# Generalized cost-effectiveness analysis of pharmaceutical interventions for primary prevention of cardiovascular disease in Thailand

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Running Title: Cost-Effectiveness of CVD drugs in Thailand

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**ABSTRACT** [First-level Header]

**Objectives:** To assess the cost-effectiveness of blood pressure (BP) and cholesterol lowering drugs for cardiovascular disease (CVD) prevention.

**Methods**: We constructed a Markov model in which the Thai population is classified by 10-year absolute CVD risk and modelled the use of BP and cholesterol lowering drugs, including a 'polypill' (three BP lowering drugs and a statin). We applied 'do-nothing' as the comparator; a health sector perspective on life time cost-effectiveness, 3% discounting of costs and effects and used probabilistic sensitivity analysis. Outcomes are expressed as average and incremental cost-effectiveness in Thai baht per disability adjusted life year averted.

**Results**: The polypill would be a very cost-effective option for CVD prevention even in people at modest risk (ten-year risk of 5-9.9%). Use of the three most cost-effective BP drugs is also associated with a net cost saving and large health gain at risk levels greater than 5%. Adding a generic statin gives a price per DALY of 0.5 (10-year risk at 20%+) to 1.5 (10-year risk at 5-9.9%) times Thai GDP per capita using lowest available annual costs. However, at current average drug prices, adding a statin would only be considered cost-effective for those with a ten-year absolute CVD risk of 20% and over.

**Conclusions:** Primary CVD prevention with the polypill or a combination of three generic BP lowering drugs is very cost-effective in the Thai population.

## Background [First-level Header]

Cardiovascular diseases (CVD) are among the leading causes of health loss worldwide [1] and in Thailand [2, 3]. CVD results in high case fatality rates during the first few days following an event [4,5]; an ongoing increased risk of death [6,7] among those who survive the initial event, and a high cost of treatment [8]. Exposure to important CVD risk factors such as raised blood pressure and cholesterol, tobacco use, and diabetes mellitus is rising in Thailand [9]. These factors are related to changes in lifestyle, including an increase in sedentary behaviour and a change in diet. As observed in many western countries, preventive action can reduce the incidence and premature mortality due to CVD [10,11].

Blood pressure- and cholesterol-lowering drugs have been proven to be effective in preventing ischaemic heart disease (IHD) and stroke [12,13]. Given limited health care resources, Thailand's health policy needs to be based not only on effectiveness but also on associated costs to determine which intervention(s) should be publicly funded and what population should be targeted. Identifying population subgroup(s) that should be targeted with interventions can be based on estimates of future risks of CVD. Recent guidelines have advocated the use of individuals 'absolute CVD risks' as the criterion for the initiation of preventive drug therapies. For each individual, this absolute CVD risk is calculated based on exposure to various determinants of CVD incidence and mathematical formulae such as the Framingham Risk Score, the Systematic Coronary Risk Evaluation (SCORE), and cardiovascular risk prediction tools for populations in Asia [14-16].

Cost-effectiveness of blood pressure and cholesterol lowering medications has been studied elsewhere; however, results differ from setting to setting [17-19]. Furthermore, studies on cost-effectiveness show differences in methodology, outcomes, cost components, and characteristics of the target population [17]. To our knowledge there have been no studies reporting the cost effectiveness of blood pressure and cholesterol lowering drugs, singly or in combination, for cardiovascular disease prevention in Thailand.

## Objectives [First-level Header]

We assessed the cost and effectiveness of different blood pressure and cholesterol lowering drugs targeting population subgroups with varying absolute CVD risk levels.

## Methodology [First-level Header]

This study was carried out as part of Setting Priorities using Information on Cost Effectiveness (SPICE) project, a collaborative project between the Ministry of Public Health of Thailand and the University of Queensland, School of Population Health, Australia.

### Definitions, incidence, and case fatality rates of cardiovascular disease [Second-level Header]

We defined a new case of CVD as a first-ever fatal or non-fatal ischaemic heart disease or stroke event, including unstable angina pectoris, myocardial infarction, ischaemic stroke (IS) or haemorrhagic stroke (HS).

There was no direct information on the incidence and case fatality rates of CVD in Thailand; we estimated these using hospital admissions data and mortality data. These two locally available data sources provided estimates of the incidence of fatal and non-fatal IHD/stroke. Hospital admission data were provided by the Ministry of Public Health which uses these data to reimburse public hospitals. As the database does not capture private hospital admissions we inflated all admissions to reflect the total number of self-reported hospital admissions by age, sex and hospital level from the 2005 Health and Welfare Survey (National Statistics Office, Bangkok, Thailand). The vital registration system has unacceptably high proportions of deaths coded to ill-defined causes, so we used data from a recent cause of death (COD) study. The study was well designed and conducted using standard methods [3,20-22]. See appendix for details in Supplementary Materials at: XXX..

### Current practice [Second-level Header]

To assess the cost-effectiveness of current practice, we first estimated its average yearly cost by adding the weighted yearly cost of the three drug components currently used: blood pressure lowering drugs,

cholesterol lowering drugs, and the combination. Similarly, the overall effects of current practice on IHD, IS, and HS were calculated, separately, as the sum of the effects of blood pressure drugs as one group, cholesterol drugs as another group and the combination of these as a third group. The appendix provides more information on the cost and effect of current practice.

Interventions analysed [Third-level Header]

We selected blood pressure- and cholesterol-lowering drug interventions that have been proven in clinical trials to be effective in preventing IHD and stroke [12,13]. Blood pressure lowering drugs were classified into five subclasses: thiazide diuretics (D), calcium channel blockers (CCB), beta blockers (BB), angiotensin converting enzyme inhibitors (ACE-i), and angiotensin receptor blockers (ARB). Statins were selected as the most cost-effective cholesterol-lowering drugs available as a generic in Thailand. The analysis was conducted for single drug interventions and combinations of drugs from different classes. When two or more drugs were used together, their effects, measured as the relative risk of disease incidence, were combined using a multiplicative equation (e.g. RR1*RR2*RR3) [25]. We also analyzed the cost–effectiveness of a theoretical 'polypill' [11] composed of a statin [12] in full dose and three blood pressure lowering drugs in half standard doses (D, CCB and ACE-i) [13]. This combination was selected based on the superior effects of the 3 drugs and their cost-effectiveness over BB and ARB.

<Insert Table 1>

We did not include aspirin in the polypill because the addition of aspirin contributes minimal additional effectiveness. Moreover, aspirin can cause serious side effects of gastrointestinal and intracranial bleeds, particularly in the elderly [27,28].

Target populations [Third-level Header]

The target population was classified based on the probability of developing a cardiovascular event over the next 10 years. Risks were estimated using risk prediction equations we developed for Thailand based on calibration of the Framingham equations [29] taking into account the contemporary incidence of IHD and

stroke. Risk factors included age, systolic blood pressure, total cholesterol, diabetes mellitus and smoking with separate equations for males and females and for IHD and stroke. The population was divided into four risk categories: <5%, 5−9.9%, 10−19.9% and 20%+ risk of IHD or stroke over the next 10 years.

### Perspective and Cost [Third-level Header]

The costs associated with the implementation of each intervention were estimated from a health sector perspective, i.e., we included the costs to government as well as the health intervention related costs to patients and their family/carers. Intervention costs included pharmaceuticals, health centre visits for 20 minutes (one visit to a specialist (obtained from the National Statistics Office, Bangkok, Thailand) and two to a primary care centre [30] per year) and laboratory tests (an annual test of urea and electrolytes for blood pressure-lowering drugs, and of lipids and liver enzymes for cholesterol-lowering drugs). We obtained the cost of drugs from the webpage of the Ministry of Public Health [31]. Drug costs used in base case analysis were the lowest annual costs (for generic versions of the drugs) whereas ranges used in the probabilistic sensitivity analysis were between the lowest and the highest costs. When two or more blood pressure lowering drugs were combined, the cost of health centre visits and laboratory tests were the same as for a single drug. For the combinations of blood pressure and cholesterol lowering drugs, the cost of a health centre visit was counted only once and the costs of laboratory tests were added. The cost of polypill intervention was the sum of the costs of each drug and one visit to a health centre with no cost of laboratory tests.

We also included cost-offsets, i.e. the cost of disease treatments that are avoided by prevention. The cost of ischaemic heart disease treatment was readily available [8]. Costs of stroke treatment were obtained from the Neurological Institute in Bangkok. All costs were converted into the 2004 Baht value using the consumer price index [32]. Drug costs and other costs associated with the implementation of interventions (costs of health centre visits and laboratory tests) are shown in Table 2. More detail is provided in the appendix.

<Insert Table 2>

### Model and transition probabilities [Third-level Header]

We developed a Markov model to assess the net costs and health outcomes associated with lifetime use of blood pressure and/or cholesterol lowering drugs in primary prevention of CVD. The model was implemented in Microsoft Excel (Microsoft Corp., Redmond, Washington). Each age, sex and absolute risk category was modelled separately to death or 100 years of age but we present aggregate results for the whole eligible target population in 2004 only. Costs and outcomes were discounted at 3%. Four health states were explicitly modelled: alive without CVD, alive after a first-ever event of IHD, alive after a first-ever event of stroke and death. Transitions between these mutually exclusive health states could occur at the end of discrete yearly cycles (Fig. 1). Transition probabilities are in the appendix, tables 1-3 in Supplementary Materials at; XXX.

