drug treatment. Figure 3-7 show graphically the distribution of blood glucose of the participants. It is accorded approximately with normal distribution.

The proportion of participants diagnosed with diabetes mellitus was summarized in Table 3-15. Four percent of participants had diabetes mellitus; two percent had impaired fasting glucose.

Table 3-14 Frequency distribution of fasting blood glucose in all 38,673 study participants

FBG		No.	%	Cumulative %
mg/dl	mmol/l #			
≥150	≥8.3	772	2.0	2.0
145 - 149	8.0 - 8.2	68	0.2	2.2
140 - 144	7.8 - 7.9	71	0.2	2.4
135 - 139	7.5 - 7.7	104	0.3	2.6
130 - 134	7.2 - 7.4	132	0.3	3.0
125 - 129	6.9 - 7.1	175	0.5	3.4
120 - 124	6.7 - 6.8	232	0.6	4.0
115 - 119	6.4 - 6.6	305	0.8	4.8
110 - 114	6.1 - 6.3	437	1.1	5.9
100 - 109	5.6 - 6.0	1875	4.8	10.8
90 - 99	5.0 - 5.5	10636	27.5	38.3
80 - 89	4.4 - 4.9	14328	37.0	75.3
70 - 79	3.9 - 4.3	7529	19.5	94.8
60 - 69	3.3 - 3.8	1674	4.3	99.1
<60	<3.3	335	0.9	100.0

1 mmol/l = 1 mg/dl * 0.0555

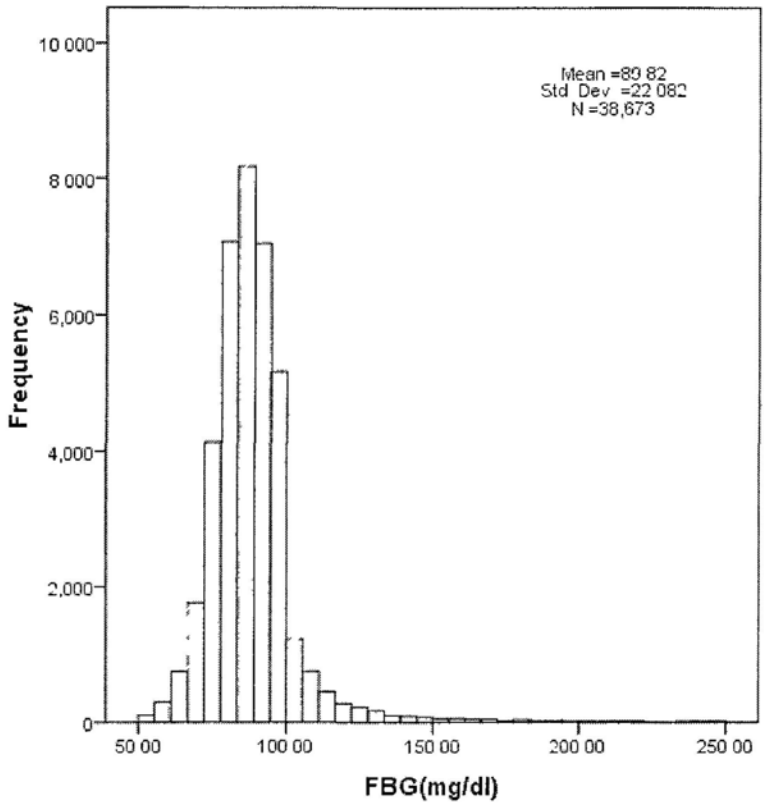

Figure 3-7 The frequency distribution of fasting blood glucose in all study participant

Table 3-15 Diabetes in the study participants

Categories	N	%
Diabetes mellitus	1553	4.0
Impaired fasting glucose	761	2.0
Normal	36359	94.0

* Based on the diagnosis criteria set by the World Health Organization in 1999. Diabetes mellitus is defined as FBG≥7.0mmol/l or OGTT≥11.1mmol/l or diagnosed in a county or better hospitals; Impaired fasting glucose is defined as fasting glucose level≥6.1mmol/l and <7.0mmol/l.

3.6 Distribution of the ten-year CVD risk

Table 3-16 presents the distribution of the 10-year CVD risk and the cumulative percentage distribution. The distribution of the predicted 10-year risk of cardiovascular events by region, gender and age is shown in Table 3-17. The 10-year overall CVD risk is 2.5%. On average, males, urban residents, and older groups had a higher risk than females, rural residents and younger people respectively. Age seems to be strongest determinant of the risk; in those ages 60-74 year the risk is 12.3 times that in those aged between 30-44 years, whereas the risk ratio is only 1.74 between men and women and 1.30 between urban and rural residents.

Figure 3-8 show graphically the distribution of 10-year CVD risk of the participants. The distribution of the original risk is highly skewed while the logarithmic value of 10-year CVD risk follows approximately a normal distribution, implying strongly the median rather than mean should be used in computing the average risk.

Table 3-16 Frequency distribution of the 10-year CVD risk in all 38,673 study participants, by region, sex and age

10-year CVD risk (%)	No.	%	Cumulative %
≥40	411	1.1	1.1
35～39	200	0.5	1.6
30～34	261	0.7	2.3
25～29	453	1.2	3.4
20～24	731	1.9	5.3
15～19	1306	3.4	8.7
10～14	2496	6.5	15.1
5～9	5770	14.9	30.1
<5	27045	69.9	100.0

