Recalibration of the Framingham Equations in the Thai Population

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Abstract

We derived equations for predicting cardiovascular disease (CVD) risks for Thai men and women, separately, over a specific time period using associations between risk factors and CVD events from the Framingham cohort study. The equations were recalibrated against the cumulative risks estimated for Thailand. Equations were developed separately for predicting risks of ischemic heart disease (IHD) and stroke. Recalibration of the Framingham equations reduced the CVD risks predicted for Thai men by 97% and for Thai women by 10%. The correction was largest at younger ages. In older women, recalibration increased the predicted risk. When compared with an existing equation for Thai men our recalibrated Framingham equation produced similar predictions for CVD risks over 8 years. However, the recalibrated Framingham equations are more flexible because they can be used for predicting risks over any time span and for women and men.

Keywords

Absolute risk, Calibration, Cardiovascular disease risk prediction, The Framingham equations, Thailand

Word count (abstract): 141

Word count (main text): 2,985
Introduction

Cardiovascular disease (CVD) is caused by multiple risk factors, such as high blood pressure, high cholesterol, smoking and diabetes. The probability that a person will have a cardiovascular event in a defined time period is determined by the synergistic effect of all these risk factors simultaneously. Studies have shown that the relationship between systolic blood pressure and CVD is continuous and log linear down to at least 115 mmHg. Similarly, blood cholesterol is positively and linearly associated with the ischemic type of CVD. This led to the concept of ‘absolute cardiovascular risk assessment’ as a more relevant guide to preventive treatment than thresholds for individual risk factors. It implies that a person at high risk of developing CVD can benefit from the reduction of blood pressure and or cholesterol, regardless of the initial levels - even if they are in the normal range. In line with this development, recent guidelines for the prevention of CVD have advocated the use of global or absolute cardiovascular risk assessment as a tool to assist in the initiation of preventive strategies.

Several tools to estimate the CVD risks of individuals have been developed. However, these equations have limited validity when applied to other populations. Calibration of the Systematic Coronary Risk Evaluation risk chart or the Framingham equations in other populations taking into account different prevalence of risk factors and underlying CVD incidence or mortality has been found to increase the validity of the equations. A Framingham equation calibrated with contemporary data also performs well in Asian populations. However, the latter equation is limited in its application to Thailand as it can only be used to estimate CVD risk in men over 8 years but not in women or over other time spans because the development was based
on a nonparametric model and contemporary data for calibration are not presented. Therefore, we set out to develop Thailand specific equations derived from the Framingham cohort data, and calibrate these to the best available information on the incidence and cumulative risks of CVD in Thailand.

**Materials and methods**

This study was undertaken as part of the Setting Priorities Using Information on Cost-Effectiveness (SPICE) project which aimed to inform the Thai Government on health priorities with improved mortality data and cost-effectiveness studies.

*Cardiovascular disease incidence and cumulative risks*

In this study CVD refers to the combination of ischemic heart disease (IHD) and stroke. IHD events include unstable angina pectoris and myocardial infarction. Stroke refers to both ischemic and hemorrhagic subtypes. Transient ischemic attacks are not included because they cause very little disability.

As the incidence of IHD and stroke were not readily available for Thailand at the time of our study we used the best available data to estimate this in a number of steps, in which we separately determined the number of fatal and non-fatal cases (Figure 1). Firstly, we identified IHD and stroke admission cases that were discharged alive from the National Hospitalization Database for 2004. This yielded the incidence of IHD and stroke cases that survived the initial period of an event. We used international classification of disease (ICD) version 10 codes I20.0, I21-I24 to identify IHD, and codes I60-I64 to identify stroke. This is consistent with definitions of IHD and stroke used for deriving Framingham equations using the publicly accessible Framingham
data. The National Hospitalization dataset was used because it contains data on admissions by disease, age, sex, hospital type and type of discharge (alive or dead). The data were collected for the purpose of reimbursement at the national level mostly in the public hospital system. The database covers universal coverage (UC) and the civil servant scheme (CS) but does not include private health insurance and employer/employee funded insurance. We adjusted for less than 100% coverage using self-reported hospital admissions from the Health & Welfare Survey, 2005 (obtained from the National Statistical Office of Thailand). We applied a proportion of first-ever IHD/stroke by age and sex from a UK study to estimate the incidence of non-fatal IHD or stroke. This study provides complete information on the first-ever proportion of IHD, stroke, separately. It is also more recent than the Chinese MONICA stroke study that reports the proportions of first-ever stroke. We did not find any Asian studies on the proportion of first-ever IHD.