<Insert Figure 1>

Model Assumptions [Third-level Header]

The effects of these three BP lowering drugs in the polypill [13] in half standard doses were assumed to be 20% lower than those in standard doses [25]. The effects of the polypill were assumed to be a multiplication of the effects of the four drugs. We assumed that the greater convenience of taking just one pill would enhance adherence and that there would be fewer side effects and less need for repeated measurement of risk factor levels [25,26]. We assumed 60% adherence for the polypill. Adherence to single drugs in full doses was assumed to be 50% [19]. The effect sizes for each drug are shown in Table 1. The cost associated with discontinuation was assumed to be the sum of one health centre visit, one laboratory test and one month of drug costs. No health benefits were assumed for persons who discontinued their medication.

Do nothing as a comparator [Third-level Header]

The cost-effectiveness of interventions is compared with a ‘do nothing’ scenario [23], which was quantified by removing the costs and effects of the blood pressure and cholesterol lowering medications used in current practice (see appendix).

### Cost-effectiveness ratios [Third-level Header]

Starting from this hypothetical 'do nothing' situation, we first calculated the average cost-effectiveness ratio (ACER) for each intervention. The ACER is equal to the difference in cost between the intervention and the 'do nothing' scenario divided by the difference in health outcomes between the two scenarios in disability adjusted life years (DALY) averted (See appendix). The cost was calculated as the intervention cost minus the averted costs of disease treatment (or cost offsets, see appendix). Interventions were considered 'very cost-effective' if the ACER was less than one times gross domestic product (GDP) per capita (Baht 110,000 in 2004) and 'cost-effective' if between 1-3 times GDP per capita [23].

Secondly, we constructed an 'expansion pathway' starting with the most cost-effective intervention. Next, we assessed the incremental cost-effectiveness ratios (ICERs) for the next best intervention(s) to be added into an optimal intervention package. The ICER was equal to the difference in cost between the next intervention and the chosen intervention package divided by the difference in health outcomes. We took into account shared costs and avoided double counting of health benefits.

### Probabilistic sensitivity analysis [Third-level Header]

Probabilistic sensitivity analysis (2000 iterations) was conducted based on distributions assigned to intervention costs and effects, and disease treatment costs, using the Ersatz software program (www.epigear.com). A lognormal distribution was assumed for intervention effects and a uniform distribution was assumed for costs in the probabilistic uncertainty analysis.

## Results [First-level Header]

Three blood pressure lowering drug subclasses (D, CCB and ACE-i) were similarly effective against IHD and stroke (Table 1). They were similar to statins in their ability to reduce IHD risk, but more effective than statins in preventing stroke. The other two blood pressure lowering drug subclasses (BB and ARB) were

somewhat less effective. Intervention costs were dominated by the cost of health centre visits and laboratory tests.

Base case analysis [Third-level Header]

A combination of three blood pressure lowering drugs (D+ACE-i+CCB) was dominant (i.e. intervention costs less than projected savings from reduced treatment costs) in all risk categories (from 5%). The combination of three blood pressure lowering drugs was more favourable than just one or two of these drugs because the additional drugs were cheap and resulted in more healthy life years gained while saving more disease treatment costs. Two other blood-pressure lowering drugs with higher average cost-effectiveness ratios were not considered in any of the drug combinations as it is unlikely that in primary prevention more than three blood pressure lowering drugs would be prescribed.

As a single drug intervention compared to no treatment, statins had a favourable cost-effectiveness ratio (Table 3). Adding statins incrementally to the more cost-effective package of three blood pressure lowering drugs, however, has a positive cost-effectiveness ratio ranging from a half to one-and-a-half times GDP per capita, depending on the absolute CVD risk category (Fig. 2 and Table 4). Current practice was judged inefficient. Although the average cost-effectiveness ratio fell below the 3-time-GDP per capita threshold, much more favourable treatment strategies are available.
<Insert Table 3>

Polypill [Third-level Header]

The polypill was a dominant intervention in all groups of over 5% 10 year CVD risk (Table 3). It produced slightly more effects than the use of the three blood pressure lowering drugs and statins together because of increased adherence, but it was much cheaper because it reduced the need for laboratory tests and health centre visits (Fig. 2 and Table 3).
<Insert Figure 2 >

### Probabilistic sensitivity analyses [Third-level Header]

The probabilistic sensitivity analyses revealed that the uncertainty bounds (upper limits of 95% confidence intervals) for the combinations of three blood pressure lowering drugs and the polypill did not exceed the decision threshold of one time GDP per capita in any risk category of 5% or greater. Adding a statin to the three blood pressure lowering drugs was associated with a 100%, 95% and 57% probability of a cost-effectiveness ratio below three times GDP per capita, for the 20%+, 10-19% and 5-9% CVD risk groups, respectively (Table 4).

<Insert Table 4>

## Discussion and conclusion [First-level Header]

Our results show that most of the drug combinations do not only improve health, but also save considerable future cost of disease treatment. Primary CVD prevention with a polypill or a combination of three generic blood pressure lowering drugs in Thailand is very cost-effective when the 10 year CVD risk is 5% or higher. We also examined addition of a statin to the three most cost-effective blood pressure lowering drugs. Against a threshold of three times GDP per capita this is cost-effective for the ten-year absolute risk category of 20%+ but perhaps not for the lower risk categories. The potential for health gain is very large if the coverage of three generic blood pressure lowering drugs is extended to everyone at even modestly increased CVD risk (ten-year CVD risk of 5% and greater). This could lead to an estimated increase in life expectancy of 0.48 year in the cohort of Thai people aged 30 and above with this risk level (4,000,000 life years gained in a population of 8,274,248).

A major strength of our study is that costs and disease parameters were based on local data. The effectiveness of CVD prevention drugs is well established in the international literature. Although most of the data on effectiveness comes from western countries, a study on associations of blood pressure and cholesterol (as risk factors) and cardiovascular disease shows that relative risks of IHD and stroke associated with an increase in these two risk factors in Thailand are comparable to those in the Asia Pacific and western populations [34]. Our analysis is limited by several assumptions. We assumed the same

effects for the drugs of the same class as there was no study of primary prevention that directly compared individual drugs within the same class and measured health outcomes. Two Cochrane reviews of trials that evaluated the dose-related BP lowering efficacy of different ACE-inhibitors and of different ARBs against placebo, however, showed no clinically meaningful BP lowering differences between different ACE-inhibitors or ARBs [35,36]. We assumed a 50% adherence rate for interventions which is lower than reported in trials but similar to findings in routine care elsewhere [33]. The adherence rate is not a critical assumption in calculating cost effectiveness ratios as both costs and effectiveness of interventions increase or decrease in the same direction. We assumed higher adherence for the polypill because one pill is more convenient to take and it would have fewer side effects due to reduced doses of blood pressure lowering drugs and the general safety profile of statins [11]. We did not model the cost and consequences of adverse drug reactions. Although the literature reports the proportion of people with adverse drug reactions, data on the cost associated with treatment of these were not available in Thailand. Most side effects of these drugs, however, are minor [25,26].

A similar study in Argentina shows different results [19]. Population wide approaches (health education through mass media and reduction of salt in bread through voluntary agreement with industry) and a polypill used in a moderate risk group with ten-year CVD risk of 10% and higher were the cost-effective interventions. Treatment with blood pressure lowering drugs and statins, and the polypill for population subgroups with absolute CVD risks below 10% were not cost-effective against a threshold of one GDP per capita. This is due to the much higher costs of drugs in Argentina [19]. Similarly, primary prevention of CVD using statins in the UK population with coronary heart disease risks of below 3% per year (±30% risk over 10 years) was not cost-effective, [18] again due to high drug prices.

The design used in this study [23] provides information on the potential to reallocate healthcare resources for more efficient prevention of CVD in the country. Currently, CVD preventive drug treatment has very low coverage, is not targeted to those at increased absolute risk and is inefficient because expensive drugs are prescribed in preference to cheap generics. Given the potential health gain and cost savings of disease treatment in the future we recommend that Thailand's first priority is to reallocate health care resources towards greater utilization of generic drug combinations.

Once a polypill is locally produced a follow up study should be conducted to evaluate whether the drug produces the expected reduction in CVD incidence and adherence. The barriers to the utilization of generic drugs for CVD prevention should also be further investigated. Although generic drugs are very cost-effective for cardiovascular disease prevention, putting a large proportion of the population on lifelong medication (>15 million Thais have ten-year CVD risks of >5%) may not be considered desirable. Further research for CVD prevention in Thailand should focus on the cost-effectiveness of interventions that reduce exposure to risk factors for CVD such as smoking cessation [38], salt reduction strategies [10], and diabetes mellitus prevention [39].

Acknowledgement [First-level Header]

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References [First-level Header]

[1] Lopez AD, Mathers CD, Ezzati M, et al. Global and regional burden of disease and risk factors, 2001: systematic analysis of population health data. Lancet 2006;367:1747-57.

[2] Bundhamcharoen K, Teerawatananon Y, Vos T, (eds.). Burden of Disease and Injuries in Thailand. Bangkok: Ministry of Public Health (in Thai), 2002.

[3] Porapakkham Y, Rao C, Pattaraarchachai J, et al. The burden of premature mortality in Thailand, 2005: new estimates from corrected vital registration. Popul Health Metr. In press.

[4] Thorvaldsen P, Asplund K, Kuulasmaa K, et al. Stroke Incidence, Case Fatality, and Mortality in the WHO MONICA Project. Stroke 1995;26:361-7.

[5] Norris RM on behalf of the United Kingdom Heart Attack Study Collaborative Group. Fatality outside hospital from acute coronary events in three British health districts, 1994-5. BMJ 1998;316:1065-70.

[6] Brønnum-Hansen H, Jørgensen T, Davidsen M, et al. Survival and cause of death after myocardial infarction: The Danish MONICA study. J Clin Epidemiol 2001;54:1244-50.