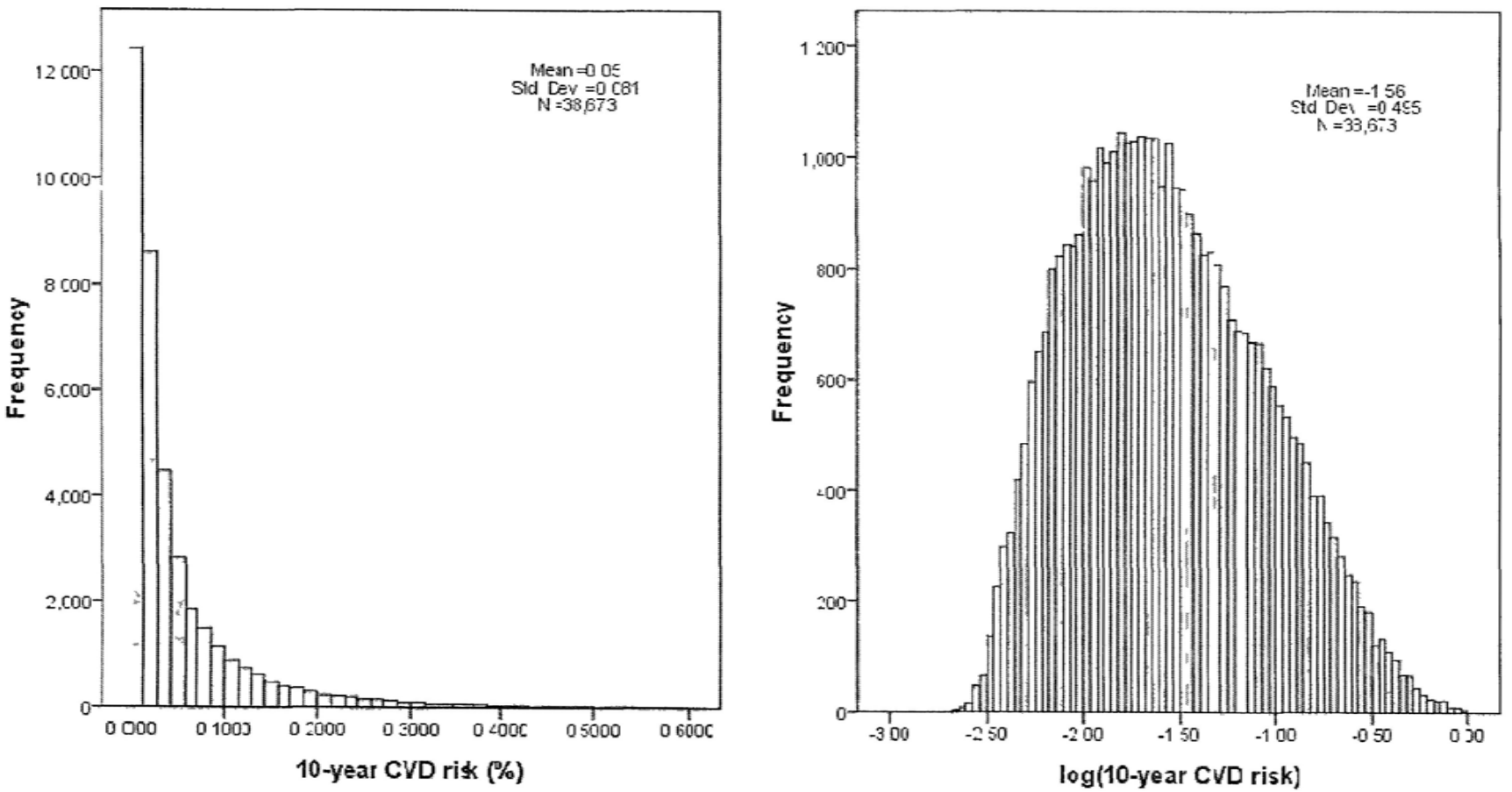

Figure 3-8 The frequency distribution of the ten-year CVD risk in all study participants

Overall, 5.3% of participants were at a high or extremely high CVD risk (⩾20%) which may require immediate drug therapy according to the 2005 Chinese hypertension guideline. 3.4% of participants are at an intermediate risk (between 15% and 20%) which can be observed for several weeks before drug therapy. Urban residents and men had a higher median risk and a higher proportion of people with a high or extremely high CVD risk than rural residents and women respectively. The median predicted CVD risk is increased markedly with age. 99.9% of individuals aged 30 to 44 had a predicted CVD risk below 15%. In middle aged adults (45~59 years), 1.5% had a high or extremely high CVD risk and 1.7% had intermediate CVD. In the elderly (60~74 years), 24.3% had a high or extremely high CVD risk and 14.0% had an intermediate CVD risk.

Table 3-17 Number and percentage in brackets of people by risk groups, region and age, in all 38,673 study participants

	10-year CVD risk categories*				Median risk (%)
	<15%	15~19%	20~29%	≥30%	
Total	35311(91.3)	1306(3.4)	1184(3.1)	872(2.3)	2.5
Region					
Urban	11898(88.7)	585(4.4)	571(4.3)	362(2.7)	3.0
Rural	23413(92.7)	721(2.9)	613(2.4)	510(2.0)	2.3
Gender					
Male	16008(88.6)	754(4.2)	713(3.9)	587(3.2)	3.3
Female	19303(93.7)	552(2.7)	471(2.3)	285(1.4)	1.9
Age (years)					
30 - 44	15954(99.9)	5(0.0)	7(0.0)	1(0.0)	1.0
45 - 59	14763(96.8)	262(1.7)	169(1.1)	64(0.4)	3.4
60 - 74	4594(61.7)	1039(14.0)	1008(13.5)	807(10.8)	12.3

* Based on the classification adopted by the Chinese guideline of prevention and control for hypertension.

Table 3-18 showed the distribution of the 10-year CVD risk by blood pressure categories. In those with extremely high blood pressure (higher than 180/110 mmHg), 34.4%(470) of them had a 10-year CVD risk lower than 15%. In those with marginally raised blood pressure (from 130/85 mmHg to 139/89 mmHg), 4.8%(241) of them had a 10-year CVD risk higher than 15%. In those with normal blood pressure (from 110/75 mmHg to 119/79 mmHg), 0.1%(7) of them had a 10-year CVD risk higher than 15%. These show that on the one hand a large percentage of people with a high blood pressure do not have a high CVD risk, and on the other

hand many with a normal blood pressure actually have high level of CVD risk. As the percentage of people with a normal blood pressure in the whole adult population is large, those with normal blood pressure but a high CVD risk are not small number.

Table 3-19 showed the distribution of blood pressure by CVD risk categories. In those with a 10-year CVD risk higher than 20%, all of them had blood pressure higher than 120/80 mmHg. In those with a 10-year CVD risk from 15% to 19%, 19.3%(252) of them had a high normal blood pressure (i.e., from 120/80 mmHg to 139/89 mmHg), and 0.5%(4) of them had a normal blood pressure (i.e., from 110/75 mmHg to 119/79 mmHg). So, it is true that some of the people with a high CVD risk may have a normal or high normal blood pressure. But the number of such people is small. In those with a 10-year CVD risk from 10% to 14%, 59.3%(1480) of them had a high blood pressure (i.e., higher than 140/90 mmHg). In those with a 10-year CVD risk from 5% to 9%, 43.4%(2504) of them had high blood pressure. In those with a 10-year CVD risk lower than 5%, 11.9%(3218) of them had a high blood pressure. So, a large percentage of people with a CVD risk lower than 15% actually had high blood pressure (i.e., higher than 140/90 mmHg).

Table 3-18 The 10-year CVD risk by blood pressure categories in all 38,673 participants

Blood pressure (mmHg)	No.	%	Mean 10-year CVD risk			% according to 10-year CVD risk groups								
			Min	Max	Median	≥40%	35%~39%	30%~34%	25%~29%	20%~24%	15%~19%	10%~14%	5%~9%	<5%
≥180/110	1365	3.5	1.3%	100.0%	22.5%	23.6	7.0	6.2	8.3	10.0	10.5	13.5	15.6	5.3
170/105~179/109	921	2.4	1.0%	57.6%	14.6%	6.3	4.0	5.9	8.8	9.3	14.4	15.9	21.8	13.6
160/100~169/104	1757	4.5	0.8%	53.6%	10.2%	1.3	2.7	3.6	7.5	8.5	11.4	15.5	26.5	23.0
150/95~159/99	2208	5.7	0.6%	45.6%	8.1%	0.4	0.8	1.9	3.8	8.5	11.9	15.6	25.9	31.2
140/90~149/94	3988	10.3	0.4%	35.2%	5.2%	0	0.0	0.4	0.9	2.8	7.7	13.4	26.3	48.4
130/85~139/89	5017	13.0	0.4%	31.0%	3.6%	0	0	0.0	0.1	1.0	3.7	10.0	22.4	62.7
120/80~129/84	8886	23.0	0.3%	24.9%	2.2%	0	0	0	0	0.1	0.7	4.5	14.0	80.7
110/75~119/79	7411	19.2	0.3%	16.5%	1.5%	0	0	0	0	0	0.1	1.4	8.9	89.6
<110/75	7120	18.4	0.2%	14.1%	0.9%	0	0-	0	0	0	0	0.2	3.3	96.5

Table 3-19 Blood pressure by cardiovascular risk groups in all 38,673 participants

10-year CVD risk	No.	%	Mean SBP	Mean DBP	% according to blood pressure groups								
					⩾180/110	170/105~ 179/109	160/100~ 169/104	150/95~ 159/99	140/90~ 149/94	130/85~ 139/89	120/80~ 129/84	110/75~ 119/79	<110/75
⩾40%	411	1.1	195	101	78.3	14.1	5.6	1.9	0	0	0	0	0
35%~39%	200	0.5	180	97	48.0	18.5	24.0	9.0	0.5	0	0	0	0
30%~34%	261	0.7	172	94	32.6	20.7	24.1	16.1	5.7	0.8	0	0	0
25%~29%	453	1.2	168	93	24.9	17.9	28.9	18.8	8.2	1.3	0	0	0
20%~24%	731	1.9	161	91	18.6	11.8	20.5	25.7	15.5	6.8	1.1	0	0
15%~19%	1306	3.4	153	89	10.9	10.2	15.3	20.1	23.7	14.4	4.9	0.5	0
10%~14%	2496	6.5	143	86	7.4	5.8	10.9	13.8	21.4	20.0	15.9	4.2	0.5
5%~9%	5770	14.9	134	84	3.7	3.5	8.1	9.9	18.2	19.5	21.6	11.5	4.1
<5%	27045	69.9	116	76	0.3	0.5	1.5	2.5	7.1	11.6	26.5	24.5	25.4

Chapter 4 Comparing the effectiveness of the two prevention approaches

4.1 General comparison of the blood pressure approach with the overall risk approach

Table 4-1 summarizes (1) the percentage of the population selected for antihypertensive drug therapy and the corresponding threshold of the 10-year CVD risk and systolic blood pressure if those with the highest CVD risk or BP are selected; (2) the estimated 10-year CVD risk reduction in the groups selected for antihypertensive drug therapy by the two approaches respectively; (3) the additional benefits (cardiovascular events avoided per 1000 people treated) of the overall risk approach compared with the BP approach.