Next, we assessed the incidence of fatal IHD and stroke. This second parameter was obtained from the mortality data available from the cause of death study conducted from 2005-2008 as part of the SPICE project. This dataset allows estimating the number of IHD/stroke deaths occurring both inside and outside hospitals. The total number of deaths from the vital registration was corrected for around 10% underreporting of deaths over the age of 5 based on data from the 2005 Survey of Population Change. Verbal autopsy techniques were used to investigate the most plausible causes of death among a representative sample of over 11,000 deaths recorded in the vital registration system in 2005. The verbal autopsy information was used to correct the vital registration records, close to half of which have an ill-defined cause assigned. The verbal autopsy interviews with family members or relatives of the
deceased included a question whether the deceased had a history of IHD or stroke. If no history of CVD was reported we assumed these were first-ever cases. We applied the proportion of IHD and stroke deaths with no history of CVD from the verbal autopsy study to the national estimates of CVD deaths, by age and sex to obtain the incidence of fatal CVD.

Lastly, total incidence of IHD and stroke was calculated as the sum of the incidence of fatal and non-fatal cases. The incidence was then used to estimate the cumulative incidence in each age group in 2004 by applying over a ten-year period (and separately for the next 8 years to allow comparisons with other published data) the relevant age-specific incidence estimates to those remaining free of disease. This cumulative incidence was then used to calibrate the Framingham equations (Figure 1).

<Insert Figure 1>

Recalibration of the Framingham equations

We developed our tools in a similar manner to the development of other published equations\(^7,12\) that used data on the associations between risks factors and IHD/stroke available from the Framingham cohort study.\(^20\) However, those published equations have been shown to systematically overestimate the incidence in some other populations\(^11\) and they contained risk factors that might not be conveniently obtained in some settings. We therefore developed CVD risk prediction equations that used risk factors conveniently obtained in general medical encounters in Thailand with recalibration against the expected cumulative risk of CVD over the years 2004-2013 for Thailand. These risk factors were age, systolic blood pressure, total cholesterol,
diabetes mellitus and smoking status. Recalibration was conducted to avoid under- or overestimation of risk. The equation development and recalibration was conducted in three steps.

First, we used publicly accessible data from the original and offspring Framingham cohorts \(^{21}\) to assess regression coefficients for each risk factor, separately for men and women, using Weibull accelerated failure-time models \(^{13}\) which are judged to have several advantages over Cox proportional hazards models because they can provide predictions for different lengths of time, and probabilities can be expressed in a more straightforward way. \(^{13}\) The Framingham cohort study is a long term follow up study starting in 1948 with a random sample of 2/3 of the adult population of Framingham, Massachusetts aged 30-62 years. \(^{22}\) The final group of the original participants consisted of 2,336 men and 2,873 women who underwent follow-up examinations every 2 years. \(^{22}\) In 1971, the study recruited offspring of the original cohort members and offspring spouses who underwent follow-up examinations every 4 years. \(^{21}\) A total of 9,373 men and 11,198 women free of previous stroke were included in the risk prediction equation for first-ever stroke, and 8,754 men and 10,783 women free of previous IHD were included in the risk prediction equation for first-ever IHD.

Second, the regression coefficients and constants (Table 1) were subsequently incorporated into equations to calculate the probability that an individual will develop an IHD or stroke event over a given time period. The calculation was done in 3 steps (Equations 1-3) in which m and u are interim variables. The final cardiovascular (IHD and stroke combined) risk over the next t years was calculated using Equation 4.
Equation 1: \[ m = \text{constant} 1 + \sum_{i=1}^{n} \beta_i X_i \]

Equation 2: \[ u = \frac{\log(t) - m}{\text{constant} 2} \]

Equation 3: \[ p = 1 - e^{-e^u} \]

Equation 4: \[ \text{CVD risk} = 1 - (1 - p_{IHD})(1 - p_{stroke}) \]

\(X_i\) are risk factors (e.g., blood pressure, total cholesterol or age).

\(\beta_i\) are coefficients estimated from the Framingham study.

t is the time of follow-up in years.

p is the predicted probability of IHD/stroke by time t.