[7] Bronnum-Hansen H, Davidsen M, Thorvaldsen P. Long-Term Survival and Causes of Death After Stroke. Stroke 2001;32:2131-6.

[8] Anukoolsawat P, Sritara P, Teerawattananon Y. Costs of Lifetime Treatment of Acute Coronary Syndrome at Ramathibodi Hospital. Thai Heart J 2006;19:132-43.

[9] World Health Organization. Health Topic and Country Page. Available from: https://apps.who.int/infobase/report.aspx?rid=114&iso=THA&ind=CHO. [Accessed March 16, 2010].

[10] Bibbins-Domingo K, Chertow GM, Coxson PG, et al. Projected Effect of Dietary Salt Reductions on Future Cardiovascular Disease. N Engl J Med 2010;362:590-9.

[11] Wald NJ, Law MR. A strategy to reduce cardiovascular disease by more than 80%. BMJ 2003;326:1419.

[12] Cholesterol Treatment Trialists' (CTT) Collaborators. Efficacy and safety of cholesterol-lowering treatment: prospective meta-analysis of data from 90 056 participants in 14 randomised trials of statins Lancet 2005;366:1267-78.

[13] Law MR, Morris JK, Wald NJ. Use of blood pressure lowering drugs in the prevention of cardiovascular disease: meta-analysis of 147 randomised trials in the context of expectations from prospective epidemiological studies. BMJ 2009 338doi:10.1136/bmj.b1665 (Published 19 May 2009).

[14] Asia Pacific Cohort Studies Collaboration. Cardiovascular risk prediction tools for populations in Asia. J Epidemiol Community Health 2007;61:115-21.

[15] Lindman AS, Selmer RM, Tverdal A, et al. The SCORE risk model applied to recent population surveys in Norway compared to observed mortality in the general population. Eur J Cardiovasc Prev Rehabil 2006;13:731-7.

[16] D'Agostino S, Ralph B, Grundy S, et al, for the CHD Risk Prediction Group. Validation of the Framingham Coronary Heart Disease Prediction Scores: Results of a Multiple Ethnic Groups Investigation. JAMA 2001;286:180-7.

[17] Mullins CD, Blak BT, Akhras KS. Comparing Cost-Effectiveness Analyses of Anti-Hypertensive Drug Therapy for Decision Making: Mission Impossible? Value Health 2002;5:359-71.

[18] Pickin DM, McCabe CJ, Ramsay LE, et al. Cost effectiveness of HMG-CoA reductase inhibitor (statin) treatment related to the risk of coronary heart disease and cost of drug treatment. Heart 1999;82:325-32.

[19] Rubinstein A, Garcia Marti S, Souto A, et al. Generalized cost-effectiveness analysis of a package of interventions to reduce cardiovascular disease in Buenos Aires, Argentina. Cost Eff Resour Alloc 2009;7:10-.

[20] Polprasert W, Rao C, Adair T, et al. Cause of death ascertainment for deaths that occur outside hositals in Thailand: application of verbal autopsy methods. Popul Health Metr. In press.

[21] Pattaraarchachai J, Rao C, Polprasert W, et al. Cause-specific mortality patterns among hospital deaths in Thailand. Popul Health Metr. In press.

[22] Rao C, Porapakkham Y, Pattaraarchachai, J, et al. Verifying causes of death in Thailand: rationale & methods for empirical investigation. Popul Health Metr. In press.

[23] Tan-Torres Edejer T, Baltussen R, Adam T, et al., (eds.). Making Choices in Health: WHO Guide to Cost-Effectiveness Analysis. Geneva: World Health Organization, 2003.

[24] Aekplakorn W, Abbott-Klafter J, Khonputsa P, et al. Prevalence and management of prehypertension and hypertension by geographic regions of Thailand: the Third National Health Examination Survey, 2004. J Hypertens 2008;26:191-8.

[25] Law MR, Wald NJ, Morris JK, Jordan RE. Value of low dose combination treatment with blood pressure lowering drugs: analysis of 354 randomised trials. BMJ 2003;326:1427-.

[26] Van Wijk B, Klungel O, Heerdink E, de Boer A. Rate and determinants of 10-year persistence with antihypertensive drugs. J Hypertens 2005;23:2101-7.

[27] Nelson MR, Liew D, Bertram M, Vos T. Epidemiological modelling of routine use of low dose aspirin for the primary prevention of coronary heart disease and stroke in those aged >=70. BMJ 2005;330:1306-.

[28] Fowkes FGR, Price JF, Stewart MCW, et al. Aspirin for Prevention of Cardiovascular Events in a General Population Screened for a Low Ankle Brachial Index: A Randomized Controlled Trial. JAMA 2010;303:841-8.

[29] Anderson KM, Wilson PW, Odell PM, Kannel WB. An updated coronary risk profile. A statement for health professionals. Circulation. 1991;83:356-62.

[30] World Health Organization. Estimates of Unit Costs for Patient Services for Thailand. Available from: http://www.who.int/choice/country/tha/cost/en/index.html. [Accessed April 15, 2009].

[31] Drug and Medical Services Information Center. Prices of drug and medical devices. Available from: http://dmsic.moph.go.th/price.htm. [Accessed November 27, 2008].

[32] Bank of Thailand. Thailand's Key Economic Indicators. Available from: http://www.bot.or.th/BOThomepage/databank/EconData/Thai_Key/Thai_KeyE.asp. [Accessed November 6, 2007].

[33] World Health Organization. Adherence to long term therapies: evidence for action. Geneva: World Health Organization, 2003.

[34] Khonputsa P, Veerman JL, Vathesatogkit P, et al. Blood pressure, cholesterol and cardiovascular disease in Thailand. Heart Asia In press.

[35] Heran BS, Wong MM, Heran IK, Wright JM. Blood pressure lowering efficacy of angiotensin receptor blockers for primary hypertension Cochrane Database of Systematic Reviews 2008:Art. No.: CD003822. DOI:10.1002/14651858.CD003822.pub2.

[36] Heran BS, Wong MM, Heran IK, Wright JM. Blood pressure lowering efficacy of angiotensin converting enzyme (ACE) inhibitors for primary hypertension. Cochrane Database of Systematic Reviews 2008:Art. No.:CD003823. DOI: 10.1002/14651858.CD003823.pub2.

[37] Ministry of Public Health. Health care expenditure in Thailand in 2007 in Thai..Available from: http://bps.ops.moph.go.th/strategy/plan-moph/image/4.2.pdf. [Accessed 1 June 1, 2010].

[38] Asma S MG, Warren CW, Henson R. Tobacco use and the cardiovascular disease epidemic in developing countries: global crises and opportunity in the making. Ethn Dis 2003;13(Suppl. 2):S81-7.

[39] Grundy SM, Benjamin IJ, Burke GL, et al. Diabetes and Cardiovascular Disease : A Statement for Healthcare Professionals From the American Heart Association. Circulation 1999;100:1134-46.

**Table 1: Effectiveness parameters used in cost-effectiveness analysis of blood presure and cholesterol lowering drugs**

| **Parameter** | **Point estimate (uncertainty range and distribution)** | | | **Source** |
|---|---|---|---|---|
| First-year discontinuation rate | 50% (37.5% to 62.5%) for single drugs, 40% (30% to 50%) for polypill Uniform distribution | | | Estimate |
| **Relative risk** | **Ischemic heart disease** | **Ischemic stroke** | **Hemorrhagic stroke** | |
| Diuretic | 0.86 (0.75 to 0.98) Lognormal distribution | 0.62 (0.53 to 0.72) Lognormal distribution | 0.62 (0.53 to 0.72) Lognormal distribution | Law MR et al. (2009) |
| ACEI | 0.83 (0.78 to 0.89) Lognormal distribution | 0.78 (0.66 to 0.92) Lognormal distribution | 0.78 (0.66 to 0.92) Lognormal distribution | Law MR et al. (2009) |
| BB | 0.89 (0.78 to 1.02) Lognormal distribution | 0.83 (0.70 to 0.99) Lognormal distribution | 0.83 (0.70 to 0.99) Lognormal distribution | Law MR et al. (2009) |
| CCB | 0.78 (0.62-0.99) Lognormal distribution | 0.66 (0.58 to 0.75) Lognormal distribution) | 0.66 (0.58 to 0.75) Lognormal distribution | Law MR et al. (2009) |
| Statin | 0.77 (0.74-0.80) Lognormal distribution | 0.78 (0.70-0.87) Lognormal distribution | 1.00 | Cholesterol Treatment Trialists' (CTT) Collaborator (2005) |
| ARB | [1]0.86 (0.53 to 1.40) Lognormal | [3]0.79 (0.69-0.90) Lognormal | [3]0.79 (0.69-0.90) Lognormal | Law MR et al. (2009) |

| | | | | |
|---|---|---|---|---|
| | distribution | distribution | distribution | Psaty BM et al. (2003) |
| Polypill* | 0.44 (0.34-0.54) Lognormal | 0.32 (0.24-0.41) Lognormal | 0.41 (0.31-0.52) Lognormal | Estimate based on the |
| | distribution | distribution | distribution | multiplicative effects of |
| | | | | drug components |
| Current practice | 0.99, 0.98 | 0.99, 0.97 | 0.98, 0.97 | Estimate based on |
| (men, women) | | | | proportion using drugs |
| | | | | currently |

* Polypill cost is based on the sum of the costs for each drug component. However, the true cost is likely to be less because of economies of scale in drug preparation.