From Table 4-1, we can see that, given the same number of people treated, the risk reduction of overall risk approach is always larger than that of the blood pressure approach. But the smaller the percentage of the population is treated, the greater the risk reduction by the intervention will be. As a result, the additional absolute benefits (i.e., cardiovascular events avoided per 1000 people treated) of the overall risk approach compared with the blood pressure approach increases as the percentage of the population treated decreases. There is in general a 15% to 25% increase in the number of CVD event avoided if shifting the BPA to the ORA.

The relation of the percentage of the population treated to the additional benefits from shifting from the BP approach to the overall risk approach is graphically shown in Figure 4-1.

As the absolute risk reduction of antihypertensive drugs is on average 20~30 in 1000 average hypertensive patients treated, the increase of 13 CVD events as a result of the shift in the approach is 43%~65% of the original effectiveness of the drugs if 5.5% of the total adult population are put under drug treatment. This is a gain that should not be neglected.

Table 4-1 Comparison of the absolute benefits of antihypertensive drug therapy by the blood pressure approach and that by the overall risk approach for various percentages of people treated, in 38,673 Chinese men and women aged 30~74 without previous stoke

(to be continued)

Percentage selected for drug therapy		Cutoff point		Median 10-year CVD risk		Absolute reduction in 10-year CVD risk		Additional CVD events avoided per 1000 people treated	Relative increase in CVD events avoided
Cumulative		10-year CVD risk in ORA[#]	SBP in BPA[*]	ORA	BPA	ORA	BPA		
%	No.			(1)	(2)	(1)×0.27	(2)×0.27	[(1) - (2)]×1000	[(1)-(2)]/(2)
1	394	≥40.5%	≥192 mmHg	49.5%	39.4%	13.4%	10.6%	27 (95%CI: 21~34)	25.8% (95%CI: 19.3%~31.5%)
1.6	621	≥34.7%	≥188 mmHg	43.4%	34.9%	11.7%	9.4%	23 (95%CI: 17~29)	24.3% (95%CI: 18.4%~30.8%)
2.5	984	≥28.4%	≥180 mmHg	37.6%	29.2%	10.1%	7.9%	22 (95%CI: 17~28)	28.5% (95%CI: 21.9%~35.2%)
3.5	1347	≥24.9%	≥173 mmHg	33.4%	26.5%	9.0%	7.1%	19 (95%CI: 15~22)	26.2% (95%CI: 21.7%~30.6%)
5.5	2131	≥19.6%	≥166 mmHg	27.4%	22.5%	7.4%	6.1%	13 (95%CI: 11~16)	21.7% (95%CI: 18.2%~25.9%)
8.8	3406	≥14.8%	≥158 mmHg	22.2%	18.3%	6.0%	4.9%	11 (95%CI: 9~12)	21.4% (95%CI: 17.8%~25.0%)
10.1	3896	≥13.6%	≥154 mmHg	20.6%	17.3%	5.6%	4.7%	9 (95%CI: 8~10)	19.1% (95%CI: 16.2%~21.9%)
15.5	6008	≥9.8%	≥145 mmHg	16.2%	13.6%	4.4%	3.7%	7 (95%CI: 6~8)	19.4% (95%CI: 16.2%~22.7%)
20.7	7986	≥7.6%	≥140 mmHg	13.4%	11.2%	3.6%	3.0%	6 (95%CI: 5~7)	19.6% (95%CI: 16.7%~21.8%)

Table 4-1 Comparison of the absolute benefits of antihypertensive drug therapy by the blood pressure approach and that by the overall risk approach for various percentages of people treated, in 38,673 Chinese men and women aged 30~74 without previous stoke (continued)

Percentage selected for drug therapy		Cutoff point		Median 10-year CVD risk		Absolute reduction in 10-year CVD risk		Additional CVD events avoided per 1000 people treated	Relative increase in CVD events avoided
Cumulative		10-year CVD risk in ORA#	SBP in BPA*	ORA	BPA	ORA	BPA		
%	No.			(1)	(2)	(1)×0..27	(2)×0.27	[(1) - (2)]×1000	[(1)-(2)]/(2)
25.7	9938	≥6.0%	≥135 mmHg	11.4%	9.6%	3.1%	2.6%	5 (95%CI: 4~6)	19.2% (95%CI: 16.7%~21.6%)
33	12756	≥4.5%	≥130 mmHg	9.3%	7.9%	2.5%	2.1%	4 (95%CI: 3~4)	17.6% (95%CI: 15.7%~19.6%)
36.4	14059	≥3.9%	≥128 mmHg	8.5%	7.3%	2.3%	2.0%	3 (95%CI: 3~4)	17.0% (95%CI: 14.5%~19.3%)
40.6	15708	≥3.4%	≥125 mmHg	7.7%	6.6%	2.1%	1.8%	3 (95%CI: 3~3)	16.7% (95%CI: 14.2%~18.7%)
45.6	17620	≥2.9%	≥122 mmHg	6.9%	5.8%	1.9%	1.6%	3 (95%CI: 2~3)	17.6% (95%CI: 15.2%~19.4%)
54	20883	≥2.2%	≥120 mmHg	5.7%	4.9%	1.5%	1.3%	2 (95%CI: 2~2)	14.3% (95%CI: 12.1%~15.8%)
100	38673	≥0.2%	≥ 80 mmHg	2.5%	2.5%	0.7%	0.7%	0	0

ORA: overall risk approach; * BPA:blood pressure approach. Notes: The risk prediction equation used in Table 1 was based on Asian cohorts aged 30~74 years without stroke. Factors in the risk prediction equation include gender, age, systolic blood pressure (adjusted for drug treatment), total cholesterol, and smoking status. Relative risk reduction of antihypertensive drug therapy is estimated to be 27% in meta-analyses. The estimated risk reduction equals the average ten year cardiovascular risk multiplied by relative risk reduction.