Finally, we calibrated our Framingham risk prediction estimates by applying the ratio of the average ten-year CVD risk currently observed to the average ten-year CVD risk predicted by the Framingham equations for each age- and sex range group. The Framingham predicted risks were calculated using individual data on risk factors measured for the nationally representative participants aged 30+ in the Third National Health Examination Survey conducted in 2004 (NHES III). For example, if the average 10-year Framingham-predicted risk of IHD for all Thai men aged 30-34 years was 5% and the cumulative risk of IHD for men of this age and sex in Thailand over a 10-year period was 2.5%, the calibration ratio would be 0.5. Therefore, a Thai man
Validation

We tried to validate the recalibrated Framingham equations in two ways: by comparing its predictions with those obtained using a previously published similar equation, and by testing it on data from a Thai cohort study, the Electricity Generating Authority of Thailand study (EGAT). 24

To compare the recalibrated Framingham equation predictions with those obtained from a similar equation previously published, we used an equation published by the Asia Pacific Cohort Studies Collaboration (APCSC). 12 This equation was based on data from the Framingham cohort study using only age, systolic blood pressure, total cholesterol and smoking as predictors and calibrated against the 8-year baseline cardiovascular disease-free survival of 0.966 in men from the EGAT study. 24 We used this equation for the first validation effort. The EGAT study is a follow up of the EGAT employees with 2,702 males and 797 females aged 35-54 at the beginning of the study in 1985. It measures important CVD risk factors and also the number of new IHD and stroke that occurred over the follow up period (1985 onward). 24 For comparison, we adjusted our equation by calibration with 8-year cumulative incidence of CVD estimated using the same approach as described above. We applied both equations to a national sample of Thai men aged 30 years and over whose risk factor levels were measured in the Third National Health Examination Survey 23 in 2004 (n =
18,934) and compared the average 8-year CVD predicted risks by age range between the two equations.

For the second validation effort we used the 1997-2007 data from the EGAT study.\(^\text{24}\) We used our equation to predict the number of CVD cases that would occur for men over this 10 year-period and compared this number with the number of cases that actually occurred in the study. To show the impact of the calibration of the Framingham equation, we also compared these 2 figures with the number of cases predicted using the un-calibrated Framingham equation. We also assessed the equations by estimating the area under the receiver operating characteristic (ROC) in a regression model using the EGAT dataset.

**Results**

On average, 38% and 25% of first-ever IHD events and 26% and 23% of first-ever strokes are fatal in men and women, respectively. The incidence of stroke was higher than the incidence of IHD by 75% in men and by 42% in women. The incidence of both diseases increased exponentially with age. The cumulative CVD risk was higher in Thai men until age 70 after which the risk was higher in women while the Framingham risk scores before calibration were much higher in men than in women at all ages (Table 2).

<Insert Table 2>
Age and systolic blood pressure were similarly associated with IHD and stroke in men and women. Total cholesterol was positively associated with ischemic heart disease but was not significantly associated with stroke in either sex. Associations between diabetes mellitus and IHD or stroke and between smoking and IHD or stroke did not differ significantly between women and men (Table 3).

<Insert Table 3>

Recalibration of the Framingham equations reduced the CVD risks predicted for Thai men by 97% and for Thai women by 10%. The correction was largest at younger ages. In older women, recalibration increased the predicted risk (Figure 2).

<Insert Figure 2>

The recalibrated Framingham equation predicted similar average risks of cardiovascular disease among Thai men over the next 8 years as the equation published by the APCSC. There were too few female employees in the EGAT study cohort to allow further comparisons (Figure 3).

<Insert Figure 3>

Performance of the recalibrated Framingham equation in predicting cardiovascular event in a Thai cohort
The calibration of the Framingham equation much improved the predictions of CVD in the Thai cohort. In addition, the calibrated equations performed well in predicting the number of CVD as compared to the number of CVD actually observed over the 10-year period (Figure 4). The recalibrated equation has an area under the ROC curve of 0.65. This compares to values of 0.64 for the un-calibrated Framingham equation.

Discussion

The calibration of the Framingham equations had a substantial effect on risk estimates for men, and a smaller effect in women. These observations are similar to previous studies in which the equations overestimated CVD risks in ethnic groups in the US (Japanese American and Hispanic men and Native American women)\(^{11}\), and in the UK.\(^{25}\) The differences may stem from variations in terms of ethnicity, diet and lifestyle. We only used the Framingham data to derive the equations because this was the only dataset we had access to. The variables used in the equations are easily obtained in general medical encounters.