**Table 2:** Cost parameters used in cost-effectiveness analysis of blood pressure and cholesterol lowering drugs

| Parameter | Point estimate (uncertainty range and distribution) | Source |
|---|---|---|
| **Quantities** | | |
| Number of long health centre visits (each year) | 1 | Estimate |
| Number of short health centre visits (each year) | 2 | Estimate |
| Number of tests for lipid levels (each year) | 1 | Estimate |
| Number of tests for liver function (each year) | 1 | Estimate |
| Number of tests for serum urea and electrolyte levels (each year) | 1 | Estimate |
| **Price per unit** | | |
| 1 x long health centre visit | 160 (120-200)<br>Uniform distribution | The National Statistical Office of Thailand |
| 1 x short GP visit | 130 (98-163)<br>Uniform distribution | World Health Organization |

| | | |
|---|---|---|
| 1 x test for urea and electrolyte levels | 261 (196-326)<br>Uniform distribution | The Faculty of Medical Technology, Chiang Mai University |
| 1 x test for lipid levels and liver function | 456 (342-570)<br>Uniform distribution | The Faculty of Medical Technology, Chiang Mai University |
| Annual cost of Diuretic | 48 (48-99)<br>Uniform distribution | The Ministry of Public Health |
| Annual cost of ACEI | 104 (104-370)<br>Uniform distribution | The Ministry of Public Health |
| Annual cost of BB | 132 (132-588)<br>Uniform distribution | The Ministry of Public Health |
| Annual cost of CCB | 295 (295-361)<br>Uniform distribution | The Ministry of Public Health |
| Annual cost of Statin | 503 (503-2,132)<br>Uniform distribution | The Ministry of Public Health |
| Annual cost of ARB | 892 (892-1,444)<br>Uniform distribution | The Ministry of Public Health |
| Annual cost of Polypill | 726 (730-2,565)<br>Uniform distribution | The Ministry of Public Health |
| Annual cost of Current practice | 294 for men, 414 for women | The Ministry of Public Health |

**Table 3:** Life time health gain, cost, and average cost-effectiveness ratios for single drugs and selected drug combinations by cardiovascular risk category

| **Intervention** | **Base case analysis*** | | | **Probabilistic analysis*** | | | |
|---|---|---|---|---|---|---|---|
| | **Health gain ('000s DALYs)** | **Net cost(billions Baht)** | **Cost-effectiveness ratio* (Baht/DALY)** | **Median Cost-effectiveness ratio (Baht/DALY)** | **95% uncertainty range (Baht/DALY)** | **Probability (%) of falling below:** 1 x GDP | 3 x GDP |
| Current practice | 400 | 120 | 300,000 | N/A | N/A | N/A | N/A |
| *Cardiovascular disease risk in 10 years 5−9.9%* | | | | | | | |
| Polypill | 1,100 | -12 | Dominant | 16,000 | (Dominant - 41,000 ) | 100 | 100 |
| D+CCB+ACEi | 890 | -1.4 | Dominant | 63,00 | (Dominant - 19,000 ) | 100 | 100 |
| D | 420 | 5.8 | 14,000 | 21,000 | (Dominant - 56,000 ) | 100 | 100 |
| D+CCB+ACEi+statin | 1,000 | 18 | 17,000 | 50,000 | (25,000 -77,000 ) | 100 | 100 |
| CCB | 380 | 13 | 33,000 | 45,000 | (21,000 - 75,000 ) | 100 | 100 |
| ACEi | 280 | 9.3 | 33,000 | 89,000 | (53,000 -140,000) | 82 | 100 |
| BB | 190 | 14 | 70,000 | 200,000 | (88,000 - 1,300,000) | 6 | 70 |
| Statin | 260 | 24 | 90,000 | 180,000 | (85,000 -290,000) | 11 | 99 |
| ARB | 250 | 31 | 120,000 | 310,000 | (180,000 - 620,000) | 0 | 58 |
| *Cardiovascular disease risk in 10 years 10−19.9%* | | | | | | | |
| Polypill | 910 | -16 | Dominant | 2,600 | (Dominant - 22,000) | 100 | 100 |
| D+CCB+ACEi | 720 | -7.3 | Dominant | Dominant | (Dominant – 7,000) | 100 | 100 |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| D | 330 | 0.9 | 3,000 | 8,700 | (Dominant - 40,000) | 100 | 100 |
| D+CCB+ACEi+statin | 840 | 2.9 | 3,000 | 28,000 | ( 8,800 - 49,000) | 100 | 100 |
| CCB | 310 | 5.0 | 16,000 | 27,000 | (5,800 - 24,000) | 100 | 100 |
| ACEI | 220 | 3.2 | 15,000 | 58,000 | (28,000 - 130,000) | 99 | 100 |
| BB | 150 | 6.7 | 44,000 | 180,000 | (57,000 – 1,000,000) | 18 | 82 |
| Statin | 210 | 12 | 56,000 | 120,000 | (48,000 - 210,000) | 41 | 100 |
| ARB | 200 | 17 | 83,000 | 230,000 | (120,000 - 470,000) | 1 | 86 |
| *Cardiovascular disease risk in 10 years 20+%* | | | | | | | |
| Polypill | 720 | -16 | Dominant | Dominant | (Dominant – 4,900) | 100 | 100 |
| D+CCB+ACEi | 570 | -9.4 | Dominant | Dominant | (Dominant-Dominant) | 100 | 100 |
| D | 270 | -1.8 | Dominant | Dominant | (Dominant - 21,000) | 100 | 100 |
| D+CCB+ACEi+statin | 660 | -5.2 | Dominant | 8,100 | (Dominant - 22,000) | 100 | 100 |
| CCB | 350 | 0.4 | 1,000 | 9,400 | (Dominant - 30,000) | 100 | 100 |
| ACEI | 180 | -0.1 | Dominant | 29,000 | (7,000- 62,000) | 100 | 100 |
| BB | 120 | 2.3 | 18,000 | 110,000 | (27,000 - 580,000) | 53 | 93 |
| Statin | 160 | 4 | 24,000 | 69,000 | (20,000 - 130,000) | 91 | 100 |
| ARB | 160 | 6.9 | 43,000 | 140,000 | (70,000 - 280,000 ) | 28 | 99 |

Numbers are rounded to two significant digits. D = diuretic; CCB = Calcium channel blocker; ACEi = Angiotensin converting enzyme inhibitor; BB = Beta blocker; ARB= angiotensin receptor blocker.

* Drug costs used in base case analysis are the lowest annual costs (for generic versions of the drugs) whereas ranges used in the probabilistic uncertainty analysis are between the lowest and the highest costs shown in the Ministry of Public Health webpage.

**Table 4:** Incremental cost, DALYs averted and cost-effectiveness ratio in expansion pathway of optimal mix of interventions by level of cardiovascular risk

| Priority | Intervention | Base case analysis* | | | Probabilistic analysis* | | | |
|---|---|---|---|---|---|---|---|---|
| | | | | | Median Cost-effectiveness ratio (Baht/DALY | 95% uncertainty range (Baht/DALY) | Probability (%) falling below: | |
| | | Net cost (billions Baht) | Health gain ('000s DALYs) | Cost-effectiveness ratio (Baht/DALY) | | | 1 x GDP | 3 x GDP |
| 1 | D+CCB+ACEi in 20%+ | -9.4 | 570 | dominant | dominant | (dominant - dominant) | 100 | 100 |
| 2 | add D+CCB+ACEi in 10-19% | -7.3 | 720 | dominant | dominant | (dominant – 7,000) | 100 | 100 |
| 3 | add D+CCB+ACEi in 5-9% | -1.4 | 890 | dominant | 6,300 | (dominant - 19,000) | 100 | 100 |
| 4 | add statin in 20%+ | 4.2 | 92 | 45,000 | 130,000 | (50,000 - 220,000) | 36 | 100 |
| 5 | add statin in 10-19% | 10 | 120 | 84,000 | 210,000 | (97,000 - 350,000) | 5 | 95 |
| 6 | add statin in 5-9% | 19 | 150 | 130,000 | 310,000 | (150,000 - 490,000) | 0 | 57 |

Numbers are rounded to two significant digits.

D = diuretic; CCB = Calcium channel blocker; ACEi = Angiotensin converting enzyme inhibitor;

*Drug costs used in base case analysis are the lowest annual costs (for generic versions of the drugs) whereas ranges used in the probabilistic uncertainty analysis are between the lowest and the highest costs shown in the Ministry of Public Health webpage.