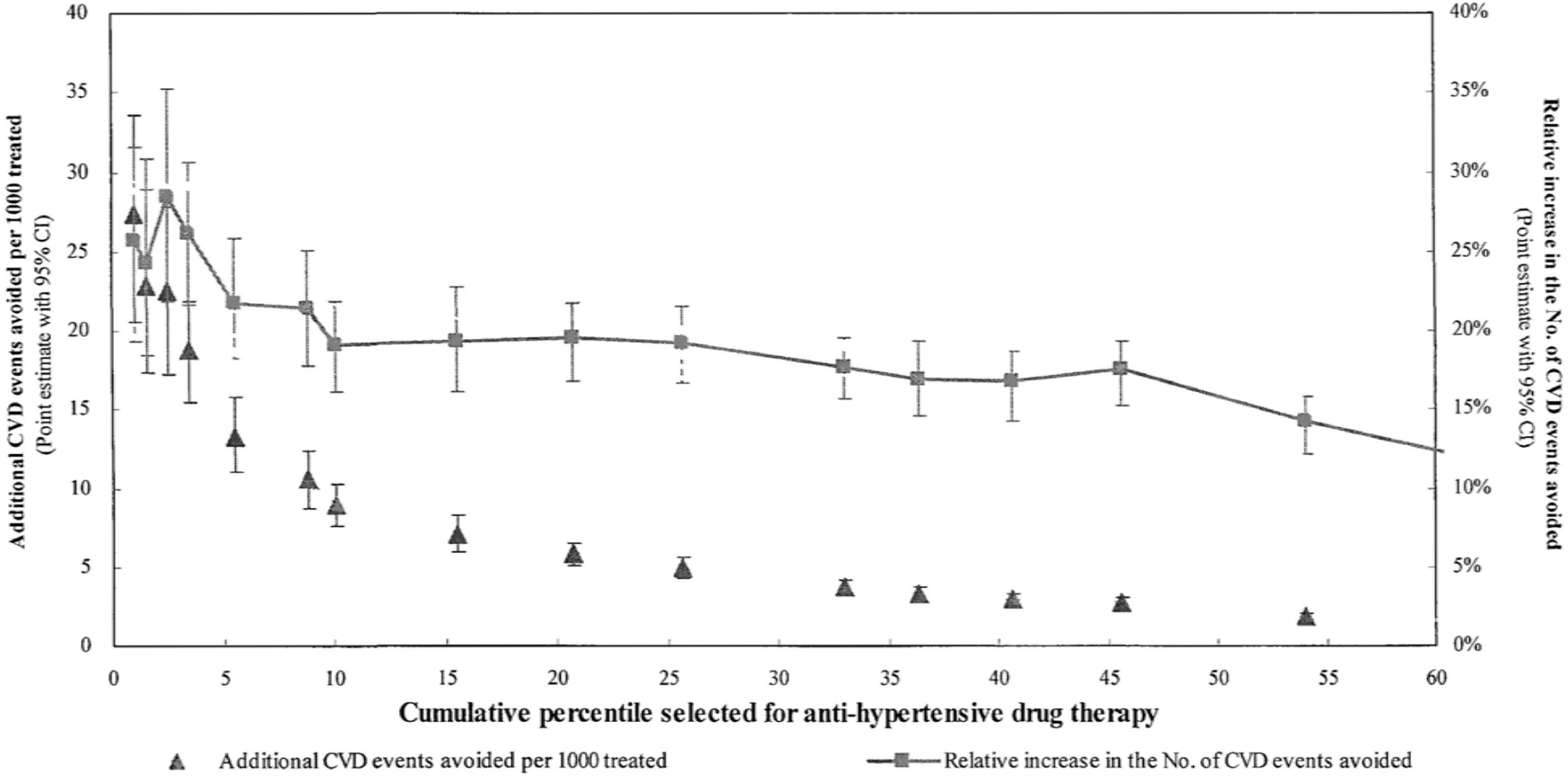

Figure 4-1 The additional CVD events prevented by shifting the BPA approach to the ORA decreases as the percentage of the population treated with drugs increases

4.2 Comparing the Chinese hypertension guideline with the overall risk approach

In this section, the effectiveness of antihypertensive drug therapy by the approach adopted in the Chinese hypertension guideline will be compared with that by the overall risk approach when the same number of people was treated by antihypertensive drugs.

4.2.1 The approach adopted in the Chinese hypertension guideline

The guideline for prevention and treatment of hypertension in China was updated in 2005[58]. The Chinese hypertension guideline recommended a drug therapy strategy based on approximate cardiovascular risk classifications defined by blood pressure and other cardiovascular risk factors, target organ damage, and associated clinical conditions. This is neither a completely blood pressure approach nor a completely overall risk approach, but a halfway approach between the two.

Factors used to evaluate patient's prognosis in CVD events were summarized in Table 4-2. Data on target organ damages, associated clinical conditions (except for stroke), family history of early onset CVD, physical activity, and C-reactive protein are not available in my dataset. These variables are seldom measured and recorded in general populations. Therefore, in my analyses, I used age, sex, smoking status, dislipidaemia, obesity and diabetes mellitus to predict the CVD risk, assuming the other factors are absent.

Table 4-2 Factors used to evaluate patient's prognosis in the 2005 Chinese hypertension guideline

Risk factors of cardiovascular diseases	Target organ damage	Diabetes	Associated clinical conditions
♦ Hypertension level 1~3	♦ Left ventricular hypertrophy	FBG≥0mmol/L (126mg/dL), or OGTT≥ 11.1mmol/L (200mg/dL)	♦ Cerebrovascular diseases
♦ Age	ECG, Ultrasound cardiograph(LVMI), or X-ray		Ischemic stroke, hemorrhagic stroke, transient ischemic attack
>55 in male or >65 in female	♦ Thickened arteries		♦ Cardiovascular diseases
♦ Smoking	Neck artery IMT by ultrasound ≥0.9mm, or atherosclerosis plaques symptoms by ultrasound		History of myocardial infarction, angina pectoris, coronary revascularization, congestive heart failure
♦ Dislipidaemia	♦ Mild serum creatinine elevation		♦ Nephropathy
TC≥5.7mmol/L(220mg/dL) or LDL-C>3.6mmol/L(140mg/dL) or HDL-C<1.0mmol/L(40mg/dL)	Serum creatinine 115~133μmol/L(1.3~1.5mg/dL) in males or 107~124μmol/L(1.2~1.4mg/dL) in females		Diabetic nephropathy, impaired kidney function [serum creatinine >133 μmol/L(1.5mg/dL) in male or >124μmol/L(1.4mg/dL) in female], proteinuria (albumin in urine >300mg/24h)
♦ Family history of early onset of CVD	♦ Microalbuminuria		♦ Peripheral vascular diseases
CVD onset age<50 in first level relatives	Albumin in urine 30~300mg/24h, Alb/Cr≥22mg/g(2.5mg/mmol) in males or Alb/Cr ≥31mg/g(3.5mg/mmol) in females		♦ Retinopathy
♦ Obesity			Hemorrhage or exudation, optic disc edema
Abdominal visceral obesity: waist circumstances ≥85cm in male or waist circumstances ≥80cm in female Obesity: BMI≥28kg/m2			
♦ Lack of physical activity			
♦ High-sensitivity C-reactive protein≥ 3mg/L or C-reactive protein≥10mg/L			

The cardiovascular risk classifications adopted in the 2005 Chinese hypertension guideline are showed in Table 4-3. The treatment recommendations based on these classifications are summarized in Table 4-4.

Table 4-3 CVD risk classifications adopted in the 2005 Chinese hypertension guideline

Other risk factors	Hypertension		
	Level 1 140~159/90~99 mmHg	Level 2 160~179/100~109 mmHg	Level 3 ≥180/110 mmHg
Having no other risk factors	Low risk	Middle risk	High risk
Having 1-2 other risk factors	Middle risk	Middle risk	Extremely high risk
Having 3 or more other risk factors, target organ damage or diabetes	High risk	High risk	Extremely high risk
Having associated clinical conditions	Extremely high risk	Extremely high risk	Extremely high risk

Table 4-4 Treatment recommendations according to the CVD risk classifications in the Chinese hypertension guideline in 2005

Risk Level	Approximate 10-year CVD risk range*	Treatment recommendation
Low risk	<15%	Monitor patients' blood pressure for a sufficient long period of time before making decisions on drug treatment.
Medium risk	15~19%	Monitor the blood pressure and other risk factors for several weeks before making decisions on drug treatment.
High risk	20~29%	Immediately start antihypertensive drug treatment and treatment on other risk factors and associated clinical condition.
Extremely high risk	≥30%	

* The approximate 10-year CVD risk range is provided in the 2005 Chinese hypertension guideline, which is claimed to be estimated based on the Framingham CVD risk prediction equation.