We derived estimates of ischemic heart disease and stroke incidence and cumulative risks for Thailand using the best available data sources to calibrate the Framingham equations. We found that the calibrated tools performed as well in predicting CVD risk over the next 8 years in Thai men as an existing equation\(^{12}\) that was based on APCSC cohorts and calibrated on the incidence of CVD in the EGAT cohort study.\(^ {24}\) This supports the criterion validity\(^ {26}\) of our equation. The difference, if any, between the
predicted and observed number of CVD cases in the EGAT cohort during the year 1997-2007 could partly be explained by the difference in socioeconomic status. The EGAT employees represent the urban middle class of the Thai population in which the incidence of CVD may be lower than in the general population.\textsuperscript{27,28}

We believe our equations have a major advantage over the APCSC equations in that they are more flexible; they allow predicting the risks of CVD over any time period, and in women and men. Our equations are by age and sex, as opposed to calibration using one average value across all ages and for men only.

A limitation of our study is the lack of information on the proportion of first-ever IHD or stroke in the hospital admission dataset. In the absence of recent Asian estimates we used estimates from a UK study\textsuperscript{17} because it provides complete information on first-ever proportion of IHD, stroke, separately. The Chinese MONICA study reported on the proportion of first-ever stroke\textsuperscript{18} but the data are rather old (1982-1995) and estimates for stroke were not provided.

Our incidence of non-fatal IHD and stroke in Thailand may be underestimated because we only included admitted cases. However, the introduction of the ‘30 Baht’ scheme in 2001\textsuperscript{29} made access to health services in Thailand almost universal and we would expect most cases of IHD and stroke to present to hospital. Also, we needed to assume that the distribution of admissions by cause in the National Hospitalization dataset (UC, CS) is the same in those not in this dataset (private health insurance and employer/employee funded insurance) within hospital types, age and sex groups. There
were no data to validate this assumption. We advise that Thailand continue to collect more data on admissions aiming to have 100% coverage.

The comparison with the EGAT study could be influenced by the time lag (7 years) between the EGAT data (1997 to 2007) used to validate the recalibrated equation and the cumulative incidence (2004-2013) used for the recalibration of the Framingham equations, and by the fact that the EGAT participants were not in all respects representative of the total Thai population. However, the changes in CVD risks that may have occurred over that period would have been mediated by the risk factors that are included in the model, which reduces the possibility for bias. Similarly, the differences between the EGAT population and the general Thai population will partly be reflected in their risk factor exposure. To the extent that this is the case, these differences should not bias the comparison.

The recalibrated cardiovascular risk assessment tool can serve the country in several ways. The tool can be used by physicians to inform their patients about their CVD risks and to discuss options for risk reduction. Primary healthcare providers can also use the tool to screen for people at high risk of CVD and thus implement more efficient CVD prevention programs. Used in cost-effectiveness studies, the tools are useful to inform policy makers of how most efficiently to target interventions for preventing CVD.

Since valid and reliable estimation of absolute CVD risks requires accurate data on the incidence of IHD and stroke we strongly recommend that Thailand continues to improve the collection of epidemiological data.
Funding

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References


**Figure 1:** Flow chart of procedures used to assess the incidence of ischemic heart disease and stroke in Thailand

**Figure 2:** Ten-year CVD risk (percent) by age and sex predicted by Framingham equations applied to the Third National Health Examination Survey dataset before and after calibration

(A) Men

(B) Women

**Figure 3:** Comparison of the 8-year cardiovascular risks (percent) predicted for Thai men aged 30 years or over in the Third National Health Examination Survey dataset between the APCSC and this study’s equation

**Figure 4:** Predicted vs. observed number of cardiovascular disease events in a Thai cohort.
Table 1: Weibull accelerated failure-time model regression coefficients of risk factors and cardiovascular disease in the Framingham heart study