**Figure 1:** Cardiovascular disease prevention model.

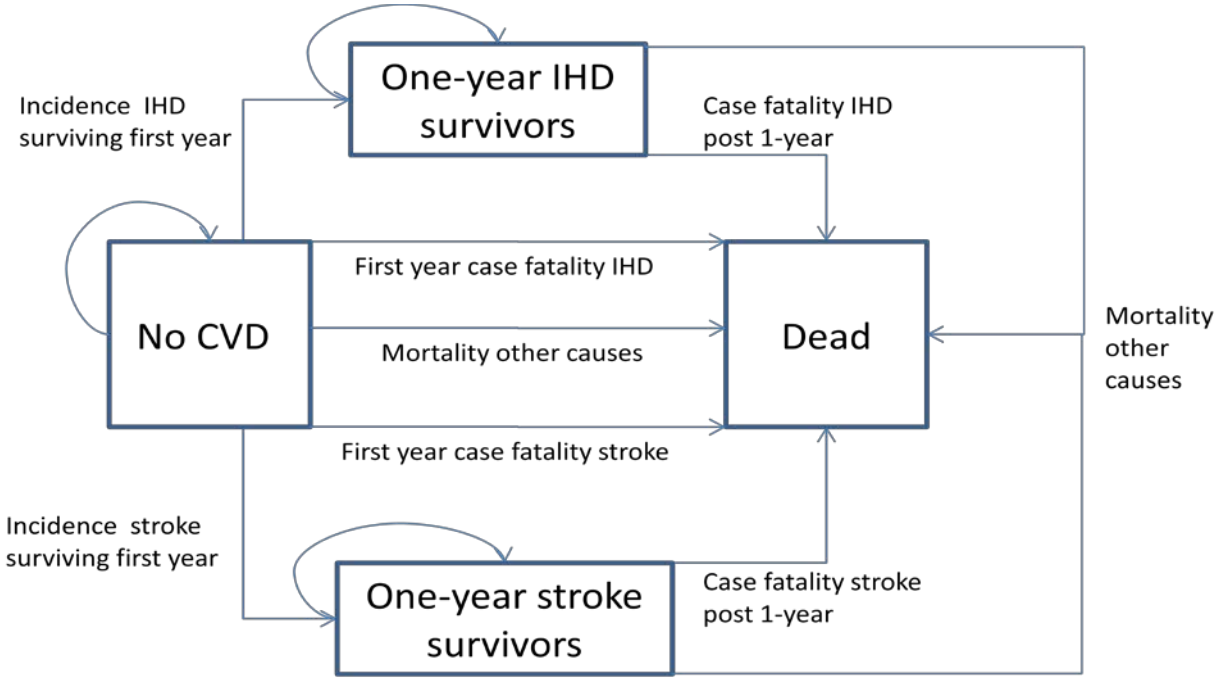
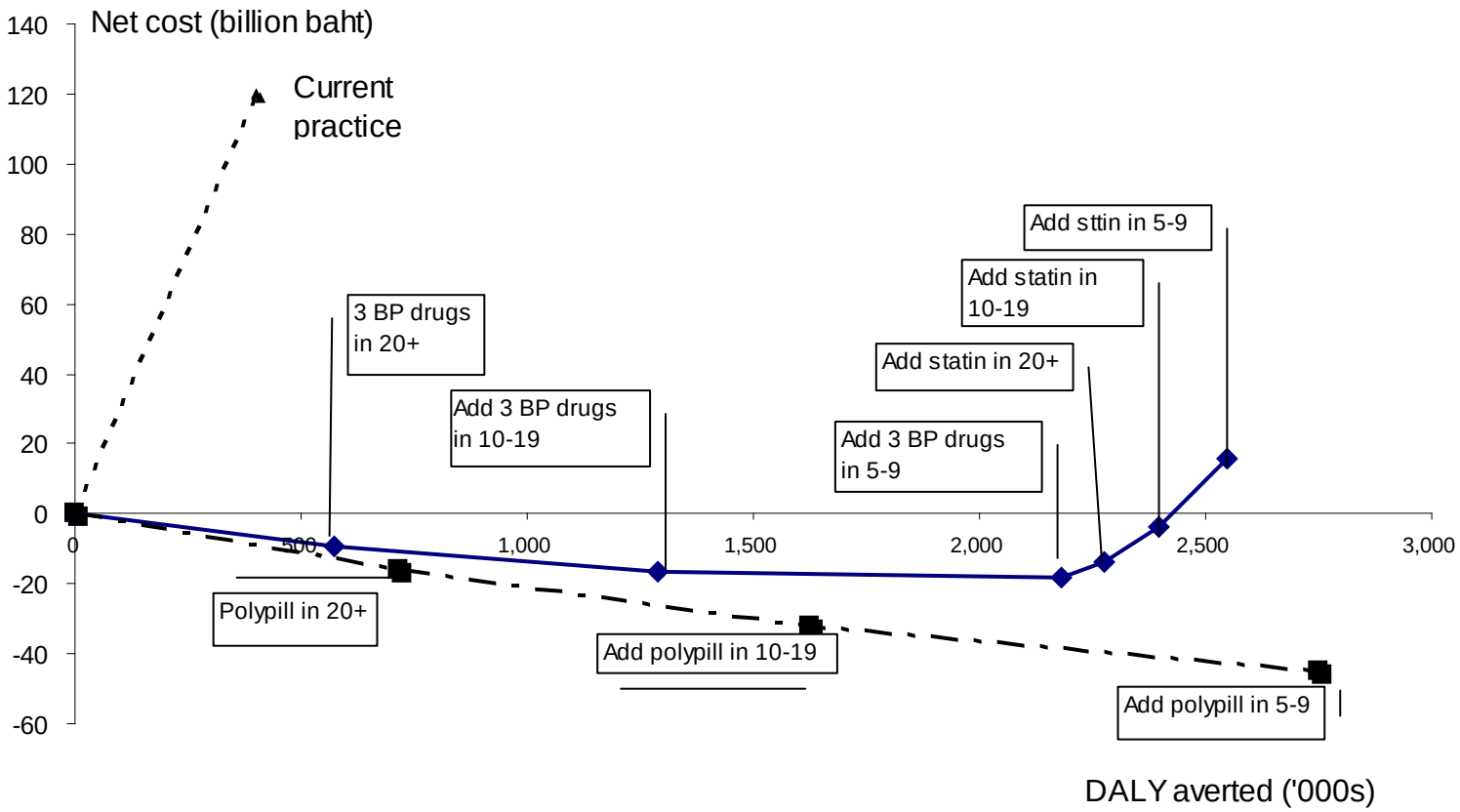


**Figure 2:** Intervention pathway of life time DALYs averted and total costs associated with the ideal mix of blood pressure- and cholesterol-lowering drugs for cardiovascular disease prevention in Thailand




Drug costs used in base case analysis are the lowest annual costs (for generic versions of the drugs) whereas ranges used in the probabilistic uncertainty analysis are between the lowest and the highest costs shown in the Ministry of Public Health webpage.

**Appendix: Modeling the Cost-Effectiveness of cardiovascular disease drugs in Thailand**

The mathematical model used to assess the cost-effectiveness of pharmaceutical interventions to reduce the burden of cardiovascular disease (CVD) is a Markov model with four explicit health states: alive without CVD, alive with ischaemic heart disease (IHD), alive with stroke and death. Transitions between these mutually exclusive health states occur at the end of discrete yearly cycles (Figure 1, main article). At each cycle the population cohort without CVD can transit to either alive with IHD or alive with stroke or dead, or remain in the alive without CVD state.

To run the model the following input parameters are required:

*Disease epidemiology and disability:*

1) incidence of first-ever IHD and stroke events by age and sex;
2) 28-day case fatality rates (CFRs) for IHD and stroke and excess mortality rates in IHD or stroke survivors;
3) disability weights (DW) for IHD, stroke and all other causes of disability; and
4) rates of mortality due to other causes,

*Effects and costs of intervention, current practice and doing nothing scenarios:*

5) effects of interventions on the incidence of IHD and stroke (measured as relative risks of IHD or stroke compared to placebo);
6) cost of each intervention including cost of hospital visits and laboratory tests; and
7) cost of IHD or stroke treatment to be used as cost-offset in an analysis from the health system perspective (cost-offsets are the costs that are prevented if the interventions are used).

*Population subgroup*

8) the relative risk of IHD/stroke compared to the average risk of IHD/stroke for the people of the same age and sex group.

**Disease epidemiology**

Disease parameters (incidence, 28-day case fatality rates and case fatality rates for 28-day survivors of ischaemic heart disease or stroke and background mortality) vary by age and sex. These parameters were estimated using best available local and international data.

***Incidence of first-ever cardiovascular events***

IHD and stroke incidence by age and sex was used to calculate the probability that an individual will transit from the alive without CVD state to the health states with IHD or stroke or to the dead state, or remain free of the CVD.

To estimate the incidence of IHD and stroke we used data from the 2004 hospital admission dataset (obtained from the Ministry of Public Health) and a cause of death study for Thailand in 2005, which was also carried out as part of the Setting Priorities Using Information on Cost-Effectiveness (SPICE) project [1-4]. The first dataset reports the total number of hospital admissions in 2004, by disease, age and sex. To account for underreporting of admissions (as private hospital admissions were not well covered) we inflated this number to match the self reported number of admissions for all causes, as surveyed in 2005, by age, sex and hospital type (obtained from the National Statistics Office, Bangkok, Thailand). Admissions for ischaemic heart disease and stroke discharged alive were multiplied by the proportion of first-ever IHD/stroke from a UK prospective cohort study [5] to estimate the incidence of non-fatal IHD/stroke in persons free of these diseases. There is no direct estimate of this proportion available in Thailand.

The second dataset, the cause of death study was used to estimate the incidence of fatal IHD/stroke. The study corrected vital registration data from 2005 by verbal autopsy interviews of 12,000 deaths complemented by medical record review in a subset of deaths that occurred in hospital. [1-4] The number of deaths due to IHD/stroke for which relatives reported no history of treatment for IHD/stroke during the verbal autopsy interview was assumed to approximate the incidence of fatal, first ever, IHD/stroke events [6]. Total incidence of IHD/stroke is equal to the sum of incidence of non-fatal IHD/stroke and incidence of fatal IHD/stroke and shown in Table 1, by age and sex.

**Appendix Table 1:** Annual incidence (per 100,000) of stroke and ischemic heart disease in the Thai population, 2004-2005

| Age (years) | Stroke | | Ischemic heart disease | |
|---|---|---|---|---|
| | Male | Female | Male | Female |
| 30-34 | 19 | 10 | 15 | 9 |
| 35-39 | 49 | 34 | 26 | 14 |
| 40-44 | 92 | 69 | 59 | 26 |
| 45-49 | 169 | 107 | 97 | 50 |
| 50-54 | 279 | 157 | 160 | 93 |
| 55-59 | 423 | 254 | 254 | 156 |
| 60-64 | 658 | 420 | 360 | 261 |
| 65-69 | 884 | 650 | 550 | 432 |
| 70-74 | 1,191 | 912 | 642 | 603 |
| 75-79 | 1,577 | 1,269 | 805 | 852 |
| 80-84 | 1,838 | 1,941 | 1,066 | 1,196 |
| 85+ | 2,895 | 2,851 | 1,716 | 2,408 |

***Short term case fatality rate***

As CVD results in high short term fatality, we separated the calculation of the total number of CVD deaths in the first year into those that occur within the first 28 days and those that survive the first 28 days but die during the following 11 months of the first year. This leaves the number of people alive with IHD/stroke post first year. The short term case fatality rate used in this cost-effectiveness modeling is equal to the number of fatal, incident cases divided by the total number of incident IHD/stroke cases (Table 2).