As shown in Table 4-5, 3% (1157) of all participants are at an extremely high risk of CVD, 3.5% (1353) at a high risk, 16.1% (6219) at a medium risk, and 3.9% (1510) at a low risk. Totally, 6.5% (2510) of participants would require immediately drug treatment according to the Chinese guideline. If hypertensive people with a low and medium CVD risk are also put under drug treatment after a certain period of observation, the number of people need to be treated will increase to 26.5% (10239) of the total Chinese population aged 30~74.

The 10-year CVD risk of patients with an extremely high risk should be above 30% according to the Chinese guideline, which is based on the Framingham equation. However, the average risk estimated by the equation developed from Asian cohorts is only 26.0%. The CVD risks estimated by the Asian equation are also lower in other Chinese guideline risk groups than those claimed by the guideline.

The average CVD risk reduction by drug therapy in people with an extremely high risk is 7.0%. It means that 14 patients need to be treated in order to avoid 1 CVD event in next 10 years.

Table 4-5 10-year CVD risk and average risk reduction by antihypertensive drug therapy in 38,673 subjects, according to the CVD risk classification in the 2005 Chinese hypertension guideline

CVD risk levels	Risk claimed in the Chinese guideline	N	%	Risk predicted by the Framingham equation			Risk predicted by the APCSC equation			Absolute risk reduction by drug therapy (B=A×0.27)	NNT
				Min	Max	Median	Min	Max	Median (A)		
Very Low risk*	Not indicated	28434	73.5	0.00%	54.60%	2.90%	0.20%	31.00%	1.70%	0.50%	214
Low risk	<15%	1510	3.9	0.10%	22.00%	4.30%	0.40%	11.40%	3.00%	0.80%	125
Medium risk	15~19%	6219	16.1	0.10%	56.80%	13.70%	0.60%	57.60%	8.70%	2.40%	42
High risk	20~29%	1353	3.5	0.90%	63.50%	25.70%	0.50%	64.20%	12.40%	3.30%	30
Extremely high risk	≥30%	1157	3	1.30%	75.20%	26.70%	1.30%	100.00%	26.00%	7.00%	14
Total		38673	100	0.00%	75.20%	4.60%	0.20%	100.00%	2.50%	0.70%	150

*People with blood pressure lower than 140/90mmHg are classified as very low CVD risk, and no drug treatment is recommended for them in the Chinese hypertension guideline.

The range of the estimated CVD risk for different risk groups overlap tremendously. More detailed description of the 10-year CVD risk and absolute risk reduction in the 12 groups defined by blood pressure and other CVD risk factors in the 2005 Chinese guideline are summarized in Table 4-6. The estimated CVD risk overlaps in all the 12 groups. Importantly, the median CVD risk in some high risk groups is lower than that in some medium risk groups (14.0%) and is lower in some extremely high risk groups than that in the high risk groups.

Table 4-6 Predicted 10-year CVD risk and absolute risk reduction by antihypertensive drug therapy in 38,673 subjects, according to the 12 risk groups used in the 2005 Chinese hypertension guideline

	Blood pressure			
	Normal <140/90 mmHg	Level 1 140/90~159/99 mmHg	Level 2 160/100~179/109 mmHg	Level 3 ≥180/110 mmHg
Number of participants (%)				
No other risk factors	12738(32.9)	1510(3.9)	488(1.3)	208(0.5)
1-2 risk factors	14339(37.1)	3961(10.2)	1770(4.6)	915(2.4)
3 or more risk factors or diabetes	1357(3.5)	725(1.9)	420(1.1)	242(0.6)
Range of predicted 10-year CVD risk				
No other risk factors	0.2%~7.6%	0.4%~11.4%	1.0%~17.6%	1.3%~64.2%
1-2 risk factors	0.2%~27.4%	0.6%~45.5%	0.8%~57.6%	1.3%~99.9%
3 or more risk factors or diabetes	0.3%~31.0%	0.5%~45.6%	1.4%~56.4%	2.6%~99.5%
Average 10-year CVD risk (median)				
No other risk factors	1.1%	3.0%	5.2%	10.0%
1-2 risk factors	2.7%	7.9%	14.0%	24.1%
3 or more risk factors or diabetes	5.0%	11.2%	16.9%	34.1%
Absolute risk reduction #				
No other risk factors	0.3%	0.8%	1.4%	2.7%
1-2 risk factors	0.7%	2.1%	3.8%	6.5%
3 or more risk factors or diabetes	1.4%	3.0%	4.6%	9.2%
NNT				
No other risk factors	348	125	71	37
1-2 risk factors	135	47	26	15
3 or more risk factors or diabetes	73	33	22	11

Absolute risk reduction = the median 10- year CVD risk × relative risk reduction. Relative risk reduction is assumed to be 27%.

Notes: Those with clinical complications are generally recommended to start drug treatment immediately and thus not included in this table.

Frequency distribution of the estimated 10-year CVD risk within the four risk categories defined by the Chinese hypertension guideline is shown in Table 4-7. In the extremely high CVD risk group, 57.2% of participants have a 10-year CVD risk lower than the expected minimum of 30%. In the high risk group, 76.2% of participants have a 10-year CVD risk lower than the expected minimum of 20%, while 6.9% are at a risk no less than the expected minimum of maximum of 30%. In the medium risk group, 73.3% of participants have a 10-year CVD risk lower than the expected minimum of 15%, while 15.1% are at a risk no less than the expected maximum of 20%. In the very low risk group, 1.1% of participants have a 10-year CVD risk equals or higher than the expected maximum of 15%. These suggest that the approach adopted in the 2005 Chinese hypertension guideline could have misclassified many patients on their CVD risk and recommend drug therapy inappropriately.

Table 4-7 Frequency distribution of the 10-year CVD risk by the risk categories defined in the 2005 Chinese hypertension guideline

Estimated ten year CVD risk	10-year CVD risk categories defined by the 2005 Chinese hypertension guideline									
	Very low risk		Low risk (<15%)		Medium risk (15%~19%)		High risk (20%~29%)		Extremely high risk (≥30%)	
	N	%	N	%	N	%	N	%	N	%
≥40%	0	-	0	-	67	1.1	26	1.9	318	27.5
35%~39%	0	-	0	-	77	1.2	31	2.3	92	8.0
30%~34%	2	0.0	0	-	139	2.2	36	2.7	84	7.3
25%~29%	6	0.0	0	-	246	4.0	93	6.9	108	9.3
20%~24%	58	0.2	0	-	413	6.6	136	10.1	124	10.7
15%~19%	258	0.9	0	-	712	11.4	218	16.1	118	10.2
10%~14%	1013	3.6	2	0.1	1078	17.3	273	20.2	130	11.2
5%~9%	3271	11.5	263	17.4	1762	28.3	340	25.1	134	11.6
<5%	23826	83.8	1245	82.5	1725	27.7	200	14.8	49	4.2
Total	28802	100.0	1559	100.0	6263	100.0	1362	100.0	1171	100.0

Range of CVD risk suggested by the 2005 Chinese hypertension guideline.

Notes: Those with an-extremely high risk do not apply to those who have clinical complications.

4.2.2 Comparison of the effectiveness of the two approaches

The two approaches are compared provided that the same number of people was treated and that people with the higher CVD risk are always given higher priorities for drug treatment.

Table 4-8 summarized (1) the CVD risk of people recommended for drug treatment according to the 2005 Chinese hypertension guideline, the BPA and ORA; (2) the percentage of people recommended for drug treatment; (3) the minimal and median 10-year CVD risk of the patients recommended for the three approaches.

Table 4-9 compared the number of CVD events avoided by antihypertensive drug therapy between the Chinese guideline recommendations and the overall risk approach.

Table 4-10 compared the number of CVD events avoided by antihypertensive drug therapy between the Chinese guideline recommendations and the blood pressure approach.

From Table 4-9, we can see that, in the same number of people treated, the absolute risk reduction of the overall risk approach is always larger than that for the the Chinese guideline.