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>Men</th>
<th>Women</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Ischemic heart disease</td>
<td>Stroke</td>
</tr>
<tr>
<td>Age (years)</td>
<td>-0.037</td>
<td>-0.036</td>
</tr>
<tr>
<td>Total cholesterol (mg/dL)</td>
<td>-0.005</td>
<td>-0.006</td>
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<td>Diabetes mellitus (yes=1, no = 0)</td>
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<td>-0.695</td>
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<td>Systolic blood pressure (mmHg)</td>
<td>-0.009</td>
<td>-0.01</td>
</tr>
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<td>Smoking (yes=1, no = 0)</td>
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<td>Constant 1</td>
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<td>9.32</td>
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<tr>
<td>Constant 2</td>
<td>0.82</td>
<td>0.83</td>
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<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stroke</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>-0.081</td>
<td>-0.06</td>
</tr>
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<td>Total cholesterol (mg/dL)</td>
<td>Non-significant</td>
<td>Non-significant</td>
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<td>--------------------------</td>
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<tr>
<td>Systolic blood pressure (mmHg)</td>
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<td>-0.017</td>
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<td>Smoking (yes=1, no=0)</td>
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<tr>
<td>Constant 2</td>
<td>0.87</td>
<td>0.83</td>
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Table 2: The annual incidence and 10-year cumulative incidence of first-ever ischemic heart disease and stroke in Thailand and the Framingham predicted 10-year risk (per 100,000 populations)

<table>
<thead>
<tr>
<th>Age group</th>
<th>Ischemic heart disease</th>
<th>Stroke</th>
<th>Cardiovascular Disease</th>
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<tr>
<td></td>
<td>Contemporary annual incidence</td>
<td>Contemporary 10-year risk</td>
<td>Framingham predicted 10-year risk</td>
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<tr>
<td>Men</td>
<td>Women</td>
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<td>Women</td>
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<tr>
<td>30-34</td>
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<td>9</td>
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<td>26</td>
<td>14</td>
<td>556</td>
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<td>26</td>
<td>961</td>
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<td></td>
<td>16,189</td>
<td>20,595</td>
<td>25,760</td>
</tr>
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**Ratio Framingham/Contemporary**

| 3.53 | 1.59 | N/A | N/A | N/A | 1.16 | 0.73 | N/A | N/A | 1.97 | 1.10 |
Table 3: Hazard Ratios (95% confidence interval) for the association between risk factors and ischemic heart disease and stroke from the Framingham cohort study

<table>
<thead>
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<th></th>
<th>Age ( + 10 years)</th>
<th>Total cholesterol (+ 1mmol/L)</th>
<th>Diabetes (no, 0 yes,1)</th>
<th>Systolic blood pressure (+10 mmHg)</th>
<th>Smoking (no, 0 yes,1)</th>
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<tr>
<td><strong>Ischemic heart disease</strong></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td>1.58 (1.46, 1.71)</td>
<td>1.27 (1.17, 1.37)</td>
<td>1.75 (1.39, 2.22)</td>
<td>1.12 (1.07, 1.16)</td>
<td>1.60 (1.36, 1.88)</td>
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<tr>
<td>Women</td>
<td>1.54 (1.37, 1.72)</td>
<td>1.30 (1.19, 1.43)</td>
<td>2.31 (1.74, 3.07)</td>
<td>1.13 (1.08, 1.19)</td>
<td>1.30 (1.03, 1.65)</td>
</tr>
<tr>
<td><strong>Stroke</strong></td>
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<tr>
<td>Men</td>
<td>2.54 (2.19, 2.94)</td>
<td>Non-significant</td>
<td>1.57 (1.09, 2.25)</td>
<td>1.24 (1.16, 1.33)</td>
<td>1.61 (1.21, 2.14)</td>
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<tr>
<td>Women</td>
<td>2.05 (1.72, 2.43)</td>
<td>Non-significant</td>
<td>2.28 (1.58, 3.29)</td>
<td>1.23 (1.15, 1.31)</td>
<td>1.80 (1.29, 2.50)</td>
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</tbody>
</table>
Figure 1: Flow chart of procedures used to assess the incidence of ischemic heart disease and stroke in Thailand.

- Hospital admissions CVD discharged alive from national hospital database
- Inflated to self-reported hospital admissions in the Health and Welfare Survey
- National estimate admissions CVD discharged alive
- Proportion of first-ever events from UK study
- National estimate first-ever incidence of nonfatal CVD
- Verbal autopsy deaths with no history of previous CVD
- Inflated to national mortality estimates by age and sex
- National estimate first-ever incidence of fatal CVD
- Total incidence CVD events
Figure 2: Ten-year CVD risk (percent) by age and sex predicted by Framingham equations applied to the Third National Health Examination Survey dataset before and after calibration

(A) Men

(B) Women
Figure 3: Comparison of the 8-year cardiovascular risks (percent) predicted for Thai men aged 30 years or over in the Third National Health Examination Survey dataset between the APCSC and this study’s equation.
Figure 4: Predicted vs. observed number of cardiovascular disease events in the EGAT cohort