***Long term case fatality rate***

To calculate the case fatality in 28-day survivors of IHD and stroke (long term case fatality rate) we first enforced consistency in the epidemiological data using the DisMod II program.[7] Remission from IHD and stroke was set to zero, and data inputs were the incidence of non fatal, first-ever IHD/stroke described above and mortality rates (after subtracting the mortality within the first 28 days) from the SPICE cause of death study (Table 2).

**Appendix Table 2:** 28-day (% of new cases that die in a 28-day period) and long-term case fatality rate of stroke and ischemic heart disease in the Thai population, 2004-2005

| **Age (years)** | **Proportion fatal at 28-days** | | | | **Long term case fatality rate** | | | |
|---|---|---|---|---|---|---|---|---|
| | **Stroke** | | **Ischemic heart disease** | | **Stroke** | | **Ischemic heart disease** | |
| | **Male** | **Female** | **Male** | **Female** | **Male** | **Female** | **Male** | **Female** |
| 30-34 | 0.34 | 0.21 | 0.43 | 0.21 | 0.12 | 0.05 | 0.15 | 0.00 |
| 35-39 | 0.28 | 0.21 | 0.17 | 0.19 | 0.10 | 0.04 | 0.12 | 0.00 |
| 40-44 | 0.17 | 0.21 | 0.36 | 0.22 | 0.06 | 0.02 | 0.09 | 0.02 |
| 45-49 | 0.18 | 0.21 | 0.33 | 0.25 | 0.04 | 0.02 | 0.09 | 0.04 |
| 50-54 | 0.19 | 0.18 | 0.35 | 0.24 | 0.03 | 0.02 | 0.09 | 0.04 |
| 55-59 | 0.17 | 0.15 | 0.33 | 0.20 | 0.03 | 0.02 | 0.08 | 0.04 |
| 60-64 | 0.23 | 0.17 | 0.22 | 0.20 | 0.03 | 0.02 | 0.06 | 0.04 |
| 65-69 | 0.20 | 0.22 | 0.39 | 0.26 | 0.03 | 0.02 | 0.06 | 0.04 |
| 70-74 | 0.27 | 0.27 | 0.33 | 0.24 | 0.03 | 0.03 | 0.06 | 0.04 |
| 75-79 | 0.37 | 0.32 | 0.35 | 0.31 | 0.04 | 0.04 | 0.06 | 0.05 |
| 80-84 | 0.35 | 0.51 | 0.38 | 0.34 | 0.04 | 0.06 | 0.07 | 0.06 |
| 85+ | 0.47 | 0.60 | 0.46 | 0.52 | 0.06 | 0.13 | 0.08 | 0.10 |

***Disease disability***

Disability weights (DW) for IHD and stroke were obtained from the study on burden of disease conducted for Thailand in 1999. DWs for IHD were 0.10 and 0.06 for males and females,

respectively.[8] For stroke, they were 0.30 and 0.38 for males and females, respectively.[8]

***Mortality due to other causes***

Rates of mortality due to other causes were also based on the cause of death study for Thailand in 2005. They were calculated as the difference between total mortality, by age and sex, and the mortality due to IHD or stroke from the same study (Table 3) [1-4].

**Appendix Table 3:** Annual mortality rates of stroke ischemic heart disease and other causes in the Thai population, 2005

| **Age (years)** | **Stroke** | | **Ischemic heart disease** | | **Mortality due to other causes** | |
|---|---|---|---|---|---|---|
| | **Male** | **Female** | **Male** | **Female** | **Male** | **Female** |
| 30-34 | 0.0001 | 0.0000 | 0.0001 | 0.0000 | 0.0043 | 0.0019 |
| 35-39 | 0.0002 | 0.0000 | 0.0001 | 0.0000 | 0.0049 | 0.0021 |
| 40-44 | 0.0003 | 0.0001 | 0.0003 | 0.0000 | 0.0058 | 0.0025 |
| 45-49 | 0.0005 | 0.0003 | 0.0006 | 0.0002 | 0.0066 | 0.0031 |
| 50-54 | 0.0009 | 0.0004 | 0.0010 | 0.0004 | 0.0078 | 0.0042 |
| 55-59 | 0.0013 | 0.0007 | 0.0015 | 0.0006 | 0.0103 | 0.0064 |
| 60-64 | 0.0026 | 0.0013 | 0.0017 | 0.0010 | 0.0145 | 0.0096 |
| 65-69 | 0.0035 | 0.0015 | 0.0037 | 0.0021 | 0.0206 | 0.0148 |
| 70-74 | 0.0058 | 0.0041 | 0.0042 | 0.0030 | 0.0303 | 0.0215 |
| 75-79 | 0.0101 | 0.0073 | 0.0055 | 0.0050 | 0.0455 | 0.0332 |
| 80-84 | 0.0125 | 0.0168 | 0.0078 | 0.0081 | 0.0715 | 0.0515 |
| 85+ | 0.0223 | 0.0290 | 0.0135 | 0.0200 | 0.1151 | 0.0959 |

**Absolute cardiovascular risk category**

The cost-effectiveness of each intervention was assessed for distinct population subgroups based on age, sex and the CVD risk over the next 10 years. Risks were estimated based on the individual's risk factors using risk prediction equations we developed for Thailand. The equations were based on calibration of the Framingham equations [9] taking into account the contemporary incidence of IHD and stroke with separate equations for males and females and for IHD and stroke. Risk factors included were age, systolic blood pressure, total cholesterol, diabetes mellitus and smoking obtained from the third National Health Examination Survey in 2004 (NHES III) [10]. The contemporary incidence of IHD or stroke was used for the calibration of 10-year

absolute risk. The target population is divided into 8 subgroups based on age, sex and 10-year risk (Table 4).

**Appendix Table 4:** Target population by age, sex and 10-year cardiovascular disease risk, Thailand, 2004

| Age (years) | Ten-year cardiovascular disease risk | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | <5% | | 5-9.9% | | 10-19.9% | | 20+% | |
| | Male | Female | Male | Female | Male | Female | Male | Female |
| 30-34 | 2,360,120 | 2,468,216 | 0 | 0 | 0 | 0 | 0 | 0 |
| 35-39 | 2,308,172 | 2,429,539 | 10,980 | 2,711 | 0 | 0 | 0 | 0 |
| 40-44 | 2,072,184 | 2,237,981 | 62,607 | 12,367 | 1,220 | 436 | 0 | 0 |
| 45-49 | 1,511,656 | 1,841,455 | 203,692 | 94,316 | 16,658 | 625 | 1,522 | 0 |
| 50-54 | 725,271 | 1,248,112 | 575,356 | 224,517 | 68,737 | 50,205 | 5,457 | 1,506 |
| 55-59 | 145,976 | 563,118 | 591,865 | 406,530 | 243,206 | 152,994 | 18,497 | 11,327 |
| 60-64 | 19,711 | 146,611 | 341,121 | 452,248 | 356,047 | 228,061 | 60,910 | 65,150 |
| 65-69 | 171 | 15,399 | 113,585 | 309,207 | 384,538 | 322,910 | 149,347 | 131,991 |
| 70-74 | 0 | 0 | 24,209 | 85,981 | 242,320 | 315,165 | 199,309 | 191,592 |
| 75-79 | 0 | 0 | 1,940 | 6,940 | 92,467 | 144,467 | 192,068 | 233,730 |
| 80-84 | 0 | 0 | 0 | 0 | 32,314 | 42,919 | 220,191 | 303,765 |
| 85+ | 0 | 0 | 0 | 0 | 0 | 1,228 | 100,926 | 170,273 |
| Total | 9,143,261 | 10,950,431 | 1,925,355 | 1,594,817 | 1,437,507 | 1,259,010 | 948,227 | 1,109,334 |

**Effects and costs of intervention, current practice and doing nothing scenarios**

***Current practice***

This study used the generalized cost-effectiveness analysis (GCEA) approach. GCEA is a tool to assist in healthcare resource allocation by identifying which intervention or intervention mix is most cost-effective compared to a scenario in which no interventions are used. It allows explicit assessment of the (in-)efficiency of current practice [11]. To assess the cost-effectiveness of current practice, we took 5 steps that follow.

First, we estimated the proportion currently using blood pressure lowering drugs and/or cholesterol lowering drugs among the target population classified by ten-year CVD risk and sex. This information was obtained from the analysis of the NHES III data. NHES III reported only the proportions of people taking the whole group of blood pressure lowering drugs or cholesterol lowering drugs, but not what specific drugs were used (Table 5) [10].