Take people with an extremely high risk defined in the Chinese guideline as an example. They accounted for 3% (1157) of the 30~74 years old Chinese population without previous stroke. On average, their 10-year CVD risk is 26.0%, and

antihypertensive drug treatment can reduce the risk by 7.0% in 10 years of treatment. The CVD risk of the top 3% with highest risks according to the ORA will be 35.6% and the absolute risk reduction will be 9.6%. Given the same 3% of people treated by antihypertensive drugs, 26 additional CVD events could be avoided in 1000 people treated by shifting the Chinese hypertension guideline to the overall risk approach. In this extremely high risk group defined in the Chinese hypertension guideline, the minimal 10-year CVD risk of participants is only 1.3%, which means that antihypertensive drug therapy in such patients can only reduce the risk by 0.3% in 10 years' time. So, many patients recommended for drug treatment by the Chinese guideline will benefit much less than expected.

As recommended by the Chinese guideline, people with a high or extremely high risk of CVD should immediately start antihypertensive treatment. They accounts for 6.5% (2510) of the population. Antihypertensive drug treatment can reduce their CVD risk by 4.6%, which means that 22 people need to be treated in order to avoid one CVD event. In contrast, if the same number of people is treated according to the ORA, the absolute risk reduction will be 6.9%, which means that 14 people need to be treated in order to avoid one CVD event. This means that 24 additional CVD events could be avoided in every 1000 people treated by the overall risk approach as compared with the Chinese guideline approach.

Surprisingly, if the same number of people is treated, the effectiveness of the blood pressure approach is also larger than that according to the Chinese guideline recommendations (see Table 4-10).

Table 4-8 10-year CVD risk of the population selected for drug therapy by the Chinese guideline approach, the overall risk approach and the blood pressure approach

By the guideline	Population selected for drug therapy				The 10-year CVD risk					
	Cumulative		Corresponding 10-year CVD risk threshold in the ORA	Corresponding SBP threshold in the BPA	The guideline		ORA		BPA	
	N	%			Minimum	Median	Minimum	Median	Minimum	Median
Extremely high risk	1157	3	≥26.5%	≥177 mmHg	1.30%	26.00%	26.50%	35.60%	2.30%	27.40%
High risk or above	2510	6.5	≥17.9%	≥161 mmHg	0.50%	17.00%	17.90%	25.70%	1.70%	20.80%
Medium risk or above	8729	22.6	≥6.9%	≥138 mmHg	0.50%	10.40%	6.90%	12.60%	0.80%	10.50%
Low risk or above	10239	26.5	≥5.8%	≥133 mmHg	0.40%	8.50%	5.80%	11.20%	0.80%	9.40%
All participants	38673	100	≥0.2%	≥80 mmHg	0.20%	2.50%	0.20%	2.50%	0.20%	2.50%

Notes: Guideline refers to the 2005 Chinese hypertension guideline; ORA refers to the overall risk approach; BPA refers to the blood pressure appraoch.

Table 4-9 Comparison of the number of CVD events avoided by antihypertensive drug therapy between the Chinese guideline approach and the overall risk approach

Population selected for drug therapy		Absolute risk reduction		Additional CVD events avoided per 1000 people treated	Relative increase in CVD events avoided in the ORA
Guideline	Corresponding 10-year CVD risk threshold in the ORA	Guideline (1)	ORA (2)	(3)= [(2)-(1)]×1000	(4)=[(2)-(1)]/(1)
Extremely high risk	≥26.5%	7.0%	9.6%	26 (95%CI: 23~31)	37.0% (95%CI: 32.5%~43.5%)
High risk or above	≥17.9%	4.6%	6.9%	24 (95%CI: 22~25)	51.3% (95%CI: 47.3%~54.6%)
Medium risk or above	≥6.9%	2.8%	3.4%	6 (95%CI: 5~7)	20.6% (95%CI: 17.8%~23.1%)
Low risk or above	≥5.8%	2.3%	3.0%	7 (95% CI: 6~8)	31.0% (95%CI: 28.2%~33.8%)
All participants	⩾0.2%	0.7%	0.7%	0	0.0%

Notes: Guideline refers to the 2005 Chinese hypertension guideline; ORA refers to the overall risk approach.

Table 4-10 Comparison of the number of CVD events avoided by antihypertensive drug therapy between the Chinese guideline recommendations and the blood pressure approach

Population selected for drug therapy		Absolute risk reduction		Additional CVD events avoided per 1000 people treated	Relative increase in CVD events avoided in the BPA
Guideline	Corresponding SBP threshold in the BPA	Guideline (1)	BPA (2)	(3)= [(2)-(1)]×1000	(4)=[(2)-(1)]/(1)
Extremely high risk	≥177mmHg	7.0%	7.4%	4 (95%CI: 1~6)	5.2% (95%CI: 1.5%~8.5%)
High risk or above	≥161mmHg	4.6%	5.6%	10 (95%CI: 9~12)	22.5% (95%CI: 18.7%~27.0%)
Medium risk or above	≥138mmHg	2.8%	2.8%	0 (95%CI: 0~1)	1.0% (95%CI: -1.2%~3.5%)
Low risk or above	≥133mmHg	2.3%	2.5%	2 (95%CI: 2~3)	10.2% (95%CI: 7.8%~12.5%)
All participants	≥80mmHg	0.7%	0.7%	0	0.0%

Notes: Guideline refers to the 2005 Chinese hypertension guideline; BPA refers to the blood pressure approach.

4.3 Comparing the actually treated with the overall risk approach

There are 6.7% (2614) participants who are currently taking antihypertensive drugs. These people are neither determined by the overall risk approach nor by the blood pressure approach. They are determined by local doctors based on their current knowledge and clinical experience affected by local guidelines. Suppose the same number of people were treated by antihypertensive drugs, but determined completely by the overall risk approach (people with the highest CVD risks are selected for treatment), would the effectiveness of drug treatment of these people be higher than that for those who are currently using antihypertensive drugs?

In this section, the estimated effectiveness of current antihypertensive drug therapy in those currently under treatment will be compared with that by the overall risk approach assuming that the same number of people was treated. People with the highest CVD risks are selected for antihypertensive drug treatment in the overall risk approach.

Characteristics of people currently treated with antihypertensive drugs and those selected by the overall risk approach are compared in Table 4-11. In the overall risk approach, there are more males, more elderly people (aged 60~74) and more smokers than in the currently treated people. 56.9% of the people currently treated with antihypertensive drugs have a 10-year CVD risk lower than 15%, while all of the people selected by the overall risk approach have a 10-year CVD risk above 15%.

All of those selected by the overall risk approach have a blood pressure above 120/80mmHg, with 98.9% above 130/89mmHg. Among people currently treated by antihypertensive drugs, 38.9% have an extremely high or high CVD risk, 42.5% have a medium risk, 5.3% have a low risk, and 13.3% have a very low risk according to the Chinese hypertension guideline.

Table 4-11 Composition of people currently treated with antihypertensive drugs and the same number of people that are identified for drug treatment by the overall risk approach

	All participants		People selected for drug treatment			
			Currently treated*		Overall risk approach	
	N	%	N	%	N	%
Total	38673	100%	2574	100%	2574	100%
Age groups						
30 ~ 44	15967	41.3	217	8.4	10	0.4
45 ~ 59	15258	39.5	1160	45.1	332	12.9
60 ~ 74	7448	19.3	1197	46.5	2232	86.7
Gender						
Male	18062	46.7	1071	41.6	1611	62.6
Female	20611	53.3	1503	58.4	963	37.4
Region						
Large cities	6902	17.8	926	36.0	724	28.1
Small or medium-sized cities	6514	16.8	541	21.0	445	17.3
1st class rural area	6518	16.9	352	13.7	444	17.2
2nd class rural area	6179	16.0	231	9.0	313	12.2
3rd class rural area	6662	17.2	422	16.4	387	15.0
4th class rural area	5898	15.3	102	4.0	261	10.1

* People who are currently treated with antihypertensive drugs in the past two weeks. The blood pressures is adjusted by an increase of 6%.

Table 4-12 summarized the effectiveness of drug therapy in people currently using antihypertensive drugs and that in the same number of people if selected and treated according to the over all risk approach. The median CVD risk of people currently using antihypertensive drugs are about half of that of people selected by the overall risk approach, and so is the CVD risk reduction. Provided the same number of people is treated, 35 (95%CI: 34~37) additional CVD events could be avoided in 1000 treated in people according to the overall risk approach as compared with people currently taking antihypertensive drugs. In those who were currently under treatment, the minimal 10-year CVD risk is as low as 0.5%. As is mentioned before, more than half of the people currently treated with antihypertensive drugs have a 10-year CVD risk lower than 15%. These people will not benefit as much as expected by the Chinese guideline. If we shift the resources used on people with low CVD risks to people with higher CVD risks, we can double the effectiveness of drug treatment without increasing the resources currently used.

Table 4-13 compared the effectiveness of drug therapy in people currently using antihypertensive drugs with that in those identified by the blood pressure approach. The absolute effectiveness of actual practice (3.3% reduction in CVD risk) is even worse than what could be expected by the blood pressure approach (5.5% reduction in CVD risk). Provided the same number of patients treated, 22 more CVD events could be avoided in every 1000 patients treated (relatively an increase of 66.6% in CVD events prevented) if we utilize the same resources of current practice to treat according to the blood pressure approach.

Table 4-12 Comparison of the effectiveness of drug therapy in people currently using antihypertensive drugs with that in those identified by the overall risk approach

	Currently treated*	Overall risk approach
Number (%)	2574 (6.7%)	2574 (6.7%)
Minimal 10-year CVD risk	0.5%	17.7%
Median 10-year CVD risk	12.3%	25.4%
Absolute risk reduction	3.3%	6.9%
Number needed to treat (NNT)	30	15
Additional CVD events avoided per 1000 people treated	35 (95%CI: 34~37)	
Relative increase in CVD events avoided	106.2% (95%CI: 101.5%~110.6%)	

* People who are currently treated with antihypertensive drugs in the past two weeks.

Table 4-13 Comparison of the effectiveness of drug therapy in people currently using antihypertensive drugs with that in those identified by the blood pressure approach

	Currently treated*	Blood pressure approach
Number (%)	2574 (6.7%)	2574 (6.7%)
Minimal 10-year CVD risk	0.5%	1.7%
Median 10-year CVD risk	12.3%	20.5%
Absolute risk reduction	3.3%	5.5%
Number needed to treat (NNT)	30	18
Additional CVD events avoided per 1000 people treated	22 (95%CI: 20~25)	
Relative increase in CVD events avoided	66.6% (95%CI: 58.7%~74.4%)	

* People who are currently treated with antihypertensive drugs in the past two weeks.

Chapter 5 Discussions and conclusions

5.1 Summary of the main findings

For primary prevention of cardiovascular diseases through anti-hypertensive drugs, blood pressure had long been used to determine whether a patient should receive treatment or not. However, blood pressure alone is not the best predictor of a patient's benefit from treatment. The relative benefit of anti-hypertensive drug therapy is largely homogeneous regardless of patient characteristics and therapeutic settings [33-40]. This implies that the absolute benefit will be directly determined by an individual's baseline cardiovascular risk, which is determined by all the CVD risk factors in a person on top of blood pressure. Further empirical evidence from meta-regression of RCTs [56] shows that the standardized regression coefficients of absolute benefit with baseline risk is greater than that with the initial blood pressure. Furthermore, initial blood pressure contributes little to the effectiveness after adjusting for baseline risk and reduction in blood pressure. These findings suggest baseline risk is stronger a predictor of the absolute effectiveness than initial blood pressure.

However, these results provide no direct evidence about the additional number of CVD events that could be avoided by shifting from the blood pressure approach to the overall risk approach if the same number of people are selected from the same

population and are treated with drugs. This would be important information for decision makers and clinicians to judge whether the shift is truly worthwhile. To obtain this information, an RCT is not feasible, while a cohort design will require a large number of study subjects and years of follow up, which would be far beyond the feasibility of any PhD projects. Thus, we conducted this modeling study using cross-sectional data of a representative sample of Chinese population to compare the two approaches in the number of CVD events that could be avoided using anti-hypertensive drugs. The relative risk reduction is estimated from a meta-analysis of blood pressure lowering RCTs, which would be more precise than an estimate from any single trial or cohort study. The 10-year CVD risk at baseline is estimated by using a CVD risk prediction equation which is the most suitable for Chinese populations.

5.1.1 The effectiveness of the ORA is always better than that of the BPA

This study shows that given the same number of people treated, the absolute benefit of the overall risk approach is always larger than that of the blood pressure approach unless everyone in the population is treated. Thirty CVD events will be avoided in every 1000 people treated if the blood pressure approach is used and all the 20.7% of the population with systolic blood pressure 140 mmHg or above are all treated. If the overall risk approach is used to identify the same number of people (i.e., 20.7% of all study participants) for drug treatment, compared to the blood pressure approach, 6 additional CVD events can be avoided in every 1000 people treated.

In general, the smaller the percentage of the population is treated, the greater the additional number of CVD events can be avoided by shifting the blood pressure approach to the overall risk approach. Given a realistic percentage of people that can be put under drug treatment, such as 10% of the total population, the overall risk approach can avoid 9 more CVD events in every 1000 treated than the blood pressure approach. It is relatively a 19% increase in the absolute effectiveness as compared to that can be prevented in the ten percent of hypertensive patients with the highest blood pressure in China.

5.1.2 The effectiveness of current guidelines and actual practice in China could be improved by adopting the complete overall risk approach

The Chinese hypertension guideline uses a risk estimation method that based on the Framingham risk equation which tends to overestimate the risk in Chinese populations. The method only counts the number of risk factors and classifies people into a few risk groups. This is an approximate method. As a result, many people's risk will be over- or under- rated. For example, in the extremely high CVD risk group according to the Chinese hypertension guidelines, 57.2% of them had a 10-year CVD risk lower than the expected minimum of 30%. In the high CVD risk group by the Chinese guideline, 76.2% of them had a 10-year CVD risk lower than the expected minimum of 20%. As a result, many of those who do not need to be treated according to the guidelines would be treated with drugs because of the misclassification in the CVD risk. As computers and mobile computing devices are

more and more widely used, more accurate risk prediction methods such as equations or charts should be used.

For example, the Chinese guideline recommended that people with a high or extremely high risk of CVD (6.5% of the population) should start antihypertensive treatment immediately. If the same number of patients are selected and treated according to the overall risk approach, 24 more CVD events could be avoided in every 1000 people treated. This is a 51.3% increase in CVD events prevented by shifting the recommendations of the Chinese guidelines to the complete overall risk approach.

In practice, physicians seldom make drug therapy decisions purely according to the blood pressure approach, the overall risk approach, or the clinical guidelines. Currently, some 6.7% (2614) of adult population is treated with anti-hypertensive drugs and 33 CVD events can be avoided in 1000 treated. In people who were currently using anti-hypertensive drugs, more than half of them have a 10-year CVD risk lower than 15%, which is below the cutoff for drug treatment in most western countries. This is to say that at least more than half of the patients currently treated should have not been treated according to the Chinese guidelines. The absolute effectiveness of actual practice is even worse than what could be expected if the complete blood pressure approach is used, implying many with a high blood pressure have not been treated, while many with a moderately elevated blood pressure have been treated. If the same number of patients were treated according to

the overall risk approach, 35 more CVD events could be avoided in every 1000 patients treated, relatively a 106.2% increase in CVD events prevented. These findings suggest that the actual practice is worse than the Chinese guideline which is in turn worse than the overall risk approach, implying great potentials in the drug policy and practice in China.