**Appendix Table 5:** Proportion using blood pressure and/or cholesterol lowering drugs in 2004 (%) by 10-year risk category: Thailand NHES III

| **Ten-year absolute risk (%)** | | **<5** | **5-9.9** | **10-19.9** | **>=20** | **Total** |
|---|---|---|---|---|---|---|
| **Male** | *Cholesterol only* | 0.69 | 2.28 | 2.05 | 1.1 | 1.09 |
| | *Blood pressure only* | 1.53 | 7.92 | 12.36 | 12.38 | 5.08 |
| | *Both* | 0.25 | 0.94 | 1.7 | 1.64 | 0.7 |
| | *All cholesterol* | 0.94 | 3.22 | 3.75 | 2.74 | 1.79 |
| | *All blood pressure* | 1.78 | 8.86 | 14.06 | 14.02 | 5.78 |
| **Female** | *Cholesterol only* | 0.86 | 1.88 | 2.47 | 1.43 | 1.16 |
| | *Blood pressure only* | 3.57 | 16.63 | 20.04 | 17.56 | 8.1 |
| | *Both* | 0.36 | 2.15 | 2.44 | 2.35 | 0.97 |
| | *All cholesterol* | 1.22 | 4.03 | 4.91 | 3.78 | 2.13 |
| | *All blood pressure* | 3.93 | 18.78 | 22.48 | 19.91 | 9.07 |

Second, we assessed the proportions using drug subclasses among those taking blood pressure lowering drugs or cholesterol lowering drugs. Five subclasses of blood pressure lowering drugs – thiazide diuretics (D), beta blockers (BB), calcium channel blockers (CCB), angiotensin

converting enzyme inhibitors (ACEI), angiotensin receptor blockers (ARB)–were used. Similarly, cholesterol lowering drugs were divided into statins and non-statins (Ezetimibe). The proportions of these drug subclasses were estimated using the information on drug prescription/dispensing in milligrams for the year 2009 collected at two community hospitals and the outpatient departments of one provincial and one teaching hospital. The amount of each drug in milligrams was translated into number of people using the drug by dividing it by a defined daily dose (DDD). DDD is defined by the World Health Organisation as *the assumed average maintenance dose per day for a drug used for its main indication in adults* [12]. For example, DDD of chlorothiazide (thiazide diuretics) is 0.5 gram (500 milligram). The proportions of patients taking each drug subclass were calculated for each healthcare setting and extrapolated at the national level using information on the proportions of outpatient visits at primary care centres (52%) and hospital outpatient departments (48%) between 2003 and 2007**(**obtained from the National Statistics Office). The proportions of generic and non-generic types for each drug subclass were also assessed (Table 6).

**Appendix Table 6:** Proportion using blood pressure lowering and cholesterol drug subclasses and corresponding generic type, by health centre and overall (%)

| **Outpatient visit/Drug use** | **Primary care centre** | | **Hospital outpatient department** | | **National estimate** | |
|---|---|---|---|---|---|---|
| Proportionof | Each subclass | Generic | Each subclass | Generic | Each subclass | Generic |
| **Of all blood pressure lowering drugs used** | | | | | | 82 |
| Thiazide diuretics | 32 | 100 | 10 | 98 : 2 | 22 | 100 |
| *β-blockers* | 11 | 100 | 17 | 87 : 13 | 14 | 92 |
| *Calcium channel blockers* | 19 | 100 | 38 | 54 : 46 | 28 | 70 |
| *Angiotensin converting enzyme inhibitors* | 37 | 100 | 21 | 83 : 17 | 29 | 94 |
| *Angiotensin receptor blockers* | 0 | 100 | 15 | 9 : 91 | 7 | 9 |
| **Of all cholesterol lowering drugs** | | | | | | 75 |
| *Statin* | 100 | 100 | 94 | 51 : 49 | 97 | 77 |
| *Ezetimibe* | 0 | 0 | 6 | 0 : 100 | 3 | 0 |

Third, we estimated the proportions using the combination of generic and/or non-generic blood pressure and cholesterol lowering drugs among those reporting taking both groups of drugs together. A combined proportion was equal to the multiplication of the proportions of the two drug components (Table 7).

**Appendix Table 7:** Proportion using combined (generic and non generic) blood pressure and cholesterol lowering drugs among those reporting taking the two drug groups together, Thailand 2004

| **Drug combination** | **Proportion (%)** |
|---|---|
| Generic cholesterol lowering drugs (generic) + Generic BP lowering drugs(generic) | 62 (=82 x 75) |
| Generic cholesterol lowering drugs (generic) + Non generic BP lowering drugs(non generic) | 13 (=82 x 25) |
| cholesterol lowering drugs (non generic) + Generic BP lowering drugs(generic) | 20 (=18 x 75) |
| Non generic cholesterol lowering drugs + Non generic BP lowering drugs | 4 (=18 x 25) |

Fourth, we estimated the average yearly cost of current practice by adding the weighted yearly cost of the three drug components currently used, blood pressure lowering drugs only, cholesterol lowering drugs only, and both blood pressure and cholesterol lowering drugs together. Weighted yearly cost of the each drug component was assessed as a sum of weighted yearly costs of all drug subclasses, or combinations. Weighted yearly cost of each drug subclass/combination was calculated by the multiplication of proportion using its related components (blood pressure lowering drugs only, or cholesterol lowering drugs only, or both groups), proportion using each drug subclass/combination, proportion using generic or non generic, and cost of drug subclass/combination. For example, the weighted yearly cost of generic thiazide diuretics for men was equal to the yearly cost of 687 baht multiplied with proportion using blood pressure lowering drugs only (shown in Table 5) ,proportion using thiazide diuretics, and proportion using generic type of thiazide diuretics (shown in Table 6)(0.0508 x 0.22 x 1 = 1.1%). Table 8 below illustrates how the average cost of current practice was estimated for Thai men. Total cost of current practice, for males and females separately, was the sum of weighted yearly costs of all drug components (Main document Table 2).

**Appendix Table 8:** The calculation of cost of current practice

| **Overall cost of current practice for Thai men** | **Drug subclass/combination** | **Yearly cost (baht)** | **% of individuals receiving treatment** (= P using drug group x P using drug class x P using (non) generic), p = proportion | **Weighted yearly cost (baht)** (= % individual receiving drug component x yearly cost) |
|---|---|---|---|---|
| Cholesterol lowering drugs only(generic) | *Statin* | 1,372 | 0.82 | 11.23 |
| | *Ezetimibe* | - | 0.00 | - |
| Cholesterol lowering drugs only(non-generic) | *Statin* | 21,304 | 0.24 | 50.90 |
| | *Ezetimibe* | 19,720 | 0.03 | 6.35 |
| BP lowering drugs only(generic) | *D* | 687 | 1.11 | 7.50 |
| | *BB* | 778 | 0.65 | 5.04 |
| | *CCBs* | 953 | 1.00 | 9.51 |
| | *ACEi* | 748 | 1.41 | 10.52 |
| | *ARB* | 1,594 | 0.03 | 0.55 |
| BP lowering drugs only(non-generic) | *D* | 1,757 | 0.00 | 0.08 |
| | *BB* | 7,797 | 0.05 | 4.19 |
| | *CCBs* | 8,980 | 0.42 | 37.87 |
| | *ACEi* | 11,635 | 0.09 | 10.24 |
| | *ARB* | 10,325 | 0.33 | 34.47 |
| Both Cholesterol and BP lowering drugs | *Cholesterol lowering drugs (generic)+BP lowering drugs(generic)* (62%) | 1,744 | 0.43 | 7.54 |
| | *Cholesterol lowering drugs (generic)+BP lowering drugs (non-generic)* (13%) | 11,321 | 0.09 | 10.57 |
| | *Cholesterol lowering drugs (non-generic)+BP lowering drugs(generic)* (20%) | 20,093 | 0.14 | 28.78 |

| | | | |
|---|---|---|---|
| *Cholesterol lowering drugs (non-generic)+BP lowering drugs (non-generic* (4%) | 29,670 | 0.03 | 9.17 |

| | |
|---|---|
| Average cost of drugs for current practice per person per year for men (= sum of all weighted yearly cost) | 245 |
| Average cost of laboratory test for men | 23 |
| Average cost of hospital visit for men | 26 |
| Total cost of current practice for men | 294 |
| Average cost of drugs for current practice per person per year for women (calculation not shown) | 342 |
| Average cost of laboratory test for women(calculation not shown) | 33 |
| Average cost of hospital visit for women (calculation not shown) | 38 |
| Total cost of current practice for women (calculation not shown) | 414 |
| Average cost of current practice for both sexes (calculation not shown) | 354 |

Finally, to estimate the overall effects of current practice we first calculated the effects of blood pressure drugs as one group, cholesterol drugs as another group and the combination of these as a third group. The effects of cholesterol lowering drugs were the weighted effects of statin and ezetimibe with proportions of use among those who reported using cholesterol lowering drugs of 0.97 vs. 0.03 (shown in Table 5). For example, if the RR of statins on ACS incidence from a clinical trial was 0.77, and of ezetimibe 0.67, the weighted RR on ACS of cholesterol lowering drugs was equal to (0.77 x 0.97) + (0.67 x 0.03) = 0.77. Estimation of the effect of the blood pressure lowering drug group was calculated similarly using the proportions of use in Table 5. Weighted RRs for IHD, ischaemic stroke (IS), and haemorrhagic stroke (HS) for each drug group due to current practice were calculated using the formula: weighted RR = RR x (proportion using the drug) + (100% - proportion using the drug(s)). The overall effect of current practice is the sum of the weighted RRs of all three drug groups. We assumed that those who reported taking medications in the last two weeks in NHES III were adherent to the treatment. Table 1 in the main document shows effects of current practice.