5.2 Interpretation and discussion of the main findings

In this study, we compared the absolute effectiveness of different approaches to anti-hypertensive drugs without consider costs and harms. On a population level, the absolute effectiveness is the number of CVD events that could have been avoided in the same number of patients treated for different approaches to selecting patients to treat. On an individual level, it is a possibility of having a CVD event in the future that could have been reduced by the drug treatment.

Keeping the number of patients treated identical for different compared approaches provided a necessary basis for inferring and comparing the cost-effectiveness of different approaches. But several assumptions have to be made in order to make conclusions on the cost-effectiveness valid.

First, we have to assume that patients identified for drug treatments would not need different drug strategies (including the number, types and combination of drugs) so that they would have the same or similar cost and harm profile. Obviously, the drug strategy and harm profile for different approaches would not be exactly the same because the patients selected by different approaches are not identical and may need

different drug strategies. However, this does not seem to change the overall conclusion that the ORA is more effective than the BPA. The reason is that the average blood pressure of the patients selected by the ORA should always be lower than that of the patients selected by the BPA. As a result, the higher blood pressure is more difficult to reduce and patients in the BPA may require higher doses of, combined use of, or more expensive new, drugs than the ORA. The higher doses and/or drugs used in combination would inevitably cost more and may also cause more or more severe adverse effects.

Second, the application of the ORA seems to need additional costs and efforts because blood lipids should also be measured in addition to blood pressure, in order to estimate the CVD risk. However, this increased cost may not be real as blood lipids still need be measured if individual risk factors are dealt with separately according to the guidelines for primary prevention of CVD through tackling dislipidaemia in most countries[65 66].

In addition, it should be made clear that the results of this study are meant to apply only to primary prevention. As the BPA and ORA both suggest to treat with drugs those who have already had organ damages. The conclusions in this study will thus remain valid after adding the same benefits and costs as a result of secondary prevention to both approaches.

5.3 Strengths and limitations of the study

5.3.1 Strengths

As stated above, our modeling study is possibly the best feasible design to address the research question. It can directly compare the two approaches in the same population at their best performance. Importantly, multiple cutoff values in both blood pressure and the overall risk approaches can be evaluated and compared. We are unaware of any published studies that have validly compared the effectiveness of drug therapy between the overall risk approach and the blood pressure approach in a large representative population. If any, previous studies[67] are flawed by comparing the two approaches with a different percentage of patients identified and treated.

Furthermore, we used an accurate risk prediction equation rather than just counting risk factors. This will make our comparisons more valid and precise. The risk prediction equation is also the best we can find for Chinese populations that can be used to predict the 10-year CVD risk rather than either stroke or coronary heart disease. By using CVD, it is more likely to reflect the total effect of anti-hypertensive drugs.

The 27% estimate of the relative risk reduction as the relative effectiveness of drug treatment is based on evidence from meta-analyses and is likely to be more reliable than any estimate from an individual trial. Although only one trial in Chinese populations are included in the meta-analyses, the highly homogeneous relative effect regardless of patient characteristics and therapeutic settings [33-40] would mean

the result may well be applicable to any Chinese populations. A series of sensitivity analyses were undertaken in this study, including varying the increment of change in blood pressure for those already receiving treatment and varying the relative benefit of treatment from one quarter to one third. The results show that the conclusion is robust to changes in the assumptions.

The study population represents well the general population of China. Although the response rate was only 71.3%, we have not found any studies that are larger and represent better the general population of China. For example, a previous study on the issue[67] had examined only one urban community in Shanghai. Thus, the representativeness and large sample size of the data we used in this study is likely to be the best that can be used to demonstrate the potential advantages of the overall risk approach over the blood pressure approach, over the current guideline and over the current practice. Besides, we also demonstrated the problems of the current Chinese guideline, which include misclassification and overestimation of the CVD risk of Chinese patients, which shed light on future improvement of the guidelines.

5.3.2 Limitations

First, data collected are not ideal. Blood pressure was estimated from only two measurements taken at one setting, which may overestimate average blood pressure, although the measurements were made in an environment that was not stressful. Blood lipid concentrations are based on one measurement although an average of

two measurements in different occasions would be preferable. The risk equation used did not include a family history of cardiovascular disease or other risk factors for cardiovascular disease, such as obesity and physical activity. However, these factors are not included in most risk prediction equations. So missing of such data is not a real loss. Importantly, data on past history of coronary heart disease are is not available. We made an assumption that all participants are free of coronary heart disease. Thus, generalizability of the results and findings to those with coronary heart disease should be made with caution.

Second, the risk estimation equation used in my analysis is derived from Asian cohorts who were assembled between 1961 and 1997. It is known that major risk factors of CVD were on a rise in China, especially in the past two decade[7 68] and the mortality rate of CVD has also been doubled since 1990's. So the incidence rate of CVD nowadays will be higher than the rate estimated in the equation. Thus, the 10-year CVD risk of treated people might have been underestimated. Furthermore, the risk factor level used is also based on the data from these cohorts which will be lower than that in current days. Thus, the absolute effectiveness of shifting from the overall risk approach to the blood pressure approach will thus be underestimated. This seems to be the major problem of my study. The consequence is underestimation of the effectiveness. Having said that, the underestimation is unlikely to affect the analyses and results that compare various policies in groups defined by the risk or blood pressure, which is the main part of the study.

Third, there are slightly more people from urban areas in my data than in the national census data. The CVD risk of people in urban areas will be higher than that of people in rural areas. Thus, the average risk of people selected for drug therapy by various approaches in my data would be slightly higher than what would be expected in a more representative sample. An overestimated average risk of selected people for treatment will also mean an overestimated absolute effectiveness of various policies and an overestimated relative effectiveness by shifting to the overall risk approach. Having said that, the overestimation will not affect most of the analyses and results that compare various policies in groups defined by the risk or blood pressure.

It has been argued that the value of preventing one CVD event for a 60 year old person will be much lower than that for a 30 year old person. As the average age of people selected by the overall risk approach is higher than that of people selected by the blood pressure approach, the benefit of shifting from the blood pressure approach to the overall risk approach would be smaller if life-years gained is used to estimate the effectiveness of the treatment.

Ideally, drug therapy should be considered on top of life style modification measures. Dietary advice, salt restriction, physical activity, and smoking cessation can also reduce the CVD risk. Thus, our analysis might have overestimated the CVD risk and the effectiveness by shifting from the blood pressure approach to the overall risk approach if drug therapy is provided on top of health education and lifestyle interventions.

In brief, some of the limitations may lead to underestimation of the absolute effectiveness of shifting from one approach to another, while the others may result in overestimation. Due to the limitation of the risk prediction equation that may well severely underestimate the risk, it is likely such biases could cancel each other, if they do not lead to underestimation. However, these biases are unlikely to be able to change the overall conclusion that the overall risk approach is better than the blood pressure approach, the current Chinese guidelines and current actual practice.

5.4 Conclusions and recommendations

This study showed clearly that in an absolute term the overall risk approach is always more effective than the blood pressure approach. I also quantified the additional benefit in various situations by switching to the overall risk approach. In general, additional effectiveness is inversely related to the number of people to be treated in a population: smaller the number of people to treated, more advantageous the overall risk approach would be over the blood pressure approach. Given a realistic number of people to be treated, the effectiveness can be increased by over 20% by switching to the overall risk approach. The Chinese hypertension guidelines substantively overestimate the risk and misclassify patients and thus lead to a much smaller effectiveness than the true overall risk approach. Many low risk people were currently treated with drugs. If the current practice is shifted to the overall risk approach, the number of CVD events prevented could be doubled if the same

number of people is treated according to the overall risk approach. These findings will help to improve the hypertension guidelines and to incease the effectiveness of resources used on anti-hypertensive drugs.

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