***Do nothing' scenario***

To calculate the IHD and stroke incidence rates under the null scenario (doing nothing) the resulting weighted RR for current practice is applied to the incidence of IHD or stroke under current practice to calculate the incidence of disease under the null scenario.

$$CVD\ incidence_{(null)} = CVD\ incidence_{(current)} / Weighted\ RR$$

***Intervention scenario***

The cost of implementation of interventions is composed of costs of visits to health centres, laboratory tests, and drugs. The annual cost of visiting hospitals/health centres was equal to the sum of the cost of one visit to a specialist and two visits to general practitioners for most drugs, except for the polypill for which only one visit to a specialist and no laboratory tests were assumed (Table 1, main document). The polypill is believed to be advantageous because it is convenient to take and therefore enhances adherence, besides having fewer side effects and not requiring repeated measurement of risk factor levels.[13] Costs of visits to a general practitioner are estimated at 160 Baht for the polypill and 376 Baht for other drugs. Cost of laboratory test for a statin was based on a test on serum lipids and liver enzymes (456 Baht per year) [14]. Costs of laboratory test for blood pressure lowering drugs are based on the tests for urea and electrolytes (261 baht per year). For those who discontinued using the medication, costs of discontinuation are estimated as the sum of the costs of 1 month of drug supply, 1 laboratory test and 1 visit to a health centre. Uncertainty ranges of these costs used in the probabilistic sensitivity analysis were varied by 25% in each direction using a uniform distribution (Table 9).

Since the interventions are for primary prevention of IHD and stroke, only those who survive without IHD and stroke at the beginning of each cycle are eligible to receive the intervention. The total cost of interventions for the cohort is the result of the number of non-IHD and non-stroke individuals multiplied with the yearly cost of the intervention as shown in the following equation.

*Cost of intervention = number of non-IHD and non-stroke x yearly cost of intervention per person*

Effects of interventions were obtained from systematic reviews and meta-analyses reported in the literature [15-17]. A lognormal distribution was assumed for intervention effects in the probabilistic sensitivity analysis (Table 10).

***Cost-offsets***

Cost-offsets are the costs of treating disease that can be avoided by implementing the intervention, with doing nothing as the comparator. The cost for ischaemic heart disease treatment was reported at 110,682 baht for the first month, 56,468 baht for the remainder of the first year, and 34,150 baht annually thereafter [18]. Stroke treatment on average cost 47,798 baht for the first month, 12,534 baht for the remainder of the first year, and 9,558 baht annually thereafter (obtained from the Prasat Neurology Institute in Bangkok). The costs of IHD and stroke treatment used in the probabilistic sensitivity analysis use a uniform distribution of ± 25%.

**Running the model**

To run the model for each population subgroup (sex-specific 10-year CVD risk group) two data inputs were required for the calculation of IHD and stroke incidence:

1) the mean of IHD/stroke risks calculated for each individual within a risk category relative to the average for the whole population of the same age and sex (relative risk),
2) the number of people in this age-sex-risk category.

The risk of IHD or stroke relative to the average for the whole age-sex-risk group is multiplied with the average IHD and stroke incidence for each age and sex group under the present situation (current practice) to produce the incidence of IHD and stroke specific to this group as shown below:

*Group-specific incidence = relative risk x average incidence*

The model then calculates the total number of people in the target population who develop IHD or stroke, die from IHD or stroke within the first 28 days and the first year of disease or remain non-diseased at the end of each cycle. When the target group reaches the age of 100 years, the model strops running and the number of years lived by this cohort is summed. The cost and number of disability adjusted life years (DALYs) averted for each population subgroup can then be calculated for the scenario under analysis.

***Number of disability adjusted life years averted***

Mathematically, the number of people transiting to the next state(s) is equal to the number of people in the starting state multiplied with the corresponding transition probability(s). For example, the number of people dying from IHD during the first 28 days is equal to the multiplication of number of people in the state without CVD at the beginning of the cycle, the incidence of IHD, and the 28-day case fatality rate. The number of people dying from IHD during the following 11 months of the cycle is equal to the number of people surviving the first 28 days after an IHD event multiplied with the long term case fatality rate and a factor of 11/12. The total number of deaths due to IHD during the two periods is subtracted from the number of incident IHD cases for that year, which gives the number of people remaining alive with IHD at the end of the first year. Similarly, the number of people remaining alive without IHD/stroke post first year equals the total number of people in this state at the beginning of the cycle after subtracting the total number of incident IHD and stroke cases that occur during the 1-year period, and the number of people dying from all other causes. Transitions between states with IHD/stroke post first year and dead state are estimated based on the number of people with IHD/stroke at the beginning of the cycle multiplied with the long term case fatality rate plus the number of IHD/stroke cases dying from other causes.

Life years in the model are adjusted for health loss due to disability from IHD, stroke and all other diseases as follows:

For those who survive without IHD and stroke,

*Health-adjusted life years = life years x (1- DW from other diseases)*

For those who survive with IHD,

*Health-adjusted life years = life years x (1- DW from other diseases) x (1- DW from IHD)*

And, for those who survive with stroke,

*Health-adjusted life years = life years x (1- DW from other diseases) x (1- DW from stroke)*

This enables calculating the health-adjusted life years gained or DALYs averted by the intervention from the situation where the intervention is not used. The number of DALYs averted by an intervention equals the difference between the number health life years (HLYs) lived in the intervention scenario and the number of HLYs under the "do nothing" scenario.

***Cost- effectiveness ratio***

The cost-effectiveness ratio (CER) for each intervention is calculated by dividing the total cost occurring under the use of intervention minus the cost under the null scenario by the number of DALYs averted by that cohort compared to doing nothing. This is called average cost-effectiveness ratio (ACER):

$$ACER = [Net\ cost_{(intervention)} - Net\ cost_{(null)}]/[DALY_{(intervention)} - DALY_{(null)}]$$

Net cost is equal to the cost of intervention implementation plus the cost of disease treatment under each scenario. An incremental cost effectiveness ratio (ICER) for the intervention compared to another intervention is calculated using the following equation.

$$ICER = [Net\ cost_{(intervention2)} - Net\ cost_{(intervention1)}]/[DALY_{(intervention2)} - DALY_{(intervention1)}]$$

## References


[1] Rao C, Porapakkham Y, Pattaraarchachai J, et al. Verifying causes of death in Thailand: rationale & methods for empirical investigation. Popul Health Metr. In press.

[2] Porapakkham Y, Rao C, Pattaraarchachai J, et al. The burden of premature mortality in Thailand, 2005: new estimates from corrected vital registration. Popul Health Metr. In press.

[3] Polprasert W, Rao C, Adair T, et al. Cause of death ascertainment for deaths that occur outside hositals in Thailand: application of verbal autopsy methods. Popul Health Metr. In press.

[4] Pattaraarchachai J, Rao C, Polprasert W, et al. Cause-specific mortality patterns among hospital deaths in Thailand. Popul Health Metr. In press.

[5] Rothwell PM, Coull AJ, Silver LE, et al. Population-based study of event-rate, incidence, case fatality, and mortality for all acute vascular events in all arterial territories (Oxford Vascular Study). Lancet. 2005;19(9499):1753-4.

[6] The working group for improving causes of deaths in Thailand 2005-2008. Improving causes of deaths in Thailand 2005-2008 (in Thai). Bangkok: Ministry of Public Health, 2009.

[7] Barendregt J, van Oortmarssen G, Vos T, Murray C. A generic model for the assessment of disease epidemiology: the computational basis of DisMod II. Popul Health Metr. 2003;1(1):4.

[8] Bundhamcharoen K, Teerawatananon Y, Vos T, eds. Burden of Disease and Injuries in Thailand. Bangkok: Ministry of Public Health (in Thai), 2002.

[9] Anderson KM, Wilson PW, Odell PM, Kannel WB. An updated coronary risk profile. A statement for health professionals. Circulation. 1991;83:356 - 62.

[10] Aekplakorn W, Abbott-Klafter J, Khonputsa P, et al. Prevalence and management of prehypertension and hypertension by geographic regions of Thailand: the Third National Health Examination Survey, 2004. J Hypertens. 2008;26(2):191-8.

[11] Tan-Torres Edejer T, Baltussen R, Adam T, et al., eds. Making Choices in Health: WHO Guide to Cost-Effectiveness Analysis. Geneva: World Health Organization, 2003.

[12] World Health Organization Collaborating Centre for Drug Statistics Methodology. Defined daily dose. Available from: http://www.whocc.no/ddd/definition_and_general_considera/.[Accessed27 June 2010]

[13] Wald NJ, Law MR. A strategy to reduce cardiovascular disease by more than 80%. BMJ. 2003;326:1419.

[14] The Faculty of Medical Technology. Medical Technology Service Price (in Thai). Available from: http://www.ams.cmu.ac.th/depts/amscentre/amscentre/laplist.html. [Accessed 2 April, 2009 ]

[15] Cholesterol Treatment Trialists' (CTT) Collaborators. Efficacy and safety of cholesterol-lowering treatment: prospective meta-analysis of data from 90 056 participants in 14 randomised trials of statins Lancet. 2005;366(9493):1267-78.

[16] Psaty BM, Smith NL, Siscovick DS, et al. Health outcomes associated with antihypertensive therapies used as first-line agents. A systematic review and meta-analysis. JAMA. 1997;277:739 - 45.

[17] Psaty BM, Lumley T, Furberg CD, et al. Health Outcomes Associated With Various Antihypertensive Therapies Used as First-Line Agents: A Network Meta-analysis. JAMA. 2003;289(19):2534-44.

[18] Anukoolsawat P, Sritara P, Teerawattananon Y. Costs of Lifetime Treatment of Acute Coronary Syndrome at Ramathibodi Hospital. Thai Heart Journal. 2006;19:132-43.

[19] Aekplakorn W, Abbott-Klafter J, Premgamone A, et al. Prevalence and management of diabetes and associated risk factors by regions of Thailand: Third National Health Examination Survey 2004. Diabetes Care. 2007;30(8):2007-12.